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INSTITUTE OF MEDICINE

Shaping the Future for Health

RESPONSIBLE RESEARCH:
A SYSTEMS APPROACH TO PROTECTING RESEARCH PARTICIPANTS

Since the beginning of modern history, we have sought cures for disease and injury and searched for ways to improve our lives through scientific investigation. Often, these goals can only be met by studying humans and the human condition. By volunteering to participate in research, many individuals have provided scientists with capabilities that they would otherwise lack, and in so doing, deserve society's deepest gratitude and respect.

In some studies, these volunteers assume great risks, even though the prospect for personal benefit is slim or nonexistent. When researchers ask an individual to participate in a research study, or when someone actively seeks involvement in research because of anticipated benefit, every effort must be made to ensure that their participation is voluntary and informed and that the risks they are exposed to are minimized.

Many Americans are unaware that there is a complex, multi-level system in place for protecting those who participate in research. Federal regulations for protecting research participants provide a framework through which to implement generally agreed upon ethical principles. Based on this guidance, national and international policies have evolved to create a system of protections requiring the involvement of investigators, research sponsors, research institutions, ethics review boards (called Institutional Review Boards, or IRBs, in the United States), health care providers, federal agencies, and patient and consumer groups.

However, like any large, complex system, it is not perfect, and the costs of its imperfections can be tragic. A series of research events in the late 1990s—some resulting in death—focused renewed attention on the system's ability to meet its ethical obligation to protect those who volunteer for research. There does not appear to be a single cause for these failures, but rather a confluence of factors—a combination of stresses, weaknesses, vagaries, and lack of accountability—that has pushed the system to the point where change must occur. Without active change the public trust in the research enterprise will be eroded and scientific progress toward improving life could be thwarted.

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ABOUT THIS REPORT

In response to mounting concerns about the well-being of research participants and the ability of current policies and procedures to ensure their protection, the Department of Health and Human Services (DHHS) commissioned the Institute of Medicine (IOM) to perform a comprehensive assessment of the national system for protection from research risks.[1] An IOM committee composed of scientists, clinicians, lawyers, ethicists, research administrators and consumer/patient representatives was asked to: review the ethical foundations for protecting research participants; assess and describe the current system and make recommendations for improvement; assess the potential impact of recommended changes on resource needs and how to address them; consider the effects of accreditation on improving protection activities; and determine the need for potential mechanisms for ongoing independent review of the national system.

The report also contains several recommendations about the need for ethics education, quality improvement mechanisms, better data collection and dissemination, and advice at the national level.

The report was organized to follow a research protocol through the research process; the committee targeted the essential elements and functions that should be in place at each step in the process in order to adequately protect participants. The report also contains several recommendations about the need for ethics education, quality improvement mechanisms, better data collection and dissemination, and advice at the national level.

A SYSTEMS VIEW: THE HUMAN RESEARCH PARTICIPANT PROTECTION PROGRAM

A theme central to this report is the concept of the "Human Research Participant Protection Program, or HRPPP," a term adopted by the committee to embrace a set of complementary elements and activities necessary to ensure that comprehensive protection is afforded to every research participant (see table below). The form a given HRPPP assumes is less important than the fundamental functions it must perform.

Essential Components of an HRPPP

Key Elements	Key Functions
• investigators carrying out the research • review boards responsible for evaluating the scientific and ethical integrity of proposed research • monitoring bodies, including Data and Safety Monitoring Boards/Data Monitoring Committees, ombudsman programs, and data collection centers • organizational units responsible for research conduct, regulatory compliance, and risk management • research sponsors funding the research and responsible for ensuring its ethical conduct	• comprehensive review of protocols (including scientific, financial conflict of interest, and ethical reviews) • ethically sound participant-investigator interactions • ongoing (and risk-appropriate) safety monitoring throughout the conduct of the study • quality improvement and compliance activities

Four specific conditions should be pervasive within the research culture of an HRPPP: 1) accountability for the provision of participant protection; 2) adequate resources

[1] The first phase of work by the Committee on Assessing the System for Protecting Human Research Participants focused almost exclusively on accreditation of organizations that conduct and oversee research. The committee's first report, *Preserving Public Trust: Accreditation and Human Research Participant Protection Programs*, was published in 2001.

(financial and nonfinancial) to sustain robust protection activities; 3) ethics education programs for those that conduct and oversee research; and 4) transparency, that is, open communication and interaction with the local community, research participants, investigators, and other stakeholders in the research enterprise. Each organization should tailor these prerequisite conditions to its mission, the breadth and substance of its program, and the context of its community.

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PROTECT ALL RESEARCH PARTICIPANTS

A central recommendation in this report concerns the need to ensure that protections are in place for *all* research participants. Under current law, some research can be conducted absent federal oversight and outside the current system of protections. Congressional action is needed to compel such universal protection. The committee recommends, "Adequate protection of participants requires that all human research be subject to a responsible HRPPP under federal oversight. Federal law should require every organization sponsoring or conducting research with humans to assure that all of the necessary functions of an HRPPP are carried out and should also require every individual conducting research with humans to be acting under the authority of an established HRPPP." Without enactment of this recommendation, no amount of change in the system of protections will ensure that every research volunteer is sufficiently protected against undue harm.

REFOCUS THE MISSION OF INSTITUTIONAL REVIEW BOARDS

As the demands on the research oversight system have grown, so has the reliance on IRBs to accomplish all protection tasks. This is a disservice to research participants, because IRBs find it exceedingly difficult to both manage the increasing volume of protocol actions and ensure the safety of research volunteers.

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In the committee's HRPPP paradigm, the management of organizational responsibilities (such as compliance with relevant regulations) should be assigned to institutional units other than the IRB. Often, such units already exist and may be retooled to add the relevant participant protection focus to their responsibilities. To reflect this refocused role, the committee recommends moving away from the term "Institutional Review Board," which conflates institutional interests with those of participants, and suggests adopting a more functionally appropriate term, specifically "Research Ethics Review Board, or Research ERB."

All members of the Research ERB should have a core body of relevant knowledge and a significant proportion of members should possess a specialized knowledge of human research ethics. The research organization's goal should be to create or associate with a Research ERB in which unaffiliated members, nonscientists, and those who represent the local community and/or the participant perspective comprise at least 25 percent of the membership. Further, the refocused Research ERB's deliberative objective should aim for consensus rather than majority control to avert any potential to marginalize the perspectives of nonscientist members or ethics-based concerns. No protocol should be approved without three-quarters of the voting members concurring.

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Distinguish Scientific, Conflict of Interest, and Ethics Review Mechanisms

The scientific review of protocols should be as rigorous as the ethical review. Each review requires distinct, although overlapping, expertise. Although the in-depth scientific evaluation of proposals is fundamental to comprehensive ethics review, the Research ERB need not conduct the initial scientific review. Furthermore, a process for scrutinizing potential financial conflicts of interest in any protocol is vital to the subsequent evaluation of

participant risks and benefits by the Research ERB. Summaries of the scientific and the conflict of interest reviews should be submitted to the Research ERB for its consideration in the ethics-focused deliberations.

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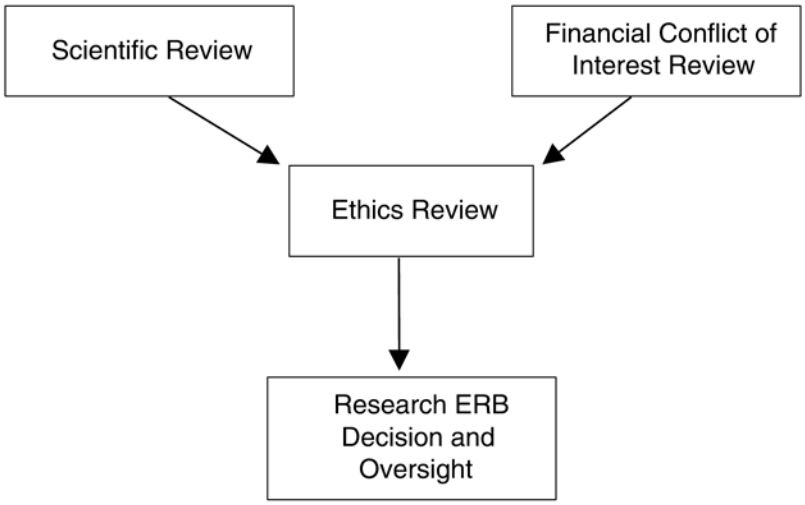
Despite the need for review from three distinct perspectives (scientific, ethical, and financial conflict of interest), the interrelated nature of these perspectives requires that a *single* body be vested with the authority to make final protocol determinations and be accountable for those determinations (see figure below). This body is and should remain the Research ERB.



The Confluence of the Research Review Process

Manage Potential Conflicts of Interest

Confidence about the current system of participant protection is undermined by the perception that harm to research participants may result from conflicts of interest involving the researcher, the research organization, and/or the research sponsor. This concern is particularly acute regarding financial conflicts of interest. Therefore, mechanisms for identifying, disclosing, and resolving conflicts of interest should be strengthened. Guidelines for acceptable levels of conflict and policies for managing conflict should continue to be developed so that common professional standards can be implemented and refined.

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In addition to managing *individual* conflicts of interest, organizations should ensure that an independent, external mechanism is in place for the evaluation of potential *institutional* conflicts. In both instances, conflict of interest information should be communicated in a timely and effective manner to the Research ERB, which should make the final assessment with regard to ensuring participant protections.

Emphasize Risk-Appropriate Protection

The degree of scrutiny, the extent of continuing oversight, and the safety monitoring procedures for research proposals should be calibrated to a study's degree of risk. Minimal risk studies should be handled diligently, but expeditiously, while studies involving high risk should receive the extra time and attention they require. Although federal regulations provide several mechanisms for expeditiously reviewing certain kinds of research involving no more than minimal risk, classifications of studies by risk level cur-

rently lack refinement and consistency, and federal oversight agencies should address this need expeditiously.

Enhance Safety Monitoring

The safety of research volunteers must be guaranteed from the inception of a protocol, through its execution, to final completion and reporting of results. Continual review and monitoring is needed to ensure that emerging information has not altered the original risk-benefit analysis. Therefore, risk-appropriate mechanisms are needed to track protocols and study personnel; provide assurances that data are valid and collected according to applicable practices; and ensure that participants' safety, privacy, and confidentiality are protected throughout a study. An area of intense concern is the ability of HRPPPs to appropriately collect, interpret, and report adverse event information. Federal oversight agencies, therefore, should harmonize safety monitoring guidance, develop standardized practices for defining and reporting adverse events, and consistently monitor all federally regulated studies that pose substantial risks to participants.

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Streamline and Increase Program Productivity

The effective oversight and management of the rapidly expanding number of multi-site studies, particularly in the high-risk clinical domain, is another area of concern; full-scale IRB review of protocols by *all* participating organizations does not necessarily increase participant protection. Therefore, the committee encourages the streamlining of multi-site trial review, recommending that one primary scientific review committee and one primary Research ERB assume the lead review functions, subject to acceptance by the local committees and boards at participating sites.

The extreme variability in the approval decisions and regulatory interpretations among IRBs is one of the weaknesses in the current protection system. To better clarify regulatory intent and appropriate ethical practices, the Office for Human Research Protections (OHRP) and relevant federal agencies should convene conferences and establish working groups to develop and disseminate best practices, case presentations, and conference proceedings.

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RECOGNIZE PARTICIPANT CONTRIBUTIONS AND PROVIDE ACCESS TO INFORMATION

Research participants and their representatives should be meaningfully included in the review and oversight of research. Open communication should ensure that all relevant stakeholders can question how protocols are developed, reviewed, and implemented. Furthermore, those who stand to benefit or be harmed by the research should have an opportunity to comment on the research design and operation, to participate in the research, and to have access to study findings. A list of questions and concerns that potential participants might have regarding their participation in research, and for which HRPPPs and researchers should provide clear answers are contained within the box below.

What a Participant Might Want to Know

Potential Benefits and Harms

- If I am ill, will this research help me?
- What are the risks to me?

Protecting Participant Interests

- What are the realistic alternatives to study participation?
- What is involved? What will I have to do?
- Who will be in charge of my care? Can I see my own doctor?
- Are checks and balances in place to protect my safety?
- How was the research reviewed and approved?
- Will I be charged anything or be compensated for my participation?
- How can I end my participation if I change my mind?
- What will happen to me when the study is over? Will I be told the results?

Study Design and Leadership

- Who designed the protocol?
- Is the protocol well designed?
- Is the investigator competent?
- Why is this research important?
- Who else is involved in this research?
- Was anyone in the advocacy community involved in the design or review of the research?

Conflict of Interest, Study-related Controversy

- Is the study controversial?
- Has anyone conducted this study already, or one like it?
- Who will benefit financially if this works? What's in it for the investigator?

Institutional Oversight

- Whom do I contact to express concerns or obtain information?

NOTE: The information in this box was supplemented by elements described in the Department of Veterans Affairs' booklet, *I'm a Veteran: Should I Participate in Research?* (VA, 2002).

To ensure that information about all clinical trials is available [to consumers and their health care providers], the committee proposes the creation of a comprehensive and soundly structured clinical trials registry for public use.

In 2000, the National Library of Medicine established a clinical trials registry, which has expanded to serve as the Food and Drug Administration-required site for submissions about clinical trials. Although the development of such registries is an important first step toward providing high-quality clinical trial information to the public, currently no centralized system exists for disseminating information about clinical trials of drugs or other interventions, making it difficult for consumers and their health care providers to identify ongoing studies. To ensure that information about all clinical trials is available, the committee proposes the creation of a comprehensive and soundly structured clinical trials registry for public use.

Revitalize Informed Consent

Informed consent should be an ongoing process that focuses not on a written form or a static disclosure event, but rather on a series of dynamic and appropriately targeted conversations between the participant and the research staff that should begin before enrollment and be reinforced during each encounter or intervention. The informed consent conversation(s), as well as the written consent document, should not be obscured by language designed mainly to insulate the institution from liability. Rather, the process should ensure that participants clearly understand the nature of the proposed research and its potential risks and benefits to them and society.

Compensate Participants for Research-Related Injury

Despite decades of discussion on the ethical obligation to compensate participants for research-related injury, little information is available regarding the number of such injuries and the cost of providing compensation for them. Providing reasonable compensation for legitimate instances of research harm is critical to restoring and maintaining credibility. To guide public policy DHHS should assemble data on the incidence of research injuries and conduct economic analyses of their costs. In the meantime, research organizations should compensate any research participant who is injured as a direct result of participating in research, without regard to fault. Compensation should include at least the costs of medical care and rehabilitation, and accrediting bodies should include such compensation as a requirement of accreditation.

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CONTINUOUSLY IMPROVE PERFORMANCE

To maximize quality and efficiency, the effectiveness of HRPPP policies and practices should be continuously assessed and improved. Protection programs can use systematic quality improvement analysis tools to determine the underlying causes of shortfalls and develop procedures to eliminate them and to improve performance. However, the lack of empiric data on the performance of protection programs, the absence of defined measurable outcomes or other criteria for their ongoing evaluation, and the scant knowledge of approaches and methods by which programs have been improved have hindered efforts to initiate quality improvement measures. Research sponsors should initiate programs and locate funding to develop criteria for evaluating program performance and enhancing quality improvement practices.

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Collect National Level Data About the System and Impose Periodic Review

The absence of sufficient data regarding human research activities significantly impedes the thorough examination of system performance. Collecting such data would be a considerable and lengthy undertaking, and some information needs may be better met through targeted studies. Scientific surveys involving representative samples rather than a full census would serve policy-setting priorities cost effectively.

To ensure the ongoing quality and relevance of the national participant protection system, it is important that continuing review of its strengths and weaknesses be provided through an independent body. If any advisory committee is to successfully guide federal policy there must be no appearance or existence of conflict in its membership or organization. The committee therefore proposes the establishment of a nonpartisan, interdisciplinary, independent body of experts and participant representatives to provide policy makers with objective public advice regarding the needs of the national protection system.

DHHS should arrange for a substantive, independent review and evaluation of HRPPP accreditation before determining its ultimate role in the participant protection system.

Assess the Value of Accreditation

As observed in the committee's first report, accreditation programs represent one promising approach to assessing the protection functions of research organizations in a uniform and independent manner, and may serve as a useful stimulus for quality improvement programs. The committee reiterates its support for pilot testing voluntary accreditation as an approach to strengthening participant protections, but repeats its recommendation that DHHS should arrange for a substantive, independent review and evaluation of HRPPP accreditation before determining its ultimate role in the participant protection system.

CONCLUDING REMARKS

Policy makers and the scientific community have an obligation to ensure that the interests and dignity of every research participant are diligently protected throughout the research process. The complexity and multifaceted nature of research requires that many offices and individuals interact to coordinate activities within a systemic HRPPP. The recommendations offered in this report are intended to guide HRPPPs and policy makers as they work to guarantee that research participants' safety and rights are protected and that the national research enterprise is worthy of the public's trust and continued support.

For More Information…

Copies of *Responsible Research: A Systems Approach to Protecting Research Participants* are available for sale from the National Academy Press; call (800) 624-6242 or (202) 334-3313 (in the Washington metropolitan area), or visit the NAP home page at **www.nap.edu.** The full text of this report is available at **http://www.nap.edu**

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