

# **Human Research Protections in Clinical Trials: A Public Perspective**

Report to the Director, National Institutes of Health  
From the NIH Council of Public Representatives  
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## **Executive Summary and Recommendations**

The Council of Public Representatives (COPR) presents this report to the Director of the National Institutes of Health (NIH) as part of its mandate to assist the NIH with enhancing public participation in NIH activities. The American public plays various roles in biomedical research: some elect to participate in clinical trials, many benefit from discoveries related to that research, and all pay for it—both directly, as a cost of medical services, and indirectly, through taxpayer-supported research.

## **Background**

Over the course of the last year, the COPR Working Group on Human Research Protections (HRP) has examined from a public perspective many of the issues that are central to human clinical trials. Many of these issues were raised in discussions that took place during the COPR meeting held in spring 2001.

It has become clear to the HRP Working Group that the protection of patients in clinical research derives from two critical, independent, and complementary tracks. One is through creation of an institutional system and culture that instills within all members of the research community the highest ethical value for human life and demands that their behavior reflects those values. The other, less apparent route is through the ability of patients to protect themselves by virtue of truly informed decision-making. This second, less recognized route of protection leads to the following overarching premise:

*Transformations in the systems of human research protections must take place at all levels within and outside of the NIH in order for the nation's vital clinical research enterprise to fulfill its promises. As part of this transformation, the NIH must pave the way to ensure that clinical research leads not only with the "high tech" of cutting-edge science, but also with the high touch of human interactions that values and empowers patients as active, informed, and respected partners.*

The COPR urges the NIH to adopt this premise as a guiding principle in pursuing its intramural and extramural research agenda. The Council recognizes that the NIH often has taken the lead in involving the public in the research process, through its advisory councils and other bodies and mechanisms. The NIH also has initiated many of the existing institutional systems of human research protections, which are substantial improvements over what had come before. It is this very history of leadership that points to the NIH as the one to initiate these next steps in strengthening the ethical basis and public support of biomedical research.

The Council believes that the issue of human research protections requires immediate national attention from a number of different directions. We speak as a voice of the public within the system of the NIH and our comments are offered from this particular perspective. With this in mind, the COPR has identified six key areas for discussion and action in this report. These are: (1) informed consent, (2) availability and transparency of information, (3) institutional review boards (IRBs), (4) conflicts of interest, (5) confidentiality and privacy, and (6) enhanced education and training of the public to better enable them to play their role of partner in the research process.

These categories, and the recommendations within them, do not include all of the issues examined by the working group, nor are they the only avenues by which the NIH can strive to meld its research activities with the overarching premise stated at the beginning of this summary. Nonetheless, within the myriad and complex issues related to human research protections, the COPR considers the recommendations elucidated here to be the most important at this time. The Council urges the NIH to implement these recommendations as an integral part of the federal research programs that it administers.

Although the language of this report often is couched in terms of clinical trials, the COPR recognizes both the similarities and the differences that can apply to behavioral and social science research. The Council further believes that the principles expressed in this document should be applied to those venues of research, though at times modification may need to be made in terms of their implementation.

The COPR will revisit this report and the recommendations contained within it on a regular basis. During this process, the Council expects to receive from the NIH a response to the recommendations contained in this report, as well as to update and revise this report and its recommendations as the environment of patient protections continues to evolve.

## **Recommendations**

### *Informed Consent*

1. Establish the principle that informed consent is an ongoing, meaningful, and educational process that is woven throughout the course of a research study. Informed consent must not be viewed simply as an event that occurs at the commencement of the study and concludes when the participant's signature is obtained. Nor should it be seen merely as a step required to satisfy specific regulations or to ensure legal protection of the institution. These are all ancillary purposes. Rather, informed consent is central to the process of the patient becoming a full, knowledgeable partner in the research endeavor. Its purpose is to confirm and re-affirm, through meaningful exchange, the willing and fully advised decision of a participant to enter and remain in a clinical trial.
2. Provide, at the clinical trial site, a list of "Frequently Asked Questions" (FAQ) for those considering participation in clinical trials. This FAQ should include the questions and other information that would assist people in making informed decisions about participating in trials. This list of points to consider should provide potential participants with the means to formulate their own personal requests for further information.
3. Develop a multi-level approach to the informed consent process that ensures easy access to all levels of information by all participants. Beyond the basic and necessary "bedrock" level of information that must be conveyed to all participants (the nature of the study, risks and benefits, etc.), individual participants must also be able to pursue and obtain increasingly complex information according to their interests, needs, and sophistication. When an individual participant wishes to seek additional information, the pathway to acquire such information should be clear, easy to navigate, available without further request, and accessible without going through the "gatekeeper" of the investigator who treats the participant in the clinical trial.
4. Encourage participants to seek additional relevant information from a source other than the clinical trial staff and/or institutional staff sponsoring the clinical trial. When considering entry into a trial, participants should be provided contact information for independent third parties who are knowledgeable in the field and who may be able to counsel and advise potential participants. Written information that offers a clear summary of the clinical trial should be provided to all participants so that those who want to pursue additional information from an outside source have a readily available resource to take with them.
5. Ensure that an adequate waiting period-between the time that trial information is made available and when consent is requested-is built into the consent process. Participants should be informed that, in the absence of extenuating circumstances such as medical

emergencies, they are not required to give consent at the time of the request. They should be encouraged to consult external sources of information and advice before agreeing to participate in the research. This waiting period would allow time for prospective participants to digest information about the trial and to consult outside sources of information and advice if they so choose.

6. Make available to trial participants, in a timely manner, any new or relevant information as it becomes available from other like trials, particularly but not exclusively concerning adverse events. In the spirit of informed consent as an ongoing process, the investigator should consider obtaining an affirmation of the patient's willingness to continue in the protocol after receiving and understanding such additional information.
7. Study the strengths and weaknesses of peer access, patient advocate, and similar systems and mechanisms to determine whether these types of interactions benefit the participants in clinical trials and, if so, how such interactions can be better integrated into the informed consent process.

### ***Availability and Transparency of Information***

1. Provide research participants with basic information about the protocol of the study. Moreover, because access to the protocol is integral to the concept of the patient as a partner in the research process, all participants should be informed that they have access to the full protocol upon request. Limited exceptions to this recommendation should be permitted by the IRB only when it can be demonstrated that access to the protocol would in fact compromise the conduct and outcome of the study.
2. Support the implementation of a system ensuring the meaningful and timely public reporting of adverse events and associated data in a single trial, in multicenter sites of a large trial, and in similar trials. This may include the reporting of adverse events in related animal studies where the events were deemed serious. The NIH should lead the way in developing this national system for reporting adverse events, ensuring that it is widely publicized and easily accessible to investigators, institutions, industry, IRBs, and in particular, among those populations currently in trials and those most likely to participate in those trials. This systemic change is a key component of enhanced decision-making and patient protection in clinical research.
3. The National Library of Medicine (NLM) should consider making available on the Internet, through MEDLINE and its successors, relevant research information published before 1966. Adding this information to MEDLINE—even with only titles or keywords available for searching—would provide researchers with access to older literature that could prove important to their clinical work. Once researchers can identify these older publications via the Internet, they could obtain print copies of these articles through libraries.

4. As a standard part of the research process, inform participants about the outcome and results of the studies in which they take part. Participants as partners in the research endeavor should be entitled to learn of those outcomes before their publication.

### ***Institutional Review Boards***

1. The NIH should lead or support, as appropriate, the study of the ability of the IRB system as it is currently structured to meet the needs of human research protections. The NIH should play a highly visible public role in the growing national dialogue of those who are examining and striving to correct deficiencies in the current system.
2. The NIH should lead or support, as appropriate, the study of individual and institutional conflicts of interest within IRB decision-making processes.
3. The NIH should make every effort to encourage senior researchers to serve on IRBs so that they can contribute their much-needed experience and expertise to IRB determinations.
4. Public members of IRBs are uniquely positioned to contribute to an understanding of the needs of research participants and the balancing of ethical issues involving research participation. The NIH should take steps to ensure the appropriate participation and support of public members on IRBs. This support should include, but not be limited to, defining the roles and responsibilities of public members who serve on IRBs and ensuring their appropriate education and training.
5. All IRB members, but particularly public members, must have adequate education and information to participate effectively in the local review process. In addition to its own efforts concerning public education and training, the NIH should encourage other appropriate agencies, such as the Office of Human Research Protections (OHRP) and professional and nonprofit organizations, to make recommendations regarding the training, education, and expectations for all who serve on IRBs. Those groups also should contribute to the preparation of IRB members for those tasks.
6. The NIH should lead or support, as appropriate, efforts to expand non-institutional or independent representation on IRBs. Such efforts may include the creation and/or support of independent, non-institutionally affiliated IRBs as a means of enhancing the professionalism of these bodies and reducing potential conflicts of interest in conducting reviews.

### ***Conflicts of Interest***

1. The financial ties of the investigator and/or institution conducting the clinical trial should be disclosed to the study participants. Through the informed consent process, participants in clinical research should have clear and direct access to relevant information about any financial ties that an investigator or institution has with the particular research project or the industry sponsor of the trial.

2. The NIH should develop an educational resource for participants that will help them to identify relationships signaling a potential conflict of interest, to understand why these relationships are important in the context of the study, and to be guided as to their right and ability to question and investigate such financial ties.
3. The NIH should work toward a system that ensures that federal dollars are directed to institutions that have in place a demonstrated, effective system for disclosing and examining financial and other interests that may, directly or indirectly, in fact or appearance, influence the objectivity or outcome of research. This should include ensuring that the grant application requires a summary demonstration of a grantee institution's system for review of such interests and that inadequate compliance with this requirement becomes a category to be identified as a potential concern when grant applications are being considered.

### ***Confidentiality and Privacy***

1. The NIH should develop and widely disseminate educational information on issues of privacy in clinical research, such as through the development of a "Frequently Asked Questions" (FAQ) list. This information should both inform the research community and provide investigators with resources to pass along to trial participants.
2. Participants must be informed about possible breaches of confidentiality and the possible consequences of such lapses. For example, participants should be warned that a breach of confidentiality can occur as a result of identifying themselves as participants in such a trial, and that such a disclosure could possibly affect their family members (e.g., in the case of genetic research) or their health insurance coverage.
3. Privacy issues should be addressed through a process that begins with the first interaction with the potential trial participant and continues throughout the course of the trial, as well as with any subsequent handling of data and published material on that trial.

### ***Enhanced Public Education and Training***

The NIH should develop model programs that establish new and tested mechanisms for educating and training the public at large and, in particular, trial participants to better equip them to become empowered and informed partners in the research process. These programs and mechanisms necessarily must address the related issue of how to instill a cultural sensitivity among those conducting research that invites, welcomes, and respects the public and the individual participant as an active partner in all aspects of research. The COPR plans to make further recommendations in this area.

### *Additional Suggested Areas of Research*

The COPR urges the NIH to plan and fund research examining the role of the participant at each phase of the clinical trial process. It is especially important to examine the relationship between the investigator and the participant and to explore ways to empower participants to become active, respected partners in the process. Such research might focus on the following:

- How effective are current approaches in the informed consent process? For example, how do potential participants weigh the information provided to them, and how do they behave as they experience this process?
- What are the best ways to communicate the risks and benefits of a particular research project to a potential participant? How can the effective exchange of information be enhanced within the informed consent process?
- How can the informed consent process be strengthened to avoid the occurrence of "therapeutic misconception," where an actual or potential patient might mistakenly believe or be led to believe that a clinical trial represents state of the art delivery of care, with an expectation of benefit? This is especially an issue in Phase I and II trials.
- How may biases or secondary motivations influence the behavior of all the players in the research process in general and in informed consent in particular?
- What types of follow-up would help potential participants decide whether to participate in a clinical study? How can potential participants' understanding of the study they are considering be enhanced through the use of written material, interactive videos, or patient advocates?
- How do potential participants process the information presented to them during an interview for a research study—for example, in terms of timing, complexity, and quantity of information?
- Do concerns for individual or family privacy affect the decision-making process?
- How do participants in clinical trials regard the reporting of serious adverse events and the existence of conflicts of interest?

Still other research needs to take a broader look at ways to increase public awareness and knowledge about the importance of clinical trials, and how the public can become a more active partner in the research process.

The main body of this report provides an in-depth discussion of the questions and concerns that were explored by the COPR in its deliberations and that served as the basis for its recommendations. The report is not intended to describe or allude to all of the many NIH activities and initiatives currently under way regarding the protection of human participants in clinical research, but rather to identify areas needing further emphasis and/or attention and to

provide guidance for both existing and new efforts in this area. The COPR will continue to examine the areas addressed in this report and will offer more detailed recommendations at a later date.

## **Human Research Protections in Clinical Trials: A Public Perspective**

### **Introduction**

*If it is to fulfill its promises, clinical research must lead not only with the high tech of cutting-edge science, but also with the high touch of human interactions that value and empower patients as full partners in the research process.*

Protection of participants in clinical research derives from two critical, independent, and complementary tracks. One is the creation of an institutional system that instills within each member of the research community the highest ethical value for human life, demands that all behaviors reflect these values, and holds institutions accountable for the enforcement of these standards. The other, less apparent strand of protection is through the ability of participants to represent themselves effectively. Participants in clinical research become equipped to protect their own interests through informed decision-making that takes individual risk-benefit analyses into account, through systems that work to empower the individual, and through relationships based on equality and mutual respect among researchers, medical providers, and patients themselves.

Today, there are few systems or resources devoted to, and few professional careers tied to, strengthening and advancing this second aspect of human research protection. Although considerable public debate and comment today is focused on strengthening institutional protections for human subjects, few consider these issues from a uniquely public perspective.

The Council of Public Representatives (COPR) at the National Institutes of Health (NIH) has been charged with a broader mission to enhance public participation in all aspects of biomedical research. This mission can be accomplished through more widely available information that is presented in a meaningful context, increased public transparency of the research process and outcomes, and creation of an environment that elevates and ensures a public voice in all discussions of the nation's research policy.

An increasingly informed public no longer considers clinical research as research done to or for individuals, but rather as research done with individuals. The paradigm for clinical research in the 21st century is one of patients invited to participate as partners in the research endeavor. This understanding of the roles of the clinical trial participant and the public at large as active partners with the scientific community must be brought forward in all discussions involving human research protections. The elevation of this partnership is fundamental to ensuring that science delivers on its promise to improve the health of the nation and that society continues to maintain and grow its substantial commitment of resources toward the advancement of the nation's scientific enterprise. With this background in mind, the COPR has approached issues of human research protections from the perspectives of the patients who participate in clinical research and of the American public, who pays for and benefits from such research.

Patients participate in clinical research for various reasons. Many come forward because of an understanding that, because of their medical circumstance, they have something truly unique and beneficial to offer science. Through their altruism, society is given an extraordinary gift. Some do so for purely pragmatic, economic reasons. They may have either inadequate or no health insurance coverage, and a clinical trial may represent their only access to care.

Some refuse to participate because of cultural and ethnic experiences or distrust of the medical community as a whole. Others are simply too frightened or unwell to deal with the idea of the unknown in clinical trials. Still others have no knowledge of clinical research and fear they will be used as "guinea pigs" in risky experiments.

Finally, there are those who have found no lasting relief from standard care and who turn to research in desperation. Such desperation can leave a participant vulnerable to false expectations and misinterpretations of the "promise" of research. On the other hand, when all avenues of standard care have been exhausted, a patient's only hope for meaning and the glimmer of possible treatment may rest in participating in a clinical trial. One danger of moving toward over-regulation or over-correction in an attempt to redress previous errors may be to take away this hope. This is an issue of public interest that cannot be overlooked.

We believe that the public viewpoint can be represented best, and at times only, by members of the public sitting as equal partners at the table where research policy decisions are being debated and decided. All must come to understand that the empowerment and involvement of research participants, together with the meaningful participation of the public, will build trust, engender wider participation, and ultimately enhance the quality of science and the efficient development of beneficial therapies. All participants in this complex scheme-government, industry, institutions, investigators, and the American public-must come together and act with decisive moral authority to strengthen the nation's system for protecting those who choose to participate in clinical research and to ensure that their contributions are meaningful and beneficial to the common good.

The discussion contained in this report relates primarily to the protection of human subjects in clinical trials; however, much of the Working Group's analysis presented here may apply to all aspects of research involving human subjects, such as behavioral and social science research. When this is the case, the Working Groups hopes that the principles expressed in this document will be applied to those venues of research, though at times modification may need to be made in terms of their implementation.

## Background

### *Recent Events*

*It is very easy to be wise (and critical) after the event; the problem is to be wise (and ethical) before the event.* – Sir Austin Bradford Hill (Hill 1963)

The 40 years since this statement was made have witnessed dramatic changes in the landscape of clinical research. Nonetheless, Hill’s simple challenge remains as profoundly true today as when it was initially made. Serious recent events—most notably the death in September 1999 of 18-year-old Jesse Gelsinger in a gene transfer clinical trial conducted at the University of Pennsylvania and the death in June 2001 of Ellen Roche, a healthy participant in an NIH-sponsored biomedical research study at Johns Hopkins University—have been the catalysts for re-engaging the nation in a dialogue surrounding protections afforded to human subjects in clinical research. Across government, efforts continue on multiple fronts to realign oversight responsibilities, reassess reporting guidelines, and expand opportunities for public input, all in an effort to develop wiser and more ethical policies that will serve to protect human subjects in research before, during, and after the event.

Many of the concerns raised in this report are being actively identified and discussed by others within government, industry, and academia:

- In September 2000, Donna Shalala, then Secretary of the Department of Health and Human Services (DHHS), assumed a leading role when she challenged “government, researchers, and research institutions to come together with a state of urgency to reform the current system of protections” (Shalala 2000).
- The Office of the Inspector General has issued several investigative reports (OIG, April 2000, 2000a–2000c).
- Unprecedented numbers of people have taken advantage of enhanced training opportunities provided by Public Responsibility in Medicine and Research for members of Institutional Review Boards (IRBs).
- Agencies within the DHHS have stepped up enforcement of existing rules, which in several cases has resulted in the temporary suspension of trials at research institutions.
- In September 2001, the National Bioethics Advisory Commission (NBAC) released an extensive report, “Ethical and Policy Issues in Research Involving Human Subjects” (NBAC 2001), which recommends major changes in the current system.
- The Institute of Medicine has agreed to conduct a two-part study on human subjects protection. The first part, released in April 2001, examines the accreditation for human subjects protection programs and standards for IRBs. The second part, due in the fall of 2002, will examine the complex framework for oversight of human research protections.

- On November 30, 2000, the *New England Journal of Medicine* called for all academic medical centers to adopt policies prohibiting equity ownership by investigators in companies sponsoring clinical trials (Drazen and Koski 2000).
- The American Association of Medical Colleges (AAMC) has established a task force on institutional conflicts of interest.
- The National Advisory Council on Human Research Protections, appointed through the Office of Human Research Protections (OHRP), promises to play a leading role in future developments in this area.

These are but a few of the recent pronouncements and actions within the public and private sectors that will enhance the protections afforded by institutions engaged in clinical research across the nation. The COPR is encouraged by this activity.

### ***Role of the COPR***

In 1998, the Director of the NIH, Harold Varmus, MD, formed the Council of Public Representatives. His action was prompted in part by a report issued earlier that year by the Institute of Medicine, “Committee on the NIH Research Priority Setting Process, Scientific Opportunities and Public Needs.” That report challenged the NIH to widen the scope and opportunity for public input by offering the following:

*The director of NIH should establish and appropriately staff a Director’s Council of Public Representatives, chaired by the NIH director, to facilitate interactions between NIH and the general public. (IOM 1998)*

At the level of the Office of the Director, the COPR became an active and chartered council of public representatives to advise the Director of the NIH. The mission of the COPR is to “assist the NIH in enhancing the participation of the public in NIH activities that have an impact upon the public, in increasing public understanding of the NIH and its programs, and in bringing important matters of public interest forward for discussion in public settings” (COPR 1998). In the three formative years since its inception, the inaugural COPR has continued to define the nature and scope of its contributions and the processes by which it will bring an active, public voice into the work of the NIH.

The COPR constitutes a diverse public group comprising patients, family members of patients, health professionals, members of advocacy groups, research scientists, students of science, and communicators in health and medicine. Members agree to leave their specific disease interests aside in service of the broader public interest and to provide input on trans-NIH issues. The COPR is in a unique position to appreciate both the importance of clinical research and the promise that it holds for improving the health and well-being of all, as well as the imperative to protect the individuals who participate in clinical studies as research subjects.

## **Forces Shaping Human Research Protection**

### ***Balancing Interests in Clinical Research***

The elusive question we face is how to establish a balance between protection of individual human research participants and the advancement of knowledge that promises to enhance the health and lives of greater numbers of people. This balance is threatened by the introduction of escalating costs associated with most clinical trials and the very real economic pressures in industry trials to get a product to market quickly.

In this dynamic among individual rights and protections, communal good, and commercial interests, ethical questions often present a very close and difficult call. We recognize that people of goodwill may disagree. We contend that when this occurs, the scale must be weighted ultimately in favor of the protection of the individual in order for the participant, society, industry, and the medical research enterprise to be served.

### ***Understanding Clinical Research***

The receipt of even basic medical care is not without risk. However, clinical research, by its very nature, may change the standard of—and increase the risk associated with—health care. The public, therefore, must be better educated and informed about the inherent risks in research.

Moreover, while participation in research is supposed to be a voluntary endeavor governed by informed consent, there is some evidence that individuals enrolled in clinical research are not always aware of their status as research subjects. The Subject Interview Study, conducted by the National Advisory Committee on Human Radiation Experimentation (ACHRE 1995), found that patients were very often confused about their past participation in clinical research. Participants were not always aware that trials generally involve unproven therapies that may or may not prove beneficial to them. In fact, few research participants surveyed by the ACHRE were able to distinguish between their “medical care” and their “research participation.” Furthermore, when a serious medical condition was at issue, and when other, demonstrated therapies had not worked, research participants felt they had little choice about enrollment in research (often a clinical trial) and were more likely to view the research as “therapeutic.” These issues remain of considerable public concern today.

### ***Regulatory Framework for Clinical Research***

The vast majority of protections for human participants in clinical research are codified at 45 CFR Part 46 (Subpart A). The language in this section governing the DHHS represents the Common Rule, the regulations that have been adopted by 15 federal agencies and departments for human subjects protections, including the Departments of Defense, Agriculture, and Education. The regulations encompass all research on humans that is “conducted, supported or otherwise subject to regulation by” the federal government. A few federal agencies that are involved in human subjects research have not subscribed to the Common Rule, including the Department of Labor, the Nuclear Regulatory Commission, and the National Endowment for the Humanities.

The Common Rule covers many aspects of the research enterprise, including the composition of IRBs and the scope of their review. The regulations also lay out criteria for IRB approval of research, including special allowances for research involving less than minimal risk and research scenarios necessitating waiver of consent. Perhaps most important is the articulation of requirements for informed consent, including the specifics of research participation, the potential risks and benefits of participation, and confidentiality concerns. Other subparts of Part 46 discuss research involving special populations, including prisoners, pregnant women, children, and fetuses.

### *The Changing Nature of Clinical Research*

Enacted in December 12, 1980, the Bayh-Dole Act (Public Law 96-517) encouraged the commercialization of discoveries arising from federally funded biomedical research in the laboratories of government agencies and grant recipients. This legislation helped to clear the way for companies to patent therapeutic discoveries and bring them to market more rapidly with a greater direct financial return. It also correlated with an explosive increase in new therapeutic products and growth in the pharmaceutical industry. The development of recombinant DNA technology, the recently announced completion of the sequencing of the entire human genome, and the potential envisioned for genomics and proteomics hold the promise of continued, even more rapid innovation in biomedical research. These rapid advances in science, however, have raised the specter of new risks: the undue influence of conflicts of interest; new threats to individual privacy and autonomy; the failure to discover, understand, and disclose adverse events occurring in the accelerated course of research, often in multicenter trials; and the inadequacy of the informed consent process, to name but a few.

Recent years have witnessed an expansion of the sites of human clinical trials beyond academic medical centers and into private clinical practice. Large pharmaceutical and biotechnology companies, in addition to the NIH, have become the major sponsors of clinical trials. As changing market forces have moved increasing numbers of participants away from university research facilities, industry has begun to offer significant and creative financial incentives to clinicians in private practice to recruit participants and to conduct clinical trials. In the past two decades, these dynamic market forces have substantially transformed the nation's clinical research enterprise.

Substantial time and cost are required to bring a drug to market. For example, new biological agents and therapies that may hold promise for millions of Americans take years to develop, are very expensive, and often come to market with a relatively short remaining patent life. From the point of laboratory discovery, companies are pressured—and in turn bring pressure to bear on the Food and Drug Administration (FDA)—to bring any new drug to market as rapidly as possible so that maximum financial return can be reaped before a generic form becomes available.

Current market incentives are for “blockbuster” drugs and procedures that have the broadest possible application. But as the promise of understanding the human genome unfolds, the practice of medicine may move away from the “one size fits all” model of the blockbuster to the use of certain therapeutic interventions—and the avoidance of others—tailored to the genetic

profile of each individual. Knowledge, especially the reporting of adverse events in small numbers of patients, will become increasingly crucial to the development and use of new biomedical interventions. Not only will this knowledge save lives, it also will allow us to “rescue” interventions that may be deadly to a small percentage of patients but beneficial to others.

A more informed and educated public has come to demand rapid translation of innovations discovered through research. The FDA has responded by instituting its Fast Track Drug Development Program. This program is designed to facilitate the development and expedite the review of new drugs that demonstrate the potential for treating serious and life-threatening conditions and for addressing unmet medical needs.

The accelerated translation of research, however, may present its own unique risks. Many Phase III trials, it is argued, do not mirror the actual, ultimate use by consumers, such as those with multiple disorders or combining multiple therapies. It is reported that new drugs entering the market are increasingly subject to relatively little Phase IV testing or post-market surveillance. At the same time, the demand for participation in clinical trials among certain informed populations is increasing, encouraged in part by advocacy efforts focused on educating participants about clinical trials and empowering them with openly available information. The American Cancer Society, for example, estimating that only about 3% of adult cancer patients participate in clinical trials, reported that it has established the goal of raising this number to 10% by fostering participant awareness and opportunities.

Better standards of living, combined with advances in medical science and technology, have created a society today in which people with chronic health problems are living longer than ever before. Both adults and children with illnesses that, until recently, were considered life threatening are now enjoying relatively normal lives. This shift has generated a public interest in research that focuses on the management of chronic illnesses, their impact on families and community institutions such as schools and workplaces, and means of prevention. Indeed, the concept of what constitutes clinical research is expanding. Because research studies do not always lend themselves to randomized clinical trials, these studies may require special consideration regarding the confidentiality of databases, blood banks, tissue repositories, and unintended impacts on vulnerable groups and segmented populations.

### *The Impact of the Information Age*

For their part, both the public and research participants are demanding and gaining access to a new kind of information and are increasingly able to use it to become directive and proactive, rather than merely receptive, in their health care decisions. This rapidly evolving transformation has been fueled in large part by the “Information Age.” The NIH Web site [ClinicalTrials.gov](http://ClinicalTrials.gov), which is now posting more than 5,000 trials, helps prospective participants navigate their own course toward participation in clinical trials (Landro 2000). This is but one example of the rapid exchange of information that threatens to widen the gap between the changing needs and capabilities of the trial participant and the perceptions and approach of the clinical investigator.

## **Areas of Institutional Concern Regarding Human Research Protections**

The various components of the “institutional arm” of human research protections is currently under intense and broad scrutiny within government, academia, and industry. Recognizing this, the COPR has approached its discussion of aspects of our system of institutional protections of human subjects in clinical research from the distinct perspectives of the NIH, the participant, and the American public.

### *Informed Consent*

Many IRBs and individual investigators are now embracing the concept of informed consent as an ongoing process that is woven throughout the course of the research effort. This perspective, however, must become more fully integrated into the research culture. Thus, not only participants but also investigators themselves must be equally prepared for their role in research. The informed consent process must ensure that participants fully comprehend the potential risks and benefits associated with their participation. They must enter into and continue in the study on the basis of truly informed, voluntary, and autonomous decisions. These are the key ethical underpinnings of the informed consent process as we understand it today.

To be effective, the informed consent process must take place within the family, community, and cultural context of the participant. It is important to inform and protect without patronizing, omitting key information, or presenting the protocol in such simple terms that much is omitted. On the other hand, it does no good to imply that informed consent has been achieved if the patient is unable to understand the information in the manner in which it has been presented.

A balance must be struck in a way that does not lose sight of the participant’s need for education through the process of informed consent. Participants have the right to take part in all medical decisions about their care. Consent is “informed” only if it is predicated on both full knowledge of the proposed research and an understanding of medical options other than those available through participation in research, including the option of no treatment at all. Participants have the right to be informed of the entire scope of the protocol used in the clinical research, to the extent that such knowledge on their part does not compromise the validity of the results (e.g., as in a double-blind, randomized trial). This information should include expectations for outcome; understanding of potential problems, side effects, and late-effects; and ultimate quality-of-life issues they may encounter. Achieving this objective requires greater public transparency of information as well as systems for delivering information on all relevant clinical research. Only in this way can the prospective patient give truly informed consent to enter into and continue participation in clinical research.

Many investigators tend to believe that the research participant will be unable to understand the technical details of research. Although it is true that different participants have different levels of interest in the details of the studies in which they take part, it is the Working Group’s contention that all participants are entitled to the amount and kind of information that it is feasible to give the participants in clinical trials and to have this information presented to them in a way that they can understand.

### ***Availability and Transparency of Information***

Greater transparency of information in all aspects of clinical research will serve to sustain public trust in clinical research, undergird patient recruitment efforts, and continue to build political and financial support. The COPR realizes that greater openness and transparency can arguably increase the risk that some trial participants will feel overwhelmed or confused. Moreover, it is likely that only a portion, perhaps only a small portion, of all participants in clinical research will be able to take full and direct advantage of expanded sources of information. However, these risks should not detract from a larger commitment to enhance the transparency and meaningful reporting of information to the American public.

One of the most contentious areas of discussion that arises when “transparency” of information is being called for is the public reporting of adverse events. In areas of novel research, the need for transparency of information and timely reporting of adverse events is especially critical and is currently the subject of public focus. The problems of who should receive information, how it should be protected, and in what fashion it should be disclosed and reported are confounded by the co-existing jurisdictions of the NIH, the FDA, and the OHRP. Each has overlapping but differing audiences, responsibilities, and information requirements. This fragmentation of oversight has resulted in some confusion and duplication of activity. Calls for consolidation and harmonization of reporting from all corners are worthy of support.

However, in an effort to reach the goal of harmonization, we must not lose sight of the public’s need for and entitlement to more comprehensive, timely reporting of adverse events that occur during the course of the trial. Harmonization should be in the direction of greater transparency and greater availability of information, not less. If we are to err with oversight of new, novel sciences, let it be in the direction of protecting patients “too much.” Increased and timely public reporting of adverse events and associated data is a key component of enhanced decision-making and patient protection in clinical research and will also lead to better decisions and better medicine. In the same spirit, the results and outcomes of clinical trials should be made available to those who have elected to participate in them. A proper role for the NIH, in this regard, is to provide clinical and statistical expertise to analyze relevant adverse events in a particular trial, in multicenter sites of the subject trial, and in “like” trials; to assess trends; and to make this information public in a timely and meaningful manner.

### ***Institutional Review Boards***

IRBs play a critical role in protecting the participants in clinical research and serve as a critical link in a network of responsibility among everyone involved in the research enterprise. IRBs, which operate in accordance with and apply local community standards, are the ultimate determinants of the extent of participant protections to be required during a research study.

By all accounts, the IRB system today is under tremendous stress. The burdens of service on an IRB are extensive for both the institution and the individual. IRB members complain of the increase in caseloads, the responsibility, and the burdens of service on their research careers. Some question whether the system as it exists today is equipped to handle the increasingly complex nature of clinical research and the rapidly expanding demands for review and protection

of human subjects. Concern is particularly warranted over a growing tendency for IRB service to be regarded as “dues” to be paid only by junior people. This attitude can discourage service on IRBs by senior investigators, to the detriment of the review process. The NIH should make efforts to counter this attitude to motivate senior researchers to serve on IRBs.

### *Conflicts of Interest*

The COPR is seriously concerned about conflicts of interest, whether on the part of individual investigators or institutions, that directly or indirectly, in fact or in appearance, influence the course, objectivity, or outcome of research. Although the significant majority of researchers have high standards of integrity, incidents of aberration are becoming more apparent. All must be mindful of the corrosive effects of even the appearance of impropriety on the nation’s continued faith in its research enterprise.

The subject of conflicts of interest has grown increasingly complex over the course of only the past few years. Today, the potential for conflicts of interest exists on multiple levels: with the individual investigator, with the institution, and among members of IRBs. Competitive pressures to bring a new drug to market, the opportunity for an investigator or the university to reap financial gain based on the conduct of scores of trials or the confirmation of positive trial results, and significant incentives reportedly paid for participant recruitment are but a sampling of the emerging financial influences on the objective, unbiased conduct of a clinical trial.

Financial relationships do not necessarily undermine the integrity of an investigator or an institution, nor do they always equate with bias or a lack of regard for the safety of participants. However, particularly in industry-sponsored trials, financial relationships and ties have been shown to affect the conduct and outcome of trials in terms of the design of the study, the recruitment of participants, the selective release of findings, and the control of trial data (Bodenheimer 2000).

Both the AAMC and the American Medical Association (AMA) have stepped forward with important guidance for their respective constituencies. The AAMC has placed primary responsibility on research institutions for the oversight of conflicts of interest (AAMC 1990). In its guidance, the AAMC considers not only conflicts that may compromise the integrity of investigators, but also any associations that appear to compromise professional judgment in conducting or reporting research. To preserve the public trust in the research enterprise, it is essential to consider these so-called “gray areas,” which involve matters of perception.

A DHHS Interim Guidance report issued in early 2001 indicated that only about 25% of all IRBs ask investigators to disclose their financial conflicts of interest. Even so, beyond required disclosure, it is not clear what effect the knowledge of investigators’ financial interests will have on participants in clinical trials. There have been no studies on how this kind of information may or may not affect participants’ perceptions of the research in which they are engaged, the investigators conducting it, and the institutions sponsoring it. Indeed, it is not unreasonable to expect that trial participants will have different levels of interest concerning how much they want to know about investigators’ financial relationships. At the very least, however, participants should have the same amount and kind of information that institutions and investigators are required to disclose publicly.

Some argue that trial participants, if they choose, should have access to further information regarding the financial ties of the individuals conducting the research, pointing to the fact that institutions have various degrees of stringency in requiring or disallowing such relationships. Not all IRBs, however, have the expertise to deal with issues concerning conflicts of interest, and in any case, IRBs are only one element in the complex web of entities governing disclosure. An entire spectrum of mechanisms exists within institutions regarding requirements to disclose financial conflicts of interest. Some institutions are very stringent, having zero tolerance for any financial holdings relating to the research in question. Others entrust ethics committees with the evaluation of investigators' financial relationships. The disclosure of equity ownership in commercial sponsors of trials is one area in which disclosure could well affect participants' perceptions of and willingness to participate in research. Currently there is a "closed loop" in which any type of equity ownership must be divulged to the research sponsor; this information is conveyed to the FDA, where it is kept confidential.

The COPR notes the recent actions of the American Society of Gene Therapy stipulating that "all investigators and team members directly responsible for participant selection, the informed consent process and/or clinical management in a trial must not have equity, stock options or comparable arrangement in companies sponsoring the trial" (IOM 1998). In a recent editorial (Drazen and Koski 2000), the *New England Journal of Medicine* has stated its support for this policy and suggested that it be widely adopted.

### ***Confidentiality and Privacy***

The exciting pace and expansion of medical research has brought more participants than ever before into clinical research, and this number continues to grow. Unfortunately, this growth brings with it an opportunity for the degradation of participant confidentiality, privacy, and autonomy. This threat poses a real and present risk to the individual, the public, and the research enterprise itself.

Breaches of confidentiality are of special concern among "vulnerable" populations, such as those with socially stigmatizing health conditions or, in the very near future, those with determined genetic predispositions for certain conditions. These individuals may face devastating consequences in obtaining or continuing health insurance, employment, housing, and social relationships if their health conditions and/or genetic status are revealed.

These reasons underscore the importance of educating participants about issues of privacy when participating in clinical research. A new DHHS privacy rule is currently under review and will be published in the near future.

### ***Health Disparities***

Healthy People 2010 has identified the elimination of health disparities as one of only two sweeping public health goals to be accomplished within this decade. In response, the NIH has developed a 5-year "Strategic Research Plan to Reduce and Ultimately Eliminate Health Disparities." Each NIH Institute has produced its own mission-specific plan as well, setting forth in greater detail ongoing and planned efforts to reduce health disparities among minority

populations. Many of these plans also call for increased participation of minorities in clinical studies as well as increasing the number of minority scientists.

As research continues to demonstrate glaring differences in the incidence, prevalence, morbidity, mortality, and burden of diseases among underserved and vulnerable groups, it is more important than ever that we improve our understanding of what causes health disparities and work to address them. The COPR believes that the NIH must play a major role in helping the American public to reach that objective.

The issue of health disparities is not unrelated to the protection of human subjects in clinical research. One of the contributing factors to health disparities is a lack of adequate information about specific medical issues relating to certain groups. The COPR can emphasize and help to convey to the public the importance of inclusion and participation of all populations in research, which will help to ensure that meaningful results of clinical research can be applied to various populations. By ensuring that clinical research populations include people of both sexes; a range of ages; and a variety of ethnic groups, social classes, and nationalities, the NIH can expand the scientific knowledge to all people, thus helping to eliminate disparities.

At the same time, however, the goal of eliminating health disparities is so complex, multifaceted, and extensive that the COPR has decided to reserve its position and recommendations for a separate document to be presented at a future COPR meeting. This deferral of the discussion of health disparities should not be perceived as reflecting a diminished importance of this topic but rather an endorsement of its significance.

### ***Social Science and Behavioral Clinical Trials***

The amount of social science and behavioral research conducted at the NIH is expanding. These studies, which will affect the understanding of health disparities, lifestyle changes, and burden of illness measures, are generally noninvasive and often involve less onerous reporting requirements. On the other hand, such trials may present a risk of breach of confidentiality, an invasion of privacy, or a threat to the dignity of not only individuals, but also entire communities, tribes, or ethnic groups. Members of IRBs who are skilled at examining biomedical research may not appreciate these differences or the unique risks and may not be trained to monitor these numerous studies appropriately.

The Social and Behavioral Science Working Group of the National Human Research Protections Advisory Committee of OHRP is working to identify, review, and address issues of human research protections that are unique to the area of behavioral and social science research. Specifically, this group has been charged with (1) developing guidelines to help IRBs more effectively administer the human subjects protection system and (2) to make specific recommendations regarding additions or changes to the Common Rule with respect to the social and behavioral sciences. The COPR will review the final report of the Social and Behavioral Science Working Group when it is presented in March 2002 and provide public comment at that time as appropriate.

## Conclusion

As an advisory body to the NIH Director, the COPR is challenged to survey the landscape of human research protections, to consider the broad array of activities now under way within the public and private sectors, and to decide how and in what manner to weigh in on behalf of the public and those individuals who make the commitment to participate in research. In all that it does, the COPR must be mindful of the expectations for the Council's role within the NIH and of its unique positioning as representatives of the American public—the true owners and beneficiaries of the nation's exciting scientific enterprise. Always, the COPR will be challenged to ask the right questions of the right people and to obtain the right responses. In the area of human research protections, the COPR hopes to do this through the blueprint for continued inquiry and discussion set forth in this report.

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