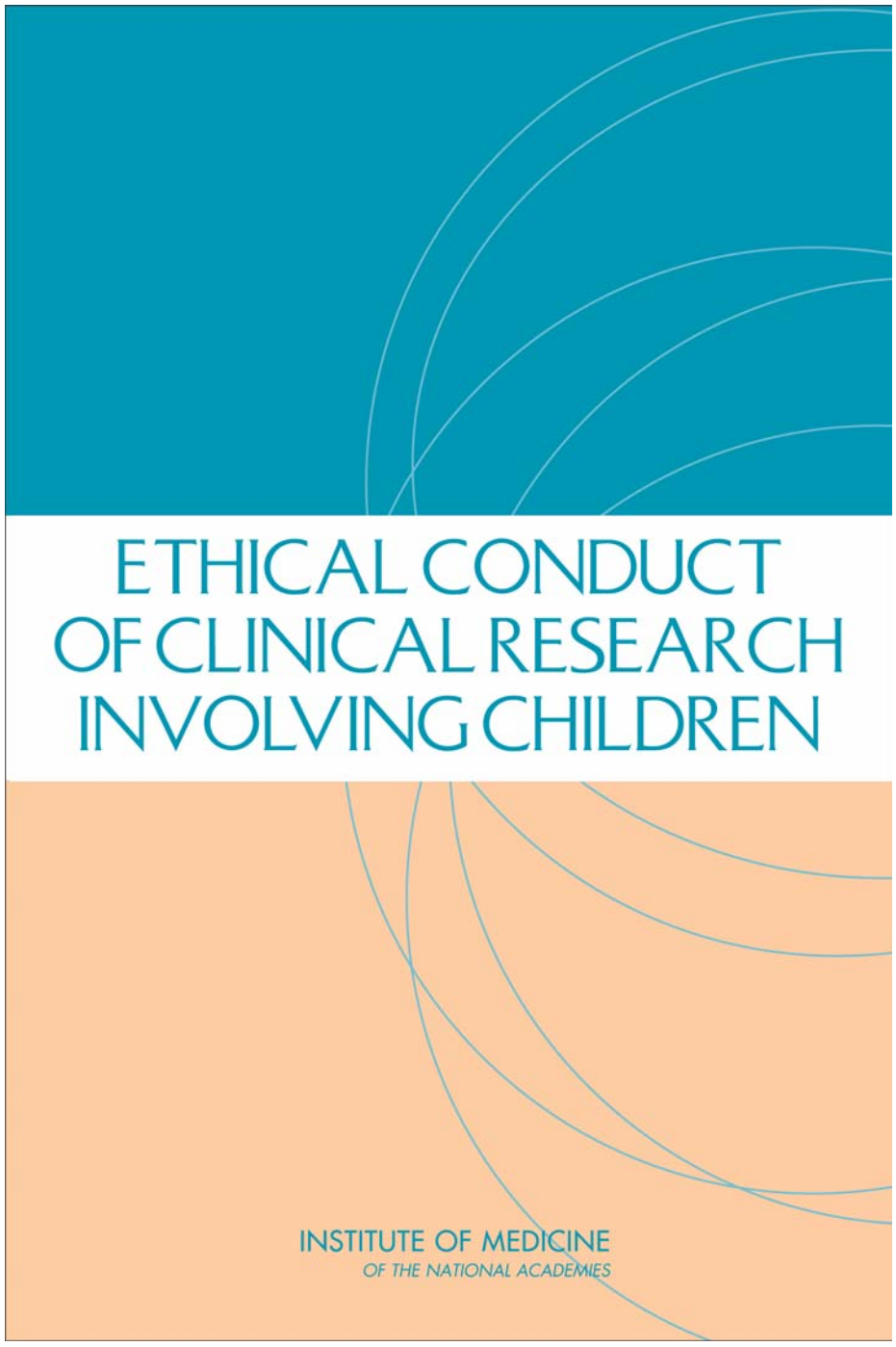
PREPUBLICATION COPY
Uncorrected Proofs



PREPUBLICATION COPY
Uncorrected Proofs

The Ethical Conduct of Clinical Research Involving Children

Committee on Clinical Research Involving Children
Board on Health Sciences Policy

Marilyn J. Field and Richard E. Behrman, *Editors*

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

THE NATIONAL ACADEMIES PRESS
Washington, D.C.
www.nap.edu

THE NATIONAL ACADEMIES PRESS 500 Fifth Street, N.W. Washington, DC 20001

NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

Support for this project was provided by the National Institute of Child Health and Development, N01-OD-4-2139,TO #115. The views presented in this report are those of the Institute of Medicine's Committee on Clinical Research Involving Children and are not necessarily those of the funding agency.

International Standard Book Number 0-309-XXXXX-X (Book)
International Standard Book Number 0-309- XXXXX -X (PDF)
Library of Congress Control Number: 00 XXXXXX

Additional copies of this report are available from the National Academies Press, 500 Fifth Street, N.W., Lockbox 285, Washington, DC 20055; (800) 624-6242 or (202) 334-3313 (in the Washington metropolitan area); Internet, http://www.nap.edu.

For more information about the Institute of Medicine, visit the IOM home page at:
www.iom.edu.

Printed in the United States of America.

The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

"Knowing is not enough; we must apply.
Willing is not enough; we must do."
—Goethe

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

Adviser to the Nation to Improve Health

THE NATIONAL ACADEMIES

Advisers to the Nation on Science, Engineering, and Medicine

The **National Academy of Sciences** is a private, nonprofit, self-perpetuating society of distinguished scholars engaged in scientific and engineering research, dedicated to the furtherance of science and technology and to their use for the general welfare. Upon the authority of the charter granted to it by the Congress in 1863, the Academy has a mandate that requires it to advise the federal government on scientific and technical matters. Dr. Bruce M. Alberts is president of the National Academy of Sciences.

The **National Academy of Engineering** was established in 1964, under the charter of the National Academy of Sciences, as a parallel organization of outstanding engineers. It is autonomous in its administration and in the selection of its members, sharing with the National Academy of Sciences the responsibility for advising the federal government. The National Academy of Engineering also sponsors engineering programs aimed at meeting national needs, encourages education and research, and recognizes the superior achievements of engineers. Dr. Wm. A. Wulf is president of the National Academy of Engineering.

The **Institute of Medicine** was established in 1970 by the National Academy of Sciences to secure the services of eminent members of appropriate professions in the examination of policy matters pertaining to the health of the public. The Institute acts under the responsibility given to the National Academy of Sciences by its congressional charter to be an adviser to the federal government and, upon its own initiative, to identify issues of medical care, research, and education. Dr. Harvey V. Fineberg is president of the Institute of Medicine.

The **National Research Council** was organized by the National Academy of Sciences in 1916 to associate the broad community of science and technology with the Academy's purposes of furthering knowledge and advising the federal government. Functioning in accordance with general policies determined by the Academy, the Council has become the principal operating agency of both the National Academy of Sciences and the National Academy of Engineering in providing services to the government, the public, and the scientific and engineering communities. The Council is administered jointly by both Academies and the Institute of Medicine. Dr. Bruce M. Alberts and Dr. Wm. A. Wulf are chair and vice chair, respectively, of the National Research Council.

www.national-academies.org

COMMITTEE ON CLINICAL RESEARCH INVOLVING CHILDREN

RICHARD E. BEHRMAN (*Chair*), Executive Chair, Education Steering Committee, Federation of Pediatric Organizations, and Clinical Professor of Pediatrics, University of California, San Francisco, and George Washington University, Washington, D.C.

ARTHUR L. BEAUDET, Henry & Emma Meyer Professor and Chair, Department of Molecular & Human Genetics, Baylor College of Medicine

RUSSELL W. CHESNEY, Le Bonheur Professor and Chair, Department of Pediatrics, Le Bonheur Children's Hospital and the University of Tennessee; Co-director, Center for Pediatric Pharmacokinetics and Therapeutics, University of Tennessee, Memphis

FRANCIS SESSIONS COLE III, Park J. White M.D. Professor and Vice Chair, Department of Pediatrics, and Professor of Cell Biology and Physiology, Washington University School of Medicine, and Director, Division of Newborn Medicine, St. Louis Children's Hospital

DEBORAH L. DOKKEN, Family Health Care Advocate, Consultant in Family-Centered Care

CELIA B. FISHER, Marie Ward Doty University Chair, Director Center for Ethics Education, and Professor of Psychology, Fordham University

ANGELA R. HOLDER, Professor of the Practice of Medical Ethics, Center for the Study of Medical Ethics and Humanities, Duke University Medical Center

LORETTA M. KOPELMAN, Professor and Chair, Department of Medical Humanities, Brody School of Medicine, East Carolina University

SUSAN Z. KORNETSKY, Director, Clinical Research Compliance, Department of Clinical Investigation, Children's Hospital Boston

ROBERT M. NELSON, Associate Professor of Anesthesia & Pediatrics, University of Pennsylvania School of Medicine and The Children's Hospital of Philadelphia

DAVID G. POPLACK, Elise C. Young Professor of Pediatric Oncology and Head, Hematology/Oncology Section, Department of Pediatrics, Baylor College of Medicine, and Director, Texas Children's Cancer Center, Houston, Texas

BONNIE W. RAMSEY, Director, Cystic Fibrosis Therapeutics Development Network Coordinating Center, Children's Hospital Regional Medical Center, and Professor of Pediatrics, University of Washington School of Medicine

DIANE SCOTT-JONES, Professor of Psychology, Boston College

STEPHEN P. SPIELBERG, Dean, Dartmouth Medical School, Vice President for Health Affairs, Dartmouth College, Professor of Pediatrics and of Pharmacology and Toxicology, Dartmouth College

Expert Advisor

ALAN R. FLEISCHMAN, Senior Vice President, The New York Academy of Medicine

Liaisons to Institute of Medicine and National Research Council Boards

Board on Health Sciences Policy: **DANIEL R. MASYS**, Director, Human Research Protections Program, and Professor of Medicine, School of Medicine, University of California, San Diego

Board on Children, Youth, and Families: **ELENA O. NIGHTINGALE**, Scholar-in-Residence, Institute of Medicine

National Cancer Policy Board: **SUSAN L. WEINER**, President, The Children's Cause, Inc.

Committee Consultants

AMY T. CAMPBELL, Senior Instructor, Department of Psychiatry and Division of Medical Humanities, University of Rochester Medical Center

ERIC D. KODISH, Director, Rainbow Center for Pediatric Ethics, Rainbow Babies and Children's Hospital

MYRA BLUEBOND-LANGER, Distinguished Professor of Anthropology, Rutgers University and Director, Rutgers University Center for Children and Childhood Studies

Study Staff

MARILYN J. FIELD, Study Director
MARGARET A. MCCOY, Research Assistant
PERRY J. LUKSIN, Senior Project Assistant

Board on Health Sciences Policy Staff

ANDREW POPE, Director, Board on Health Sciences Policy
TROY PRINCE, Board Assistant

CONTENTS

BOXES, FIGURES AND TABLES

Boxes

Figures

Tables

PREFACE

Those who care about and for children currently face a dilemma. We want children to benefit from the dramatic and accelerating rate of progress in medical care that is fueled by scientific research. At the same time, we do not want to place any children at risk of being harmed by participating in such research, even though their very involvement may be essential to improving the overall medical care of children. We also want to discourage research that is of minimal value. The concern is how best to balance these potentially conflicting objectives. Five important considerations should guide us as we seek to resolve our dilemma.

First, because of the inherent vulnerabilities arising from their immaturity, infants, children, and adolescents need additional protections beyond what is provided to competent adults when they participate in research. This principle underlies all others.

Second, the design of the research required to improve the health and well-being of infants, children, and adolescents must consider their physical, cognitive, emotional, and social development. Similarly, when children of any age become participants in such research, the protections provided must be appropriate to their stages of development.

Third, sharing in the advances in medical care for this vulnerable group includes a special emphasis on protecting them from harm caused by standard medical procedures and treatments based on research with adults when the benefits and risks for children of different ages have not been established through scientific research involving these populations. Except when it is not feasible or reasonable, research with animal and adults should precede studies with children to minimize research risks.

Fourth, the system for protecting infants, children, and adolescents involved in research, while ensuring such protection, should not unreasonably impede research that may benefit them. The contribution of rules and regulations to desired outcomes as well as possible unintended negative consequences should be considered.

Finally, all of those responsible for research involving infants, children, and adolescents need to understand the special ethical issues that are relevant to the conduct of research involving these vulnerable groups as participants and the additional protection that must be provided for them. In some cases, ethical standards will preclude some otherwise desirable research.

Overall, a satisfactory resolution of our dilemma can be achieved. Children involved in research can be appropriately protected as well as share fairly in the increasing benefits of biomedical science. This report suggests ways to balance sometimes conflicting objectives in ways that will contribute to children's health and well-being now and in the future.

Richard E. Behrman, M.D., J.D.
Committee Chair

ACKNOWLEDGMENTS

The committee and staff are indebted to a number of individuals and groups for their assistance in the development of this report. The committee learned much through workshops and public meetings it organized to obtain information and perspectives from groups and individuals knowledgeable and concerned about research involving infants, children, and adolescents. Appendix A includes the meeting agendas and participant lists and also cites the organizations that provided written statements to the committee.

Special thanks go to Carolyn Brokowski, Maureen and Joseph Lilly, Joan and Sarah Lippincott, Andrell Vaughn, and Lise Yasui, who were willing to share their experiences with the committee. Consultants Eric Kodish and Myra Bluebond-Langner, provided valuable guidance in addition to their presentations to the committee. The committee also appreciates the contributions of Amy Campbell, who prepared the background paper on state policies relevant to children's participation in research. Mark Green, a Greenwall Foundation Fellow who served as a summer intern, assisted in developing the discussion of pediatric drug research.

A number of people at the Office for Human Research Protections (OHRP), the Food and Drug Administration (FDA), and the National Institute of Child Health and Human Development (NICHD) contributed to this study. Duane Alexander and Gilman Graves at NICHD, which sponsored this study, were unfailingly constructive in their support for the committee's work. Michael Carome, Leslie Ball, and Kate Gottfried at OHRP provided useful information about the office's policies, practices, and databases. David Lepay, Rosemary Roberts, and Susan Cummins at FDA helped the committee understand FDA policies on the protection of human participants in research and also relevant policies involving other aspects of the agency's mission. In addition, the committee appreciates the information and insights offered by David Wendler and Benjamin Wilfond at the Department of Clinical Bioethics of the National Institutes of Health Clinical Center.

Meetings with researchers and institutional review board members and administrators at the Children's Hospital of Philadelphia and Children's National Medical Center (arranged with much appreciated assistance from John Sever) helped provide additional perspective on the practical realities of administering federal and institutional policies to protect child participants in research. Allison Clarke-Stewart and Virginia

Allhusen from the University of California, Irvine, generously shared the knowledge and insights into long-term research gained through their Study of Early Child Care and Youth Development. Among the many others who helped the committee clarify issues, find important information, or otherwise complete its work are Laura Rodriguez, Ellen Wright Clayton, Marion Broome, Scott Powers, George Retsch Bogart, Lisya VanHousen, Adam Fried, Suzanne Rivera, Steven Joffe, Rosemary Galvin, Juliette Schlucter, Jane Burns, Judith Argon, Lea Ann Hansen, James Chamberlain, and Jackie Moran.

Many within the Institute of Medicine were, as usual, helpful to the study staff. The committee would especially like to thank Jessica Aungst, Natasha Dickson, Judy Estep, Alex Ommaya, Sally Stanfield, Bronwyn Schrecker, and Jennifer Bitticks.

REVIEWERS

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the Report Review Committee of the National Research Council (NRC). The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published reports as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. The committee wishes to thank the following individuals for their review of this report:

Marion E. Broome, University of Alabama at Birmingham
Ellen Wright Clayton, Vanderbilt University
Ronald E. Dahl, University of Pittsburgh Medical Center
Rebecca S. Dresser, Washington University in St. Louis
Abigail English, Center for Adolescent Health & the Law
Paul L. Gelsinger, Citizens for Responsible Care and Research
Paul W. Goebel, Chesapeake Research Review, Inc.
Dale Hammerschmidt, University of Minnesota
Gregory L. Kearns, Children's Mercy Hospitals and Clinics, University of Missouri—Kansas City
Michele D. Kipke, University of Southern California/Childrens Hospital Los Angeles
Jeffrey L. Platt, Mayo Clinic
Gregory H. Reaman, Children's Oncology Group and The George Washington University
Lise Yasui, Children's Oncology Group and New Approaches to Neuroblastoma Therapy Consortium

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of this report was overseen by **THOMAS F. BOAT**, Cincinnati Children's Hospital Medical Center and University of Cincinnati, and **BERNARD LO**, University of California, San Francisco. Appointed by the NRC Report Review Committee, these individuals were responsible for making certain that an independent examination of this report was carried out in accordance with the institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Summary

In recent decades, advances in biomedical research have, each year, helped to save or lengthen the lives of tens of thousands of children around the world, prevent or reduce illness or disability in many more, and improve the quality of life for countless others. Beyond the infants, children, and adolescents directly affected, the benefits of research extend to the families, friends, and communities who love and care for them. Since the 1950s, for example, researchers have created vaccines against polio, measles, mumps, and a number of other childhood infections that have dramatically cut deaths, disability, and discomfort from these diseases. Children and their families have also benefited from research demonstrating the harm or ineffectiveness of what were once standard therapies, for instance, high-dose oxygen for premature infants.

Despite these advances, pediatricians and others have argued that infants, children, and adolescents have not shared equally with adults in advances in biomedicine. In particular, many drugs with potential pediatric uses have not been tested in studies that include children. These drugs may still be prescribed for children based on physicians' judgment about how data from studies with adults might be extrapolated to children. Because children differ physiologically from adults in myriad ways that can affect how drugs work in the body, extrapolation based on adult drug doses and children's weight or age can be dangerous and lead to underdosing, overdosing, or specific adverse effects not evident in adults.

The U.S. Congress, the Food and Drug Administration (FDA), and the National Institutes of Health (NIH) have acted in recent years to expand research involving children. Notwithstanding the expected benefits of these efforts, some caution is appropriate. Unlike most adults, children usually lack the legal right and the intellectual and emotional maturity to consent to research participation on their own behalf. Their vulnerability demands special consideration from researchers and policymakers and additional protections beyond those provided to mentally competent adult participants in research.

In the United States, research that is supported, conducted, or regulated by the U.S. Department of Health and Human Services (DHHS) is now subject to a (mostly) common set

of regulations to protect adult and child participants in research. Nonetheless, deficiencies in the conduct of human research—most of which are fairly minor but some of which result in deaths or serious injuries—continue to be revealed.

Concerns about the adequacy of the system for protecting child participants in research, combined with the public commitment to expanding clinical research involving children, provided the impetus for this Institute of Medicine (IOM) report, which was requested in the Best Pharmaceuticals for Children Act of 2002 (P.L. 107-109). The legislation charged the IOM with preparing a report that reviewed federal regulations, reports, and research and that made recommendations about desirable practices in clinical research involving children. Specifically designated topics were (1) the appropriateness of the regulations for children of various ages, (2) the interpretation of regulatory criteria for approving research, (3) the processes for securing parents' and children's agreement to a child's participation in research, (4) the expectations and comprehension of children and parents about participating in research, (5) the appropriateness of payments related to the child's participation in research, (6) compliance with and enforcement of federal regulations, and (7) the unique roles and responsibilities of institutional review boards (IRBs).

The report, prepared by a 14-member committee of the Institute of Medicine, focuses primarily on clinical research involving preventive, diagnostic, treatment, or similar interventions and direct interactions with children. It stresses three broad themes:

- *Well-designed and well-executed clinical research involving children is essential to improve the health of future children—and future adults—in the United States and worldwide.* Children should not be routinely excluded from clinical studies. No subgroups of children should be either unduly burdened as research participants or unduly excluded from involvement.
- *A robust system for protecting human research participants in general is a necessary foundation for protecting child research participants in particular.* An efficiently administered, effectively performing system with adequate resources must, however, commit additional resources and attention to meet ethical and legal standards for protecting infants, children, and adolescents who participate in research.
- *Effective implementation of policies to protect child participants in research requires appropriate expertise in child health at all stages in the design, review, and conduct of such research.* This expertise includes knowledge of infant, child, and adolescent physiology and development as well as awareness of the unique scientific, psychosocial, and ethical requirements and challenges of pediatric clinical care and research.

REGULATORY CONTEXT

In 1983, DHHS published the first regulations specifically governing federally supported or conducted research involving children (Subpart D of 45 CFR 46). This was 10 years after the first general departmental regulations on protecting human participants in research were published (now Subpart A of 45 CFR 46, also called the "Common Rule"). Similar but not identical regulations for research regulated by FDA are found at 21 CFR 50 and 56. (For simplicity in making comparisons, the regulations at 45 CFR 46 are termed DHHS regulations, even though the FDA is part of DHHS.)

Subpart A of the regulations sets forth basic requirements for all covered research, including provisions that the risk to research participants be minimized, that the risks be reasonable in relation to the anticipated benefits, that the selection of research participants be equitable, and that informed consent be obtained from participants. Subpart D provides that parents must, under most circumstances, provide permission before children (usually those under age 18 as defined by state laws) can participate in research. It also provides that, when appropriate, children should affirmatively agree or assent to participate in research.

In addition, Subpart D establishes four categories under which research involving children can be approved. Omitting reference to specific requirements for parents' permission and children's assent, these categories of approvable research are summarized in Box S1.

BOX S1
Summary of Categories of Research Involving Children That Are Approvable Under Subpart D of 45 CFR 46

Section 46.404: Research that involves no greater than minimal risk to children

Section 46.405: Research that involves greater than minimal risk but the risk is justified by the anticipated benefit to the participants and the relation of the anticipated benefit to the risk is at least as favorable as that presented by available alternative approaches.

Section 46.406: Research that involves greater than minimal risk and no prospect of direct benefit to research participants but (a) the risk represents only a minor increase over minimal risk, (b) the research involves experience reasonably commensurate with those inherent in the child's medical, dental, psychological, social, or educational situations, and (c) the research is likely to yield generalizable, vitally important knowledge about the child's disorder or condition.

Section 46.407: Research that is not otherwise approvable but that the IRB and the Secretary of DHHS determine presents an opportunity to understand, prevent, or alleviate a serious problem affecting children's health or welfare and will be conducted in accordance with sound ethical principles.

NOTE: The corresponding regulations for the FDA are found at 21 CFR 50.51 to 54.

The committee concluded that the federal regulations providing special protections for child participants are, in general, appropriate for children of different ages. They reasonably defer to state laws that define both the age at which individuals become entitled to make medical care decisions and the special circumstances under which minors may make such decisions in their own right (e.g., for care related to sexually transmitted diseases).

For the most part, the problems with the regulations relate to insufficient government guidance about their interpretation and implementation, shortfalls in data about implementation and compliance, and variability in investigator and IRB interpretations of the criteria for approving research involving children. Some of these criteria include inherently subjective elements that the committee doubts would be substantially and predictably clarified by revising the regulations. As discussed below, one change that the committee does recommend is that FDA make its policies consistent with those of DHHS that allow the waiver of parental permission for children's, especially adolescents', participation in research when permission is not a reasonable requirement to protect a child. Another recommendation is that all research

that includes infants, children, and adolescents should occur under the umbrella of a formal program for the protection of human research participants (Recommendation 8.1). Because the federal government may not have the authority to require this, state governments should consider exercising their authority to regulate research in ways that are consistent with federal regulations and supportive of multistate studies.

INTERPRETING RESEARCH RISK AND OTHER REGULATORY CONCEPTS

Categorizing, evaluating, and weighing the risks of proposed research are among the most challenging and subjective tasks for those charged with reviewing research that includes infants, children, and adolescents. The committee was specifically asked to consider the regulatory definition of "minimal risk" in the context of research involving children. It also examined several other closely related concepts in the regulations.

For purposes of approving human research, federal regulations define the term *minimal risk* as meaning "that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests" (45 CFR 46.102(i); 21 CFR 50.3(k)). That this standard invites variable interpretations has long been clear, especially for studies involving multiple sites and multiple IRBs.

Consistent with the conclusions of a number of other groups, the committee rejected an interpretation of minimal risk that would allow greater research risk for children exposed to higher than average risk of harm in their personal lives (e.g., because they are ill or live in unsafe neighborhoods). This "relative" interpretation misinterprets the minimal risk standard and undercuts its moral and social purposes for pediatric studies, which are to guide judgments about when risks are low enough to safely and ethically enroll children in studies that are not designed to benefit them. The assessment of risk should be compared or indexed to the experiences of average, normal, healthy children.

Recommendation 4.1: In evaluating the potential harms or discomfort posed by a research protocol that includes children, investigators and reviewers of research protocols should

- **interpret *minimal risk* in relation to the normal experiences of average, healthy, normal children;**
- **focus on the equivalence of potential harms or discomfort anticipated in research with the harms or discomfort that average, healthy, normal children may encounter in their daily lives *or* experience in routine physical or psychological examinations or tests;**
- **consider the risk of harms or discomfort in relation to the ages of the children to be studied; and**
- **assess the duration as well as the probability and magnitude of potential harms or discomfort in determining the level of risk.**

In Section 406 of 45 CFR 46, federal regulations permit research that involves a minor increase over minimal risk without the prospect of direct benefit if the research involves children with a disorder or condition, is likely to yield vital knowledge about that disorder or

condition, and entails research experiences that are reasonably similar to those that such children encounter in certain other situations. Consistent with the interpretation of minimal risk, the interpretation of this level of research risk should *not* allow a higher threshold of risk for children who are exposed to more risk in other aspects of their lives (Recommendation 4.2). Also, consistent with the language of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which defined this standard in 1977, the risk allowed under this category can be only *slightly* above minimal risk.

In the context of IRB determinations about whether a study can be approved under Section 406 of 45 CFR 46, the term *condition* is also ambiguous. If a characteristic of a group of children is to be designated as a condition that allows children to be exposed to a higher level of risk without a prospect of benefit, the link between the characteristic and a deficit in children's health or well-being should be supported by scientific evidence or clinical knowledge.

Recommendation 4.3: In determining whether proposed research involving a minor increase over minimal risk and no direct benefit can be approved, the term *condition* should be interpreted as referring to a specific (or a set of specific) physical, psychological, neurodevelopmental, or social characteristic(s) that an established body of scientific evidence or clinical knowledge has shown to negatively affect children's health and well-being or to increase their risk of developing a health problem in the future.

The committee further recommends that IRBs make (and record in their minutes) explicit determinations about each of the regulatory criteria that must be met for the approval of research involving children (Recommendation 4.4). To assist investigators and IRBs, the committee recommends that the DHHS Office for Human Research Protections (OHRP) develop explicit guidance and examples for IRBs and investigators based on the findings presented in this IOM report and the work that it cites (Recommendation 4.5). In addition, the Secretary's Advisory Committee on Human Research Protection is encouraged to continue work to develop consensus assessments about the risk of common research procedures, including rationales for the categorization of procedures judged to involve either minimal risk or a minor increase over minimal risk (Recommendation 4.5).

UNDERSTANDING AND AGREEING TO CHILDREN'S PARTICIPATION IN RESEARCH

Informed consent is widely regarded as a cornerstone of ethical research. Because children (except for adolescents under certain conditions) do not have the legal capacity to provide informed consent, the concepts of parental *permission* and child *assent* have been developed as standards for ethical research involving children. (The term *parent* is used here to include guardians as well.)

Parents asked for permission for a child's participation in clinical research are often making decisions under great stress and time pressure. Some prefer to trust the physician's assessment rather than make their own, and investigators must be acutely sensitive to the influence that they wield in discussions with parents of ill or injured children. As is also the case for adults considering their own participation in research, a significant minority of parents

may misunderstand the purpose of the research, especially when the research tests a therapy for a serious medical condition. Nonetheless, the goal of informed agreement by parents remains an important protection for children, both when participation in research is initially sought and through the course of a study.

The capacity to make voluntary, informed decisions clearly evolves from birth through adolescence and into adulthood. It also clearly varies among individuals of the same age. The committee found some disagreement and mixed evidence about the age at which children can be meaningfully involved in discussions and decisions about their research participation given various research contexts. Again, despite this uncertainty, the goal should be to involve children in discussions and decisions about research participation as appropriate given their cognitive and emotional maturity and psychological state. Involving children in discussions and decision making respects their emerging maturity, helps them prepare for participation in research, gives them an opportunity to express their concerns and objections and, possibly, allows them to influence what happens to them.

As many others have argued, informed consent—and, by extension, permission and assent—should be viewed as a process and not a form. This goal remains less a reality than an aspiration. IRBs should focus more of their attention on the adequacy of the process for securing permission and assent in proposed research protocols. Discussions with parents and, as appropriate, children should allow sufficient time for questions and, if necessary, further explanations. Such discussions should precede the presentation of a permission or assent form.

Recommendation 5.1: To focus attention on the *process* of requesting parents' permission and children's assent to research participation, investigators should provide and IRBs should review protocol descriptions of

- **who will request permission and assent;**
- **how and when permission and assent will be requested;**
- **who should be contacted if the parents have questions or concerns about the research; and**
- **for studies that extend over considerable periods of time, when and how permission and assent may be requested again, for example, as children reach important developmental milestones.**

Although the research literature is limited and not entirely consistent, it supports a gradual expansion of the involvement of children in discussions and decisions about their participation in research. For younger children, the emphasis should be on providing basic information about what will happen, responding to their questions and concerns, and—particularly when the research does not offer the prospect of direct benefit—recognizing when children do not want to participate. As children mature, they can participate more fully in discussions and decisions about their participation in research. Older adolescents may not have the legal capacity to make decisions in their own right, but research generally suggests that the substance of the assent process can be similar to the substance of the consent process for adults *if* that process is properly designed to accommodate people of various educational, social, and cultural backgrounds.

Recommendation 5.6: In designing and reviewing procedures for seeking a child's assent to participation in research, investigators and institutional review boards should aim to create assent processes that consider and respect the child and the family as a unit as well as individually. The process for requesting assent should

- **be developmentally appropriate given the ages and other characteristics of the children to be approached;**
- **provide opportunities for children to express and discuss their willingness or unwillingness to participate;**
- **clarify for parents and children (as appropriate) the degree of control that each will have over the participation decision; and**
- **when appropriate, describe to children and parents the kinds of information about the child that will or will not be shared with the parents.**

One particularly sensitive issue is when adolescents should be free to consent to research participation without parental permission. Certain studies that are important to adolescent health and well-being will not be feasible without such a waiver. The research reviewed here suggests that the DHHS regulations appropriately provide for waivers, including a requirement that a suitable mechanism is provided to protect children when parental permission is waived. FDA should revise its rule on the waiver of parental permission to be consistent with DHHS rules (Recommendation 5.4).

PAYMENT RELATED TO RESEARCH PARTICIPATION

Ethical standards for participation in research require that the agreement to participate be freely given; that is, it should not be either coerced or unduly influenced by psychological, financial, or other pressure. The major concern about payments related to research participation is that they may unduly influence and distort decisions about research participation made by individuals in their own right or by parents on behalf of their child.

Survey and other information available to the committee suggested that many IRBs and research institutions do not have written policies to guide reviews of research payment practices. By developing written policies on payments to parents and children, IRBs can consider ethical issues outside of the context of an individual protocol. Such deliberation will help achieve a fairer and more consistent approach to making decisions on appropriate payments. In general, these policies should provide that payment be discussed during the process of seeking parents' permission and the child's assent to participation in research.

Recommendation 6.1: Institutional review boards, research institutions, and sponsors of research that includes children and adolescents should adopt explicit written policies on acceptable and unacceptable types and amounts of payments related to research participation. These policies should specify that investigators

- **disclose the amount, the recipient, the timing, and the purpose (e.g., an expense reimbursement or a token of appreciation to a child) of any payments as part of the process of seeking parents' permission and, as appropriate, children's assent to research participation;**

- **avoid emphasis on payments or descriptions of payments as benefits of participating in research during the permission or assent process; and**
- **obtain institutional review board approval for the disclosure of information about payments in advertisements and in permission and assent forms and procedures.**

Certain types of payments to parents or adolescents are usually, if not always acceptable, for example, reimbursement for reasonable expenses that are necessary for participation in research. Other payments are never appropriate, for example, paying parents for permitting their child to be exposed to a greater research risk. Compensation to parents for lost wages or time may be appropriate under carefully scrutinized circumstances. One objective of IRB and institutional policies on payments related to children's participation in research should be to encourage equal access to study participation, regardless of a family's economic status, while avoiding practices that risk exerting undue influence over the parents' and children's consideration of the child's participation in research (Recommendation 6.2). To respond to the diverse barriers to children's participation in research, nonfinancial alternatives that equalize participation opportunities should also be considered, for example, adjusting the times or places for research visits for parents who cannot take time off from work.

REGULATORY COMPLIANCE, QUALITY IMPROVEMENT, AND ACCCREDITATION

The dearth of information about human research and human research protection programs in general and about pediatric research and research protection programs in particular makes it impossible to describe adequately the implementation and enforcement of federal regulations and, likewise, hinders evaluation and improvement efforts. As one of its recommendations for strengthening the system for protecting human participants in research, the 2003 IOM report *Responsible Research* proposed that DHHS commission studies to gather basic information about the current system as needed to identify problems and track improvements. This committee agrees.

Recommendation 7.1: To help identify what further guidance, education, or other steps may be needed to protect child participants in research, the U.S. Department of Health and Human Services—with direction from the U.S. Congress, if necessary—should develop and implement a plan for gathering and reporting data on

- **research involving children, including the categorization of studies by the relevant section of federal regulations (45 CFR 46.404 to 407 and 21 CFR 50.51 to 54), and**
- **implementation of the regulations that govern research involving children, including data from the Office for Human Research Protections and the Food and Drug Administration on their inquiries, investigations, and sanctions related to such research.**

The committee recognizes that such data collection responsibilities will require a considerable investment of resources by OHRP and, particularly, FDA, given the latter's more extensive oversight activities. Nonetheless, in calling for the present IOM study, the U.S. Congress has already recognized the concerns presented by research involving children and the

regulations applicable to that research. If necessary, it should be prepared to direct and fund the collection of necessary data on research involving children.

For most public policies, including those related to the protection of child participants in research, the path to the desired results depends in large measure on the voluntary actions of private individuals and organizations. Within the arena of human research protections, voluntary quality improvement efforts should, if successful and sustained, strengthen the overall system of human research protections within which the policies for children are embedded.

Consistent with recommendations in earlier IOM reports, the committee supports the further development and systematic evaluation of accreditation for human research participant protection programs. For accrediting organizations to assess programs that encompass research involving children, these organizations themselves need expertise in child health and research involving children (Recommendation 7.2).

ROLES AND RESPONSIBILITIES IN PROTECTING CHILDREN INVOLVED IN RESEARCH

The benefits to the health of children collectively from involving more children individually in clinical research are compelling. Also compelling are the moral and legal obligations of all involved in research to specially protect children who are not able to provide informed, reasoned, and voluntary consent to their participation in research in their own right.

This report focuses on those who conduct, review, regulate, and fund research, but the central role of parents must be recognized and respected. Parents have a most intimate and profound duty and desire to protect and promote their child's safety and well-being in research, as in all realms of life. By improving the initial and continuing process for securing parental agreement to a child's participation in research, investigators, IRBs, research institutions, and others can support parents in fulfilling their responsibilities and, thereby, help them feel that they have done the right thing for their child, whatever their decisions about research participation. Box S2 summarizes some questions that parents may want to ask about their child's participation in research.

BOX S2
Questions Parents May Want to Ask When Considering Their Child's Participation in Clinical Research

- What is the purpose of the research? Who is paying for it?
- Where will the research be done? How long will it last?
- What kinds of procedures and/or tests will be involved? How will they differ from what would happen if my child doesn't participate?
- What are the possible short-term and long-term harms and benefits (if any) of the study? How do they compare with treatments that my child is receiving or might receive without being in the research?

- Will the research procedure(s) hurt? If so, for how long? What can be done to prevent or limit pain? Are there other side effects?

- What will I have to do if my child is part of the study? What will my child have to do?

- Will I have to pay anything if my child is part of the study? Will my child or I be paid anything for participating?

- Who do I call with questions or in an emergency? What will happen if something goes wrong?

- What will I be told during the study and after it is finished?

- How can I withdraw my child from the study? Will that affect my child's care?

- Who will know that my child is in the study? What information will they get?

Investigators

In clinical research, the investigator has the ultimate responsibility for ensuring the safety, rights, and welfare of individuals participating in research and for seeing that all members of the research team adhere to the requirements for valid, ethical research. This is the case whether the investigator has a major role in designing the research or uses a design developed by a research sponsor or others. Likewise, he or she is responsible for the safety and welfare of child participants in research, whether the study includes only children or also includes adults.

Box S3 summarizes some of the major responsibilities of clinical investigators who conduct research that includes infants, children, or adolescents. To varying degrees, research institutions, sponsors of research, and regulators understand—or should understand—that investigators' success in fulfilling their responsibilities depends significantly on supportive administrative, financial, educational, and other systems, both local and national. The infrastructure provided by these systems should stretch from the initial education of investigators through the eventual dissemination of research findings and likewise should extend to all settings and types of practice.

BOX S3
Key Responsibilities of Investigators for the Ethical Conduct of Clinical Research Involving Infants, Children, and Adolescents

- Achieve and maintain appropriate training, credentials, and skills to perform or supervise all clinical and research procedures required for a study that includes children.

- Achieve and maintain appropriate training and knowledge to meet the ethical and regulatory requirements for conducting research that includes children.

- Ensure that research protocols involving children conform to ethical and scientific standards for such research.

- Submit proposals and proposal amendments for scientific and ethical review and approval before beginning or modifying research and, as required, during the course of research.

- Disclose potential conflicts of interest to appropriate parties.

- Conduct the study in accord with the approved protocol.

- Ensure that the processes for securing parents' permission and children's assent to research participation meet ethical and regulatory standards and are effective and active through the duration of the study. Provide rationale and propose appropriate protections consistent with federal and state laws if waiver of parent permission is sought.

- Communicate with children participating in research in developmentally appropriate ways and with guidance from their parents about what will happen to them throughout the course of the research.

- Support appropriate safety monitoring and reporting of adverse events.

- Report protocol violations, errors, and problems as required to research sponsors, regulators, or IRBs.

- Disclose research results to the scientific community and the public.

- Communicate research results, as appropriate, to research participants or participant communities.

SOURCE: Adapted from IOM, *Responsible Research: A Systems Approach to Protecting Research Participants. Washington, D.C.: National Academy Press,* 2003a

Institutional Review Boards and Research Institutions

Much of the administrative infrastructure and activity that contribute to competent and ethical IRB and research institution performance will support equally the protection of adult and child participants in research. Beyond this foundation, research institutions that conduct studies that include children and IRBs that review such studies have further ethical and legal responsibilities that require special attention. Box S3 summarizes these responsibilities, which begin with educating IRB members, investigators, and others about their ethical and legal obligations to protect child participants in research.

BOX S4
Key Ethical and Legal Responsibilities of IRBs and Research Institutions Involved with Clinical Research That Includes Infants, Children, and Adolescents

- Educate IRB members and, as needed, IRB pediatric consultants about the ethical, legal, and scientific standards for approving research involving children and their appropriate interpretation.

- Educate investigators who conduct research that includes infants, children, or adolescents about their ethical, legal, and scientific responsibilities.

- Apply ethical and regulatory standards for the initial and continuing review and approval of research protocols involving children, including careful evaluation and categorization of research risks.

- Provide for adequate expertise in child health and research in the review of protocols that include children, including assessment of whether those conducting the studies have adequate pediatric expertise.

- Make available reference materials and resources on research involving children, including information on research ethics, as part of IRB or research administration web sites and educational programs.

- Conduct ongoing assessments to guide improvements in IRB performance in reviewing and monitoring research involving children.

- Develop explicit policies or guidelines on important topics for which additional guidance to IRB members or investigators is needed.

A critical obligation of IRBs is to bring appropriate expertise to the review of research involving infants, children, and adolescents. As more children participate in clinical trials and other research, the need grows for both investigator and IRB expertise in the biological, medical, behavioral, and emotional development and needs of children. The following recommendation applies to independent, central, and other IRBs as well as to those affiliated with biomedical and social science research institutions and children's hospitals:

Recommendation 8.3: Institutional review boards (IRBs) that review protocols for research involving infants, children, and adolescents should have adequate expertise in child health care and research. They should have at least three individuals with such expertise present as members or alternates during meetings in which a research protocol involving children is reviewed. Among them, these individuals—who may be generalists or specialists—should have expertise in pediatric clinical care and research, the psychosocial dimensions of child and adolescent health care and research, and the ethics of research involving children. As appropriate for specific studies, IRBs should consult with other child health experts and with parents, children, adolescents, and community members who can provide relevant family or community perspectives.

Publicly accessible information about IRB procedures and guidance related to the design and review of protocols that include children is limited and highly variable, which

makes it difficult to judge this dimension of IRB and institutional performance. Some publicly accessible IRB websites display little readily identifiable information or guidance for investigators or IRB members related to research that includes children. For example, some websites have protocol checklists or application forms that include no items or an incomplete list of items that highlight requirements for research involving children (and no obvious alternative document with the relevant items). Federal agencies have found deficiencies in IRB practices related to the review of research involving children, particularly in the description of the bases for IRB decisions in the meeting minutes. More complete and specific protocol checklists or application forms would help highlight the ethical and regulatory standards for approving and conducting research involving children and should improve compliance with those standards.

Recommendation 8.4: For their policy manuals, web sites, and other resources, institutional review boards (IRBs) and research institutions should provide easily understood and easily located information that directs investigator and IRB member attention to the ethical principles and special regulatory requirements that apply to the conduct and review of research that includes infants, children, and adolescents.

Federal Policymakers and Regulators

For approximately a half-century, federal agencies responsible for conducting and sponsoring biomedical research and for regulating medical products have—sometimes directed by Congress—played a major role in developing policies to protect human participants in research. In recent years, they have paid increasing attention to the application of those policies by investigators, IRBs, and research institutions and to the education of these parties about their responsibilities.

The guidance and other resources that OHRP and FDA have made available strongly shape if not dominate local IRB policy manuals and resource links. Although investigators and IRB members at research institutions should have good local support as recommended above, they and others—including policymakers and others interested in ethical and regulatory standards for clinical research—should also find it easy to locate guidance and information on government websites. FDA, which now has an Office of Pediatric Therapeutics within the Center for Drug Evaluation and Research, has a web page dedicated to pediatric research with links to a variety of resources, including FDA regulations and guidelines for such research. The OHRP website has limited resources relevant to research involving children and they can be difficult to locate.

Recommendation 8.6: The Office for Human Research Protections, the Food and Drug Administration, the National Institutes of Health, and other agencies with relevant responsibilities that include research involving children should each provide—in an easily identifiable document or set of linked documents—comprehensive, consistent, periodically updated guidance to investigators, institutional review boards, and others on the interpretation and application of federal regulations for the protection of child participants in research.

DHHS has moved to significantly improve the process for reviewing proposals for research involving children that IRBs have referred to the Secretary for approval under the provisions of 45 CFR 46.407. That effort, with support from the Secretary's Advisory Committee on Human Research Protections, should continue with the objective of establishing an open and publicly accessible process for reviewing referred protocols (Recommendation 8.7). DHHS should also develop guidance to help IRBs determine when it is appropriate to refer protocols for review. The referral of proposed research for "national" review should be reserved for "exceptional situations" and research of "major significance" and protocols should only be approved if they are expected to produce vitally important knowledge.

The committee encourages the continued investment by OHRP in its quality improvement initiative, with attention to the special requirements and challenges of research involving children. OHRP, FDA, and other agencies should also continue to cooperate in the development of educational programs for use by government agencies, IRBs, research institutions, pediatric academic societies, and other groups.

In addition, agencies should fund research and demonstration projects to expand the knowledge base for improving the performance of the system for protecting child participants in research. They can, for example, test strategies to improve the quality and consistency of reviews for multisite research projects and reduce unnecessary burdens and frustrations for their investigators and sponsors. Such improvements will not eliminate tensions between the goal of protecting today's children from research harms and the goal of advancing research that improves the health and well-being of tomorrow's children. They can, however, help all parties feel more confident that policymakers and IRBS are trying to identify and remove needless burdens on researchers.

The full list of committee recommendations follows.

Ethical Conduct of Clinical Research Involving Children:
Complete List of Recommendations

Recommendation 4.1 In evaluating the potential harms or discomfort posed by a research protocol that includes children, investigators and reviewers of research protocols should

- interpret *minimal risk* in relation to the normal experiences of average, healthy, normal children;
- focus on the equivalence of potential harms or discomfort anticipated in research with the harms or discomfort that average, healthy, normal children may encounter in their daily lives *or* experience in routine physical or psychological examinations or tests;
- consider the risk of harms or discomfort in relation to the ages of the children to be studied; and
- assess the duration as well as the probability and magnitude of potential harms or discomfort in determining the level of risk.

Recommendation 4.2 In evaluating the potential harms or discomfort posed by a research protocol that includes children who have a disorder or condition but no prospect of benefiting from participation, investigators and reviewers of research protocols should

- interpret *minor increase over minimal risk* to mean a slight increase in the potential for harms or discomfort beyond minimal risk (as defined in relation to the normal experiences of average, healthy, normal children);

- assess whether the research procedures or interventions present experiences that are commensurate with, that is, reasonably comparable to experiences already familiar to the children being studied on the basis of their past tests or treatments or their knowledge and understanding of the treatments that they might undergo in the future;
- consider risks of harms or discomfort in relation to the ages of the children to be studied; and
- assess the duration as well as the probability and magnitude of potential harms or discomfort in determining the level of risk.

Recommendation 4.3 In determining whether proposed research involving a minor increase over minimal risk and no direct benefit can be approved, the term *condition* should be interpreted as referring to a specific (or a set of specific) physical, psychological, neurodevelopmental, or social characteristic(s) that an established body of scientific evidence or clinical knowledge has shown to negatively affect children's health and well-being or to increase their risk of developing a health problem in the future.

Recommendation 4.4 For purposes of determining whether proposed research involving a minor increase over minimal risk and no direct benefit can be approved, institutional review boards should make a determination that

- the children to be included in the research have a disorder or condition;
- the research is likely to generate vital knowledge about the children's disorder or condition;
- the research procedures or interventions present experiences that are commensurate with, that is, reasonably comparable to, experiences already familiar to the children being studied on the basis of their past tests or treatments or on their knowledge and understanding of the treatments that they might undergo in the future; and
- the research does not unjustly single out or burden any group of children for increased exposure to research risk on the basis of their social circumstances.

Recommendation 4.5 The Secretary's Advisory Committee on Human Research Protections (U.S. Department of Health and Human Services) should continue the work of its predecessor committee by developing additional consensus descriptions of procedures or interventions that present minimal risk or no more than a minor increase over minimal risk. In addition, the Office for Human Research Protections and the Food and Drug Administration should cooperate to develop and disseminate guidance and examples for investigators and institutional review boards to clarify important regulatory concepts and definitions (including definitions of minimal risk, minor increase over minimal risk, condition, and prospect of direct benefit).

Recommendation 4.6 Institutional review boards should assess the potential harms and benefits of each intervention or procedure in a pediatric protocol to determine whether each conforms to the regulatory criteria for approving research involving children. When some procedures present the prospect of direct benefit and others do not, the potential benefits from one component of the research should not be held to offset or justify the risks presented by another.

Recommendation 5.1 To focus attention on the *process* of requesting parents' permission and children's assent to research participation, investigators should provide and IRBs should review protocol descriptions of

- who will request permission and assent;
- how and when permission and assent will be requested;
- who should be contacted if the parents have questions or concerns about the research; and

- for studies that extend over considerable periods of time, when and how permission and assent may be requested again, for example, as children reach important developmental milestones.

Recommendation 5.2 When appropriate for research involving children with acute illnesses or injuries, investigators and institutional review boards should provide for ongoing processes for permission and assent that will accommodate a family's evolving understanding of the child's condition, the child's emotional state and decision-making capacity, and the child's changing medical and psychological status. These processes are not matters of signing or updating forms but, rather, of continuing communication based on appreciation of the difficult and even overwhelming circumstances in which parents may be asked to make grave decisions about their child's future.

Recommendation 5.3 Investigators—with assistance and oversight from institutional review boards, research institutions, and research sponsors—should design procedures for seeking parental permission for a child's participation in research that are sensitive to educational, cultural, and other differences among families and include provisions for

- educating—not merely presenting information to—parents about issues critical to informed decision making and, as appropriate, assessing the degree to which these critical issues are understood;
- writing consent and permission materials in the simplest language that still conveys essential information about the study; and
- providing competent, trained translators and interpreters, when needed, and otherwise assisting parents with limited English-language proficiency with making informed decisions.

Recommendation 5.4 Institutional review boards should consider granting waivers of parental permission for adolescent participation in research when

- the research is important to the health and well-being of adolescents and it cannot reasonably or practically be carried out without the waiver (consistent with 45 CFR 46.116(d) and 45 CFR 408(c)) or
- the research involves treatments that state laws permit adolescents to receive without parental permission (consistent with the definition of children at 46 CFR 402(a))

and when

- the investigator has presented evidence that the adolescents are capable of understanding the research and their rights as research participants and
- the research protocol includes appropriate safeguards to protect the interests of the adolescent consistent with the risk presented by the research.

Recommendation 5.5 The Food and Drug Administration should adopt policies consistent with federal regulations at 45 CFR 46.408(c) that allow institutional review boards with appropriate expertise to waive requirements for parental permission in research, provided that additional, appropriate safeguards are in place to protect the child's or the adolescent's welfare.

Recommendation 5.6 In designing and reviewing procedures for seeking a child's assent to participation in research, investigators and institutional review boards should aim to create assent processes that consider and respect the child and the family as a unit as well as individually. The process for requesting assent should

- be developmentally appropriate given the ages and other characteristics of the children to be approached;
- provide opportunities for children to express and discuss their willingness or unwillingness to participate;
- clarify for parents and children (as appropriate) the degree of control that each will have over the participation decision; and

- when appropriate, describe to children and parents the kinds of information about the child that will or will not be shared with the parents.

Recommendation 5.7 Guidance and education for investigators and members of institutional review boards should make clear that federal regulations allow discretion—based on children's developmental maturity—about the way in which information is presented to children and the manner in which assent is documented. Investigators and institutional review board members should apply that knowledge in determining what procedures will best serve the goals of assent for particular research protocols and populations.

Recommendation 5.8 To increase investigator competence in communicating with children and parents about research participation, educational programs for investigators and research staff who expect to do research involving children should include training and evaluation in developmentally appropriate and family-sensitive processes for seeking permission and assent.

Recommendation 5.9 Federal agencies, private foundations, and advocacy groups should encourage and support research on existing and innovative permission and assent processes and information materials to support improvements in these processes and guide the education of investigators and institutional review board members.

Recommendation 6.1 Institutional review boards, research institutions, and sponsors of research that includes children and adolescents should adopt explicit written policies on acceptable and unacceptable types and amounts of payments related to research participation. These policies should specify that investigators

- disclose the amount, the recipient, the timing, and the purpose (e.g., an expense reimbursement or a token of appreciation to a child) of any payments as part of the process of seeking parents' permission and, as appropriate, children's assent to research participation;
- avoid emphasis on payments or descriptions of payments as benefits of participating in research during the permission or assent process; and
- obtain institutional review board approval for the disclosure of information about payments in advertisements and in permission and assent forms and procedures.

Recommendation 6.2 In addition to offering small gifts or payments to parents and children as gestures of appreciation, investigators may also—if they minimize the potential for undue influence—act ethically to reduce certain barriers to research participation when they

- reimburse reasonable expenses directly related to a child's participation in research;
- provide reasonable, age-appropriate compensation for children based on the time involved in research that does not offer the prospect of direct benefit; and
- offer evening or weekend hours, on-site child care, and other reasonable accommodations of for parental work and family commitments.

Recommendation 6.3 Research organizations and sponsors should pay the medical and rehabilitation costs for children injured as a direct result of research participation, without regard to fault. Consent and permission documents should disclose to parents (and adolescents, if appropriate) the child's right to compensation and the mechanisms for seeking such compensation.

Recommendation 6.4 Investigators and their staffs may appropriately be reimbursed for the costs associated with conducting research. Payments in the form of finder's fees or bonuses for enrolling a specific number of children or adolescents are unethical and should not be permitted.

Recommendation 7.1 To help identify what further guidance, education, or other steps may be needed to protect child participants in research, the U.S. Department of Health and Human Services—with direction from the U.S. Congress, if necessary—should develop and implement a plan for gathering and reporting data on

- research involving children, including the categorization of studies by the relevant section of federal regulations (45 CFR 46.404 to 407 and 21 CFR 50.51 to 54), and
- implementation of the regulations that govern research involving children, including data from the Office for Human Research Protections and the Food and Drug Administration on their inquiries, investigations, and sanctions related to such research.

Recommendation 7.2 Organizations that accredit human research protection programs should

- provide for expertise in child health in their own activities;
- develop explicit provisions for evaluating whether institutional review boards are appropriately constituted and are prepared to review research involving children; and
- involve parents, children, and adolescents who have experience with pediatric clinical research in discussions to identify their concerns with the conduct of research.

Recommendation 8.1 Federal law should require that all clinical research involving infants, children and adolescents be conducted under the oversight of a formal program for protecting human participants in research.

Recommendation 8.2 To strengthen the base of qualified pediatric clinical investigators, federal and state policymakers and research institutions should support

- education in the fundamentals of pediatric clinical research, including research ethics, in all educational programs for pediatric subspecialists and
- additional advanced education in pediatric clinical research, including research ethics, for those who seek careers in this field of research.

Recommendation 8.3 Institutional review boards (IRBs) that review protocols for research involving infants, children, and adolescents should have adequate expertise in child health care and research. They should have at least three individuals with such expertise present as members or alternates during meetings in which a research protocol involving children is reviewed. Among them, these individuals—who may be generalists or specialists—should have expertise in pediatric clinical care and research, the psychosocial dimensions of child and adolescent health care and research, and the ethics of research involving children. As appropriate for specific studies, IRBs should consult with other child health experts and with parents, children, adolescents, and community members who can provide relevant family or community perspectives.

Recommendation 8.4 For their policy manuals, web sites, and other resources, institutional review boards (IRBs) and research institutions should provide easily understood and easily located information that directs investigator and IRB member attention to the ethical principles and special regulatory requirements that apply to the conduct and review of research that includes infants, children, and adolescents.

Recommendation 8.5 The federal government, research institutions, research sponsors, and groups of institutional review boards should continue to test and evaluate means to improve the efficiency as well as the quality and consistency of reviews of multicenter studies, including those involving infants, children, and adolescents.

Recommendation 8.6 The Office for Human Research Protections, the Food and Drug Administration, the National Institutes of Health, and other agencies with relevant responsibilities that include research involving children should each provide—in an easily identifiable document or set of linked documents—comprehensive, consistent, periodically updated guidance to investigators, institutional review boards, and others on the interpretation and application of federal regulations for the protection of child participants in research.

Recommendation 8.7 The Office for Human Research Protections and the Food and Drug Administration should

- continue their activities to establish an open and publicly accessible review process for considering research protocols referred by institutional review boards for review under 45 CFR 46.407 and 21 CFR 50.54;
- create a standing panel that would meet as needed to consider such proposals; and
- provide detailed guidance on the interpretation of the federal regulations governing research involving children to reduce unnecessary referrals of protocols.