DEVELOPING A NATIONAL REGISTRY OF PHARMACOLOGIC AND BIOLOGIC CLINICAL TRIALS

WORKSHOP REPORT

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

Developing a National Registry of Pharmacologic and Biologic Clinical Trials

Workshop Report

Committee on Clinical Trial Registries

Board on Health Sciences Policy

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.

This study was supported by internal unrestricted funds. Any opinions, findings, or conclusions expressed in this publication are those of the author(s) and do not necessarily reflect the view of the organizations or agencies that provided support for this project.

ISBN 0-309-10078-X

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

Advising the Nation. Improving 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. Ralph J. Cicerone 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. Ralph J. Cicerone and Dr. Wm. A. Wulf are chair and vice chair, respectively, of the National Research Council.

www.national-academies.org

COMMITTEE ON CLINICAL TRIAL REGISTRIES

PHILIP A. PIZZO (*Chair*), Stanford University School of Medicine, Stanford, California
GAIL H. CASSELL, Eli Lilly and Company, Indianapolis, Indiana
ELLEN WRIGHT CLAYTON, Vanderbilt University Medical School, Nashville, Tennessee
DAVID R. COX, Perlegen Sciences, Mountain View, California
NANCY DUBLER, Montefiore Medical Center and The Albert Einstein College of Medicine, Bronx, New York
ROBERT GIBBONS, University of Illinois, Chicago
LYNN R. GOLDMAN, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland
BERNARD D. GOLDSTEIN, University of Pittsburgh, Pittsburgh, Pennsylvania
MARTHA N. HILL, Johns Hopkins University School of Nursing, Baltimore, Maryland
ALAN LESHNER, American Association for the Advancement of Science, Washington, D.C.
DANIEL MASYS, Vanderbilt University Medical Center, Nashville, Tennessee
JONATHAN D. MORENO, University of Virginia, Charlottesville
E. ALBERT REECE, University of Arkansas, Little Rock
MYRL WEINBERG, National Health Council, Washington, D.C.
MICHAEL J. WELCH, Washington University School of Medicine, St. Louis, Missouri
MARY WOOLLEY, Research!America, Alexandria, Virginia

Study Staff
ANDREW M. POPE, Study Director
AMY HAAS, Administrative Assistant
DAVID CODREA, Financial Associate
JANICE MEHLER, Editor
CORI VANCHIERI, Consultant

BOARD ON HEALTH SCIENCES POLICY*

PHILIP A. PIZZO (*Chair*), Stanford University School of Medicine, Stanford, California
LESLIE BENET, University of California, San Francisco
DAVID BLUMENTHAL, Harvard Medical School and Massachusetts General Hospital, Boston, Massachusetts
GAIL H. CASSELL, Eli Lilly and Company, Indianapolis, Indiana
ELLEN WRIGHT CLAYTON, Vanderbilt University Medical School, Nashville, Tennessee
DAVID R. COX, Perlegen Sciences, Mountain View, California
NANCY DUBLER, Montefiore Medical Center and The Albert Einstein College of Medicine, Bronx, New York
ROBERT GIBBONS, University of Illinois, Chicago
LYNN R. GOLDMAN, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland
BERNARD D. GOLDSTEIN, University of Pittsburgh, Pittsburgh, Pennsylvania
MARTHA N. HILL, Johns Hopkins University School of Nursing, Baltimore, Maryland
ALAN LESHNER, American Association for the Advancement of Science, Washington, D.C.
DANIEL MASYS, Vanderbilt University Medical Center, Nashville, Tennessee
JONATHAN D. MORENO, University of Virginia, Charlottesville
E. ALBERT REECE, University of Arkansas, Little Rock
MYRL WEINBERG, National Health Council, Washington, D.C.
MICHAEL J. WELCH, Washington University School of Medicine, St. Louis, Missouri
MARY WOOLLEY, Research!America, Alexandria, Virginia

IOM Staff
ANDREW M. POPE, Board Director
AMY HAAS, Board Assistant
DAVID CODREA, Financial Associate

*IOM Boards do not review or approve individual reports and are not asked to endorse conclusions and recommendations. The responsibility for the content of the report rests with the authoring committee and the institution.

Independent Report 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 National Research Council's (NRC's) Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report 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. We wish to thank the following individuals for their review of this report:

George Lundberg, Medscape General Medicine
Sherry Marts, Society for Women's Health Research
Harold Sox, *Annals of Internal Medicine*
Sharon Terry, Genetic Alliance
Alastair Wood, Vanderbilt University School of Medicine

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the final draft of the report before its release.

The review of this report was overseen by **Melvin Worth,** Scholar in Residence, Institute of Medicine and **Elaine Larson,** Columbia University School of Nursing. Appointed by the NRC and the Institute of Medicine, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully consid-

ered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Foreword

The Honorable John Porter
Partner, Hogan & Hartson, LLP

Keynote Presentation, June 27, 2005

What an exciting day this is for biomedical research and global health. This evening the Gates Foundation and the Foundation for the National Institutes of Health will announce its initial grants of approximately $450 million for research on diseases affecting people in the world's poorest countries. These Grand Challenges in Global Health grants carry the promise of transforming health in places long mired in poverty, disease, and early death. All of us, I believe, are anxious to see real progress toward improved health and productivity of the people in the developing world.

These grants should remind us that discovery alone is insufficient to improve human health. New pharmaceuticals, biologics, and devices must be tested for safety and efficacy, and clinical trials are the only way to translate from the laboratory to the health and well- being of individuals.

In a free and democratic society like ours, public support for biomedical research funding is vital and public trust in the integrity and the processes of discovery and translation is the *sine qua non* of public support. It might be argued that the only trust and support that are really necessary are those of policy makers—the Administration and Congress. But it is remarkable how well public trust in a free society is reflected in the trust of the public's elected representatives. Where the public trusts, their representatives generally also trust. Where the public lacks trust, so do their representatives. It works both ways.

The vote several weeks ago in the House of Representatives on stem cell research was extremely significant, whether the President ultimately vetoes new stem cell lines or not. It reminded leaders that the leash on departing from public opinion can be a short one and that public trust in science in our country is still strong. Likewise, the vote last week in the

House on funding for public broadcasting was a strong slap on the wrist for its detractors and a timely reminder of where in our media the public's trust most strongly resides. Elected representatives understand that they depart from where public trust lies at their peril.

Public trust in America is based on public perception. Sometimes that perception is grounded in knowledge and evidence, but sometimes it is not. Yet, in politics and public policy, perception—true or false—is the reality. If we are to ensure that the reality is grounded in truth, we must work to plant knowledge and evidence in the minds of both the public and their elected representatives.

Public perception is often formed through the lenses of the media. One example is the April 2002 cover of *Time* magazine. It showed a photo of a woman in a hospital gown inside a cage, with the headline that read "How Medical Testing Has Turned Millions of Us into Human Guinea Pigs." Although the pictures, the captions, and the headlines are often provocative and even untrue, the articles are often well written in language people can understand. But how many see only the pictures, the captions, and the headlines?

We are reminded how important it is to public perception—and therefore public trust and support—that we have science journalists who can translate the complexities of research into language that the lay reader can understand. These talents are vitally needed in a society with rapidly changing technologies. I wonder how many universities encourage study in this area and how much emphasis the scientific community places on urging the formal development of these important skills. Research!America is giving recognition to achievements in this area. How many other organizations give priority to this kind of recognition and encouragement?

Misperception is not the only factor that may undermine public trust in science. Research fraud, negligence or incompetence, lack of transparency, poor patient education, and lack of standards and patient protections in clinical trials can undermine public trust in the process of translating discovery to improved human health. Most significantly, the bad news always makes page 1. All we need to remind us of the danger to translational research is to say "Tuskegee." That episode more than 50 years ago continues to reverberate through the African-American community and to deter participation of African Americans in clinical trials today. Ask anyone involved in lupus or sickle cell research of the difficulties they encounter, and then ask yourself how important public trust is to the success and support of biomedical research and clinical trials.

Names like Enron, WorldCom, Tyco, ImClone—although not all related to research—remind us how fraud and corporate abuse undermine support for markets that depend on public confidence in the data regarding investments. Their lapses led to vast new government regulations deemed necessary to protect the integrity of our free enterprise economic system. In addition, thinking of the CIA or of the abuses of some by Catholic clergy and what those events have meant to those two institutions should reinforce the importance of public trust to the work of science.

It is significant that the strategic direction of our nation's largest federal medical health research agency, the National Institutes of Health (NIH), not only acknowledges the importance of public trust and support, but has identified strategies to build on both. Director Elias Zerhouni's NIH Roadmap Initiative demonstrates an understanding of the importance of cultivating public engagement in research as well as the necessity of policy-maker support in sustaining our national investment. The NIH Roadmap is particularly noteworthy because it identifies "reengineering of the clinical research enterprise" as one of its three central themes.

Dr. Zerhouni has shown great leadership in identifying the need for more rapid translation. He also recognizes that without public trust and participation, acceleration in the pace of discoveries in the life sciences simply will not be achieved.

On June 21, 2005, *The Wall Street Journal* ran a front-page article on a new NIH program designed to bridge the gap between academic research and development in industry. This program has been designed to entice private companies to invest in higher risk research by offering to pay for and carry out early clinical trials of experimental drugs. The NIH project has begun with an invitation to drug makers to participate in a clinical trial network that would clear away some of the cost and risk of drug development for the companies while providing access to top government and academic scientists. This program explores and tests creative approaches that serve the public interest and thus helps to build public trust. The public expects and supports collaboration among industry, academia, and government—91 percent of respondents in a recent Research!America poll said exactly that.

Clearly, we have moved a long way from support for the research enterprise, which alone was once a sufficient appeal to policy makers, to the health and health care of the American people. Yes, we still can and do argue that we must maintain U.S. technological leadership; that we

must meet the competition emerging from China and India and, increasingly, from Europe; and that investment in biomedical research is a major driver of our country's economic growth.

But the bottom line, the reason why accountability is stressed and why clinical trials are so important, is policy makers' connection with and concern for the health and well-being of the American people.

This is what drives support for research today and why the clinical trial process that is transparent, understood, and protective of the enrolled patient, and produces evidence with a high degree of confidence in its accuracy, is so important to the public trust. Development of a publicly accessible comprehensive clinical trial registry, it seems to me, would be a key component—but not the sole component—of efforts to build public trust in clinical research.

This public trust will also require programs to ensure that the public understands what clinical research is; knows what is being done and why; understands what the risks and benefits are when participating in clinical trials; believes in and trusts the research institutions as well as the researchers themselves; and knows where to go, what to do, and how to do it to be an effective advocate for clinical research.

Science, our educational system, and the media have, quite frankly, not done a very good job of educating the people and their representatives on the basics of science, on how research is conducted in the laboratory today, on the exciting blending of many disciplines working together toward discovery, on the need to continue research and development of the tools produced by the physical sciences that are vital to further life science advances, and on the absolute need for clinical trials to test discovery and protect the public at large.

Research!America polling shows—uniformly across all jurisdictions—that the majority of the American people cannot name one place where research is conducted in the United States. The same probably would have been true of the U.S. Congress 10 years ago, but we can be proud that we have made some progress there. But much remains to be done.

If public support depends on public trust, if public trust depends on public perception, and if public perception depends on truth and knowledge, scientists need to share their understanding, their passion, and their exciting research with the public. They need to work closely with science journalists, with policy makers, and with the people in their communities.

If each one will do only a little more, I believe more young people in America will be inspired to pursue careers in science and research, the

public perception of science will be strengthened, and public support will increase for investments in research and the clinical trials necessary to protect and improve human health.

At the base of it all is public trust.

Preface

Medical journal editors, the pharmaceutical industry, and the World Health Organization have all proposed some form of clinical trial registry for drugs and biologics. Other organizations, including the American Medical Association and the Association of American Medical Colleges, have supported the creation of a registry. These proposals have several features in common, such as public accessibility, broad inclusion of clinical trials, and most of the key data elements. However, so far the parties have disagreed as to inclusion of other elements such as trial results and have not determined the mechanisms for implementation and compliance. To help make progress on this issue, the Institute of Medicine's (IOM's) Board on Health Sciences Policy (HSP) of the National Academies hosted discussions among interested parties, leading to this report.

On December 1, 2004, HSP invited leaders from several of the major constituencies to discuss areas of common ground and unresolved issues (see Appendix A for participants). Following that meeting, the Board formed a committee, some of whose members held additional discussions with journal editors and pharmaceutical and biotech leaders about the merits and importance of specific elements to be included in a workable clinical trial registry for drugs and biologics.

The IOM committee posted background material regarding these issues on its website prior to convening a workshop on June 27, 2005, in Washington, D.C. The 150 workshop participants included public advocate groups, medical journal editors, pharmaceutical representatives, government representatives, and others (see Appendix B for the agenda, speakers, and participants).

This report summarizes the views expressed by workshop participants and includes background information to provide the context

for workshop discussion based on the committee's planning work. It includes information and perspectives gathered prior to and at the workshop, describing progress made toward a national registry for clinical trials and points for further consideration. Chapter 1 is a summary of the issues surrounding creation of a clinical trial registry and the contributions of this project. Chapter 2 describes the importance of a national clinical trial registry, drawing together views expressed throughout this project. Chapter 3 describes diverse perspectives and activities toward creating a national clinical trial registry. Chapter 4, describing potential elements of a registry, intersperses background material with comments made by workshop participants. Chapter 5, on implementation issues, also includes background material interspersed with comments made by participants.

Although the Committee on Clinical Trial Registries is responsible for the overall quality and accuracy of the report as a record of what transpired at the workshop, the views contained in this report are not necessarily those of the committee. The purpose of the workshop and the resulting report is to continue to elicit broad input to inform future efforts to build a clinical trial registry that supports the public health.

Philip Pizzo, Chair
Committee on Clinical
Trial Registries

Contents

List of Tables

1

Summary

To improve public confidence in clinical research, a number of public and private groups have called for a publicly accessible, comprehensive, and transparent registry of relevant information on clinical trials for drugs and biologics. The public and various entities within the medical community (health care providers, researchers, medical journal editors, pharmaceutical companies, health insurers, and regulators) have different expectations and perceived needs regarding a public clinical trial registry.

In December 2004, after the International Committee of Medical Journal Editors (ICMJE) published its requirements for clinical trial registration, the Institute of Medicine (IOM) Board on Health Sciences Policy invited medical journal editors, pharmaceutical and biotech industry leaders, and representatives from the National Institutes of Health (NIH) and Food and Drug Administration (FDA) to discuss public access to biomedical and clinical research data. Following that meeting, the IOM appointed a committee whose members held further discussions with medical journal editors and pharmaceutical and biotech industry leaders regarding possible components and mechanisms for implementation of a clinical trial registry that would meet the public's need for disclosure while supporting innovation in development of new therapeutics. Based on those discussions, the following goals were suggested for a central registry:

1. To provide patients and their health care providers with adequate and reliable information about clinical trials that may be enrolling patients.

2. To provide health care providers, patients, and others with the results of a clinical trial once the trial is completed and the product is available for prescription.
3. To link each clinical trial initiated with a reported outcome, thereby preventing selective or biased reporting of results.
4. To meet the first three goals in a way that protects proprietary research data, as necessary, and preserves innovation.

The committee's discussions also suggested that the next steps toward implementing a registry that accomplishes these goals would likely include the following:

- Identification of uniform standards for data disclosure—both at trial inception and for completed trials—that apply to all entities conducting human clinical trials, whether privately or publicly funded.
- Creation of a process that balances the interest in protecting confidential and proprietary research data with the need to allow the broadest access possible to clinical trial information.
- Creation of a mechanism to ensure compliance, with associated consequences for noncompliance.
- Assignment of responsibilities for developing and managing the registry to a nonprofit organization or trusted government agency, such as the National Library of Medicine (NLM).

The IOM Committee on Clinical Trial Registries hosted a workshop on June 27, 2005, to obtain much-needed input from members of the public, public advocate groups, and the broader community of journal editors, pharmaceutical and biotech leaders, NIH, and the FDA. Participants discussed the data elements that have been at the core of debate and commented on issues of compliance and implementation of a national clinical trial registry.

Most of the possible content fields for a clinical trial registry are not being debated. The discussions at the workshop centered on the following five concepts:

- The purposes of a registry.
- Inclusion or exclusion of exploratory trials.
- The need for a delayed disclosure mechanism for certain fields in the registry at the time of trial initiation (hypothesis statement,

primary and secondary outcome measures, and projected year of trial completion).

- The timing and format for reporting results of completed trials.
- The appropriate roles for Institutional Review Boards, the FDA, and others in ensuring compliance.

Questions remained at the end of the workshop, but activities toward implementing and expanding clinical trial registration have continued. Since September 2005, any trial beginning after July 1, 2005, must have registered before enrolling the first patient. Any trial that began before that date must have been registered prior to submitting the article to one of the ICMJE journals. The international pharmaceutical industry working withNLM has begun registering all but exploratory clinical trials on ClinicalTrials.gov, and providing the results of clinical trials on marketed products on ClinicalStudyResults.gov, an Internet database launched September 2004 by the Pharmaceutical Research and Manufacturers of America. The World Health Organization has finalized its position on global clinical trial registration and convened a group to develop a mechanism for advising on requests to delay release of one or more data items until a specified date.

2

The Need for Clinical Trial Registries

WIDESPREAD AGREEMENT THAT SOME FORM OF REGISTRY IS NEEDED

Clinical trial registries have four potential functions: (1) list and track the status of clinical trials, (2) provide information for patient recruitment, (3) provide a complete record of all trials to aid in doing systematic reviews of the evidence, and (4) report results of the trials. This information has many audiences: patients, health care providers, researchers, medical journal editors, pharmaceutical companies, health insurers, and regulators. These audiences have differing needs for data and for translation of information contained in the registry; however, they all have needs that are not adequately met by other sources.

Selective publication of clinical trial data does not provide a complete picture. Both advertently and inadvertently, there is an understandable bias toward disclosure of favorable results, commonly known as the "file drawer phenomenon." The pharmaceutical industry does not have a compelling reason to publish the results of clinical trials that do not support the introduction of new products. Researchers and journal editors are generally more enthusiastic about publishing positive results than negative results. When the results are inconclusive, there is much less interest in peer-reviewed publication. For both safety and efficacy data, outcomes are more likely to be reported if there are statistically significant differences.

A recent empirical study found that 62 percent of 82 publicly and privately funded randomized controlled trials had major discrepancies between the primary outcomes specified in the protocols and those reported (Chan et al., 2004). Reports may also appear without acknowledgment that they are one of a larger corpus of evidence and that other

similarly designed trials with the same agents may have drawn different conclusions.

Usually a body of evidence, rather than a single trial, is required to influence the thinking of clinicians, researchers, patients, and medical policy experts. This body of evidence, in fact, forms the basis of regulatory review and approval of pharmaceutical products. Responsible decision making requires awareness of both positive and negative clinical trial results, along with confidence that the findings are available and accessible.

Accordingly, key stakeholders in the medical community have suggested that if clinical trials were registered in a systematic fashion at their inception, followed by the posting of summary results for the study, and both were easily accessible to interested parties, then the full range of clinical evidence surrounding an investigative therapy would become part of the public record. In addition, once a drug has been approved, the registry provides a complete record that can serve as input for decisions by guideline developers, insurers, and those who monitor quality of care in the United States.

DIVERSE EXPECTATIONS AND PERCEIVED NEEDS

The public and various entities within the medical community have different expectations and perceived needs regarding a public clinical trial registry:

- **Individuals suffering from various diseases**, and their family members, want to know that appropriate therapies are being offered and that patient safety is being secured. In addition, more and more patients today want the ability to search on their own for research that pertains to their disease and potentially to enroll in a clinical trial if suitable.
- **Health care professionals** need both unbiased summary information derived from all trials conducted on a drug or therapy, and the capacity to look at the clinical data from any single study. They do not want to confine their review to the approved drug labeling or articles published in medical journals.

- **Researchers** may generate new ideas for investigations or look for data trends by accessing all the trials conducted on a drug or therapy.
- **Medical journals** have an enormous impact on clinical practice and medical policy. When journal editors receive clinical trial manuscripts for publication, they are concerned that they fully understand the research. They want to know if clinical trials exist that may conflict with the submitted manuscript. Furthermore, they want to know if the authors failed to follow the original research plan because discrepancies may reflect serious defects in the research. Indeed, the integrity of the journal is at stake, as is the entire scientific enterprise, when research is published through the peer-review process.
- **Regulators** would find the information in a registry useful in developing policies regarding clinical research.
- **Health insurers** want to keep abreast of evidence-based results as the basis for insurance coverage policy.
- **Sponsors of research** who are developing a new therapy or drug incur great expense. Some of the information is highly proprietary and confidential to the parties who sponsor research. Industry is concerned that if all proprietary information were required to be made broadly available to the public at the outset of clinical trials, then they could not recoup their investment because competitors in the United States or abroad copied their innovations. At the same time, they recognize their responsibility to do everything possible to assure patient safety and to secure the public trust.

In striking a balance among these competing interests regarding the scope of clinical trial registries, an overriding goal is to sustain public trust in the integrity of clinical research and in the process for translating research into new drugs and biologics.

3

Current Registry Activities

CLINICALTRIALS.GOV: CURRENT CLINICAL TRIAL DISCLOSURE REQUIREMENTS

All entities that conduct clinical trial research on drugs that may be marketed in the United States are required by law to disclose the clinical research data pertaining to the development of that product to the U.S. Food and Drug Administration (FDA) in order to file a New Drug Application or Biological License Application. Before any compound may be given to humans, several factors must be reviewed and approved by the FDA: the hypothesis being tested, details of the research protocol including primary and secondary endpoints, and the biologic and chemical properties of the compound. The FDA continues to review a drug's development, authorize its continuation or not, and ultimately approve its use in humans—a process that takes an average of 10 years.

Since February 2000, all entities (whether federally or privately funded) conducting clinical trials of experimental treatments (drugs or biologics) for serious or life-threatening diseases and conditions have been required to submit certain information to the public clinical trial registry ClinicalTrials.gov. This registry was established by the Department of Health and Human Services' (DHHS's) National Library of Medicine as a result of Section 113 of the FDA Modernization Act of 1997 (see Appendix C). ClinicalTrials.gov was established to allow patients, health care providers, and researchers to explore options for or enroll in relevant clinical trials.

Table 3-1 shows the information as currently defined that must be submitted to ClinicalTrials.gov within 21 days of first patient enrollment for all clinical trials involving serious and life-threatening diseases and conditions.

TABLE 3-1 Required Data Fields for the DHHS Clinical Trial Registry at ClinicalTrials.gov

Unique Protocol ID Number	Study Sponsor
Verification Date	Brief Title (in lay language)
Brief Summary (in lay language)	Study Design, Study Phase, Study Type
Condition or Disease	Intervention
Study Status	Eligibility Criteria/Gender/Age
Location of Trial	Contact Information

Although ClinicalTrials.gov has been a valuable tool to enable patients and health care providers to understand the research occurring in various therapeutic areas and to locate clinical trials in which to enroll, it has certain limitations within its legislative mandate:

- It applies only to serious and life-threatening conditions.
- There is no mechanism to ensure compliance by all entities performing clinical trials.
- It does not include disclosure of study results.
- Required data fields are not always completed in an informative manner.

For these reasons, several groups have called for the *mandatory* registration of additional clinical trials as well as the registration of more extensive clinical trial information and the posting of a summary of clinical trial results. In addition, a number of clinical trial registries have been created in the public sector and by several pharmaceutical companies. The most prominent, and probably influential, proposals for registry requirements—by the International Committee of Medical Journal Editors (ICMJE), the international pharmaceutical industry and, most recently, the World Health Organization (WHO)—were presented at the workshop and are described below.

INTERNATIONAL COMMITTEE OF MEDICAL JOURNAL EDITORS

Harold Sox, Editor of *Annals of Internal Medicine*, gave a presentation on steps taken by the editors of 13 major international medical journals to promote clinical trial registration. In a joint statement entitled "Clinical Trial Registration: A Statement from the International Committee of Medical Journal Editors" that was published concurrently in their journals in September 2004 (see Appendix D), the editors announced that their journals would require registration of a clinical trial as a condition of consideration for publication beginning July 1, 2005. In an editorial (also in Appendix D) published on June 9, 2005, the ICMJE reiterated its position and endorsed the new proposal by WHO (see below), which has similar elements.

Specifically, the editors called for the registration of trials at or before the onset of patient enrollment. The ICMJE defines a clinical trial as "any research project that prospectively assigns human subjects to intervention and has at least one prospectively assigned concurrent control or comparison group to study the cause-and-effect relationship between an intervention designed to modify a health outcome and the health outcome." Studies designed for other purposes, such as to study pharmacokinetics or major toxicity (i.e., Phase I trials), would be exempt. The ICMJE policy does not require reporting of clinical trial results. Table 3-2 lists the specific data fields required by the ICMJE.

TABLE 3-2 Data Fields Required by the ICMJE as a Condition of Publication

1. Unique Trial Number	11. Research Ethics Review
2. Trial Registration Date	12. Condition
3. Secondary IDs	13. Intervention(s)
4. Funding Source(s)	14. Key Inclusion and Exclusion Criteria
5. Primary Sponsor(s)	15. Study Type
6. Secondary Sponsor(s)	16. Anticipated Trial Start Date
7. Responsible Contact Person	17. Target Sample Size
8. Research Contact Person	18. Recruitment Status
9. Title of the Study	19. Primary Outcome
10. Official Scientific Title of the Study	20. Key Secondary Outcomes

JOINT PHARMACEUTICAL INDUSTRY POSITION

In describing the joint position published by the international pharmaceutical industry, Dr. Alan Breier, Vice President, Medical and Chief Medical Officer, Eli Lilly and Company, noted that the U.S. pharmaceutical industry had been considering guidelines for registries before the international position was adopted. In October 2002, the Pharmaceutical Research and Manufacturers of America (PhRMA) developed a voluntary set of principles to communicate the guidelines by which the pharmaceutical industry would conduct clinical trials and how results would be communicated. These principles were revised in June 2004.

In January 2005, the international pharmaceutical industry, represented by the European Federation of Pharmaceutical Industries and Associations (EFPIA), the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), the Japanese Pharmaceutical Manufacturers Association (JPMA), and PhRMA, released a consensus global policy entitled "Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases" (see Appendix E). This joint position was developed, in part, in response to the requirements set forth by the ICMJE.

The Joint Position of the pharmaceutical industry calls for expansion of the existing DHHS clinical trial registry, ClinicalTrials.gov, to include the ICJME-required information (see Table 3-2) not just for serious and life-threatening conditions, but for all studies except exploratory studies, when a trial is initiated. Registration would occur within 21 days of the initiation of patient enrollment.

To reduce occurrence of "the file drawer phenomenon," the joint pharmaceutical industry position also committed to make the following outcomes information available on a public registry:

- The results of all clinical trials, other than exploratory trials, conducted on a drug that is approved for marketing and is commercially available in at least one country will be registered, regardless of outcome.
- If trial results for an investigational product that has failed in development have significant medical importance, sponsors will post if possible.
- If trial results are published in a peer-reviewed medical journal, the database will include a citation or link to the journal article and/or a summary of the results in a standard, nonpromotional

format, such as the ICH E3 summary format (see Appendix F), that includes a description of the trial design and methodology, results of the primary and secondary outcome measures, and safety results.

Differences between the published positions of the ICMJE and the pharmaceutical industry (e.g., when to report primary and secondary outcome measures) offered further evidence of the need to reach some consensus or conciliation of expectations and wishes regarding clinical registries and clinical trial reporting.

THE WORLD HEALTH ORGANIZATION PROJECT

As the IOM was carrying out its discussions, WHO began work to set standards for a global clinical trial registry platform that would act as an umbrella for existing national registries. At the June 27 IOM workshop, a WHO representative presented the international position on clinical trial registration developed in April 2005 by global representatives of the medical journals, academia, public health, regulatory arena, the Cochrane Collaboration, and the pharmaceutical industry. The WHO registry position calls for registration of "any research project that prospectively assigns human participants or groups to one or more health-related interventions to evaluate the effects on health outcomes." It excludes exploratory studies that are not designed to influence health practice and that serve only to set direction for future testing.

The stakeholders convened by WHO agreed on a set of 20 data items that should be included with each registered trial. After soliciting public comments, WHO issued, in October 2005, a revised list of data items for what they call the International Clinical Trials Registry Platform. Both versions are shown in Table 3-3.

According to the June 27 presentation by WHO scientist Metin Gulmezoglu, the registry project has five objectives:

- Provide standards for trial registration and results disclosure
- Launch a linked network of certified registers with global search capability and unique numbering system
- Advocate for compliance with registry requirements
- Advise and help build registry capacity
- Establish a self-funded business model by 2006

TABLE 3-3 WHO Minimum Data Set

Item #	Original (April 2005)	Version 2.2 (October 21, 2005)
1	Unique Trial Number	Primary Register and Trial ID
2	Trial Registration Date	Date of Registration in Primary Register
3	Secondary IDs	Secondary IDs
4	Funding Source(s)	Funding Source(s)
5	Primary Sponsor	Primary Sponsor
6	Secondary Sponsor(s)	Secondary Sponsor(s)
7	Responsible Contact Person	Responsible Contact Person
8	Research Contact Person	Research Contact Person
9	Title of the Study	Public Title
10	Official Scientific Title of the Study	Scientific Title
11	Research Ethics Review	Research Ethics Review
12	Condition	Disease or Condition Studied
13	Intervention(s)	Intervention(s)
14	Key Inclusion and Exclusion Criteria	Key Inclusion and Exclusion Criteria
15	Study Type	Study Type
16	Anticipated Trial Start Date	Date of First Enrollment
17	Target Sample Size	Target Sample Size
18	Recruitment Status	Recruitment Status at Time of UTRN [Universal Trial Reference Number] Request
19	Primary Outcome	Primary Outcome(s)
20	Key Secondary Outcomes	Secondary Outcomes

*WHO identified Data Items 10, 13, 17, 19, and 20 as ones for which a sponsor might wish to delay release of the information. WHO plans to convene a group to develop a mechanism to advise on requests to delay release of one or more data items until a specified date.

Local registries would be certified by a central office against certain specifications. Dr. Gulmezoglu expects that national registries, disease-based registries, and other certified registries would join. Local registries could be created in local languages, but the minimum data set information would be transmitted to the central registry in English. The registry would have a search function within a minimum data set. Results would be linked when a trial is completed. WHO plans to provide training and capacity building for national initiatives and for the pharmaceutical industry.

FEDERAL AND STATE LEGISLATION

The need for a publicly accessible clinical trial registry has become a legislative focus. At the federal level, three different Fair Access to Clinical Trial Information (FACT) Acts have been introduced in the House and Senate. At the state level, 55 bills have been introduced in 20 states calling for the registration of clinical trial information. However, state-by-state legislation on this topic would become a significant hurdle for drug development because many clinical trials involve patients in numerous states.

Kate Reinhalter, Legislative Assistant in Rep. Edward Markey's [D-MA] office, stated that federal legislation is necessary to ensure uniform standards and compliance. She described some points from a bill that Reps. Markey and Rep. Henry Waxman [D-CA] have since introduced as the most recent FACT Act (H.R. 3196) (see http://thomas.loc.gov/homr/gpoxmic109/h3196_ih.xml). The bill would create a database that expands on ClinicalTrials.gov. Sponsors of privately and publicly funded clinical trials would be required to provide public access to basic information on studies before they begin and to provide public access to the results of clinical studies, including primary and secondary outcomes and significant adverse events. It would also create penalties for noncompliance.

SUMMARY OF FEATURES OF CURRENT AND PROPOSED REGISTRIES

The narratives above show there are many similarities and few points of contention among the groups that have proposed or endorsed the establishment of a national clinical trial registry. Table 3-4 summarizes their positions on information posted at initiation of the trial, information posted when the trial is complete, and compliance.

TABLE 3-4 Comparison of Registry/Disclosure Policies

Organization/ Sponsor	Registry: Trials Posted When Initiated		Results Database: Information Posted When Trial Completed			How Co Verified
	Trial Phase	**Information Posted**	**Trial Phase**	**Format**	**Product Scope**	
ICMJE	Clinical trials testing cause and effect. Excludes Phase I. Some Phase II determined case by case by journal editor.	Same as the WHO minimal data set of 20 items (see below).	N/A	N/A	Any product for which publication is desired.	Will cons for publi if it is reg before en of first pa by 9/13/(
PhRMA	All hypotheses-testing clinical trials will be posted at initiation to the registry, www.ClinicalTrials.gov.	Provide information consistent with www.ClinicalTrials.gov: Brief title, trial description, trial phase, trial type, trial status, trial purpose, intervention type, condition or disease, key eligibility criteria, location of trial, and contact information.	Hypothesis-testing clinical trial results posted to www.ClinicalStudyRe-sults.org.	Reference citation unless results on marketed product have not been published; then provide a clinical trial summary.	Product marketed or intended for marketing in United States.	Posting is tary. Reg policy sta "Member establish of verific make pub they adhe standards
Joint Position of the Pharmaceutical Industry	All clinical trials except exploratory to www.ClinicalTrials.gov.	Provide information consistent with www.ClinicalTrials.gov: Brief title, trial description, trial phase, trial type, trial status, trial purpose, intervention type, condition or disease, key eligibility criteria, location of trial, and contact information.	All clinical trials except exploratory posted to a publicly accessible database.	Clinical trial summary **AND/OR** reference citation.	Product marketed anywhere in the world.	Compani establish of verific make pub they adhe standards

Fair Access to Clinical Trials Act **Rep. Waxman with 36 cosponsors—H.R. 3196**	Excludes trials designed to detect major toxicity and pharmacokinetics (except in special populations).	Primary and secondary endpoints, eligibility criteria, trial dates, number of subjects, and Principal Investigator information. Medical condition; scientific title with name of intervention, condition, and outcome under study; ethics review; start date; purpose; eligibility criteria; funding source; statement that product is unapproved or approved but investigated for what use; completion date; primary and secondary outcomes; hypothesis being tested; total subjects; contact information; study design; methods; phase; type; note of any restrictions on results discussion; periodic updates.	All clinical trials except those designed to detect major toxicity and pharmacokinetics (except in special populations).	Structured abstract determined by (Q: DHHS?) Secretary. Results will include: primary and secondary outcomes presented as quantitative data, AE data, demographic data, and trial dates.	All products, approved or unapproved.	Secretary audit; pos initiation for IRB a Civil mo penalties, notificati noncomp
World Health Organization (from WHO website, http://www.who.int/ictrp/results/en/, accessed 10/21/05)	Excludes exploratory studies.	Trial ID number, date of registration, secondary ID numbers, funding sources, primary sponsor, secondary sponsor, contact persons, public title, scientific title,* research ethics review, condition studied, intervention(s),* inclusion/exclusion criteria, study type, date of first enrollment, target sample size,* recruitment status at time of Universal Trial Reference Number request, primary* and secondary* outcomes.	Registers are encouraged but not required to provide links to trial results. "Results reporting remains a top concern of the Registry Platform and will be addressed in more detail starting in mid-2006."	At least as much detail as ICH–E3 format.	Products marketed anywhere in the world as well as products in development.	WHO wi for comp

* Delayed reporting may be considered for these items.

4

Content of a Clinical Trial Registry

This chapter describes the guiding principles for clinical trial registration and the key fields in a registry. For each topic, background material is followed by comments made by some of the speakers and participants at the June 27 workshop.

GUIDING PRINCIPLES AND GOALS FOR CLINICAL TRIAL REGISTRIES

Based on the premise that registries must provide the public with sufficient information to provide public health and safety benefits, the committee's initial discussions suggested that the following guiding principles were desirable for a clinical trial registry:

- Be global in perspective.
- Offer access to the public at no charge.
- Be located on a single website or linked via a single portal.
- Be open to all prospective registrants.
- Be managed by a not-for-profit organization or trusted government agency.
- Have the capacity for electronic searches.
- Provide a mechanism to ensure the validity of the registration data.
- Have a process to ensure adherence to the registry standards.
- Avoid reducing the incentive to do clinical research, whether public or privately funded.

A clinical trial registry that follows these principles could be expected to meet the following goals:

1. To provide patients and their health care providers with adequate and reliable information about clinical trials that may be enrolling patients.
2. To provide health care providers, patients, and others with the results of a clinical trial once the trial is completed and the product is available for prescription.
3. To link each clinical trial initiated with a reported outcome, thereby preventing selective or biased reporting of results.
4. To meet the first three goals in a way that protects proprietary research data, as necessary, and preserves innovation.

However, a clinical trial registry is NOT intended to replace the advice of a health care professional regarding benefits and risks nor is it intended to replace the comprehensive information on a product label as required by the relevant regulatory authorities. It is also not intended to replace peer-reviewed publication—although the veracity of journal publications could be better assured by the presence of a transparent and more comprehensive mandatory clinical trial registry. Furthermore, to meet its purposes, a registry should provide only objective, scientific information about the clinical trial and not promote a product.

Comments on Guiding Principles and Goals for Clinical Trial Registries

Marjorie Speers, Executive Director of the Association for the Accreditation of Human Research Protection Programs, began her workshop presentation about the needs of patients and the public by stating that, in the debate over registries, the purposes of such registries have been blurred. Are they intended merely to inform the public about an ongoing or proposed clinical trial? Are they intended to be vehicles to recruit individuals into clinical trials? Are they intended to assist physicians in treating patients? Are they intended to prevent the suppression of negative results? Are they intended to build the public's trust in clinical trials? All of these purposes have been expressed at one time or another.

Alan Breier, Vice President, Medical and Chief Medical Officer, Eli Lilly and Company, suggested that different platforms might be needed

to address the different purposes. He suggested that using a clinical trial registry as an enrollment tool is a separate aim that should be addressed elsewhere. Eli Lilly's patient surveys indicate that people considering or enrolling in a clinical trial want to ask questions and engage in discussion with a live person.

Jerome Yates, representing the American Cancer Society, stated that 90 percent of patients who query a clinical trials source need follow-up answers to their queries. Could the patient advocate community help to answer questions?

Dr. Speers agreed there should be some type of help function for those who require assistance and some type of consultation service when the public has questions about a particular study.

Alan Goldhammer, Associate Vice President, U.S. Regulatory Affairs, Pharmaceutical Research and Manufacturers of America (PhRMA), submitted this comment to the Institute of Medicine (IOM) website: "PhRMA supports the four goals that IOM has identified regarding the establishment and use of clinical trial registries….The WHO [World Health Organization] document notes that '…one or more of data items 10, 13, 17, 19, 20 may be regarded as sensitive for competitive reasons by the sponsor who may wish to delay release of the information.'" He asked that this key point—"the need for confidentiality to preserve innovation"—be highlighted in the final IOM summary.

Jeanne Ireland, Elizabeth Glaser Pediatric AIDS Foundation, commented that "only a mandatory system with a breadth of information will improve the public trust."

Catherine De Angelis, Editor-in-Chief of the *Journal of the American Medical Association*, noted that three things must happen with a clinical trial registry: (1) It must be managed by a nonprofit organization; (2) it must be able to support pertinent information; and (3) it must be available to anyone freely.

Dr. Breier echoed those sentiments, stating that such a registry needs to be global, free, and publicly accessible. "A clinical trial done in Russia can be just as important to patients in the United States and vice versa—everybody counts. We live in a global world so having a global approach to this becomes also critical or we have significant gaps." He expressed concern that writing summaries in patient-friendly language may edge the summaries toward being viewed as promotional.

Michael Manganiello, representing the National Institutes of Health's (NIH's) Council of Public Representatives, asked if there would be an education campaign to help the registry reach its intended users.

Sharon Terry, Genetic Alliance, asked what kind of education campaign would be tied into the development of a new registry. How could the tremendous number of patient groups with expertise and branches in various states, plus provider groups, be tied in so that people are aware of what the registry is and use it themselves or for their patients?

Hugh Tilson, Centers for Education and Research on Therapeutics, described the development of a clinical trial registry as a "huge social intervention, which therefore requires proper evaluation," including cost-effectiveness analysis. Any registry approach developed needs to be pilot tested. He also suggested research to determine what the stakeholders want and what the impact on patient and other stakeholder behaviors and public health will be. He called for research on how to summarize a body of data and suggested that a new education agenda would include how doctors can communicate about the entire, evolving body of research, and how to educate the media.

P. Pearl O'Rourke, Director of Human Research Affairs, Partners HealthCare System, Inc., noted that a trial is an active and alive entity, and raised questions about how the registry would incorporate planned and unplanned changes. Sometimes preliminary findings indicate a need for changes in the study design, she noted, and amendments are added and adverse events occur. "How are we going to accurately place these details into a registry? For example, my interest in enrolling in a trial may well be altered if 15 of the last 17 people had a big adverse event. How will early termination be handled? Particularly if it was terminated because of scientific misconduct, how are you going to document that in a registry?"

Robert Temple, Director of the Office of Medical Policy in the Center for Drug Evaluation and Research, Food and Drug Administration (FDA), asked: "Do we mean for this to include trials that are poorly designed and ill controlled? We see trials all the time in which people on one drug are just switched to another drug, and FDA's Division of Drug Marketing, Advertising, and Communications sends out scads of letters saying that's no good, that's not an adequate study. Do we want all those in there? I wouldn't think so."

TRIALS TO BE REGISTERED

The International Conference on Harmonization differentiates exploratory trials from hypothesis-testing or confirmatory clinical trials as follows: Hypothesis-testing (confirmatory) clinical trials are well-controlled studies designed to provide meaningful results by examining prestated questions (hypotheses) using predefined statistically valid plans for data analysis, allowing solid conclusions to be drawn to support specific product claims. Pilot or exploratory studies are, by design, intended to provide preliminary information about a disease or condition, endpoints that might be measured to evaluate treatment efficacy, the profile of a possible new treatment, etc. These studies are performed to generate hypotheses and aid decision making for possible future product development.

According to these definitions, some of Phase II and all of Phase III (registration) and Phase IV (post-marketing) would be considered hypothesis testing (confirmatory). In discussing which clinical trials should be included in a registry, the workshop participants gave particular attention to the subset of Phase II studies that are deemed "exploratory."

The three main proposals—those of the International Committee of Medical Journal Editors (ICMJE), the international pharmaceutical industry, and WHO—are broader than the requirement for ClinicalTrials.gov, which calls for posting of trials regarding serious and life-threatening conditions. These groups would require registration of all prospective, hypothesis-driven, interventional clinical trials (i.e., all confirmatory trials, not just those for serious or life-threatening illnesses and conditions) upon trial initiation. They all exclude Phase I trials.

Comments on Trials to Be Registered

Committee Chair Philip A. Pizzo and Sharon Terry, President and Chief Executive Officer (CEO) of the Genetic Alliance, a patient advocate group, called for inclusion of exploratory trials in registries, expressing concern that exploratory studies will be increasingly used to test hypotheses. As patient selection uses more sophisticated genetic profiling, the potential exists that smaller exploratory studies may cross the line into hypothesis testing. Miriam O'Day, Senior Director of Public Policy at the Alpha-1 Foundation, a patient advocate group, made a simi-

lar point, noting that exploratory studies may be especially important for genetic studies.

Dr. Temple also suggested that some trials considered "exploratory" be included. Phase II trials are well-designed trials for the most part. "They may have multiple hypotheses and be exploratory in that sense, but they're often used as part of the critical database."

William Vaughan sent a statement from Consumers Union to the IOM website: "It is essential that the goals, specifications, and endpoints of clinical trials be registered and made public." He added, "Though in some cases it may not be necessary to register and disclose results from Phase I and some Phase II trials, we urge the Institute to err on the side of more public information, not less."

Industry representatives expressed concern that early exploratory studies should not be included for the following reasons:

- Early exploratory trials are designed only to set direction (i.e., to generate hypotheses) for possible future studies; they are not designed to provide definitive or confirmatory answers of safety or efficacy of drugs under development.
- Approximately 90 percent of compounds in exploratory trials fail in development.
- In many cases, exploratory trials involve small numbers of healthy volunteers and are of short duration; posting this information could leave patients with the misperception that more clinical trials are available for enrollment than in actuality.

Dr. Speers called for including "at least advanced Phase II trials."

Dr. O'Rourke, noting the differences between Phase I and Phase IV trials and the desirability of a comprehensive registry, suggested requiring different data points for these different phases. Phases III and IV would have robust information, while Phase I might provide a more general description.

"We should err on the side of inclusivity and register all trials, including exploratory Phase II trials," stated Alfred Sandrock, Vice President of Medical Research-Neurology at Biogen Idec, Inc. He also suggested that the registry do its best to capture trials in the post-marketing setting, that is, the Phase IV trials. The FDA may not be fully aware of some of these trials, and some of the results may be hidden. He noted, however, that these personal views are shared by Burt Adelman, Executive Vice President of Development at Biogen Idec, Inc., but are

not entirely consistent with those of the Biotechnology Industry Organization (BIO). BIO has endorsed the concept of a clinical trial registry for marketed products, but has not supported a requirement for registering clinical trials involving drugs that are not available for commercial use.

Specifically, James C. Mullen, President and CEO of Biogen Idec and chairman of the BIO Board of Directors, sent these comments:

> We support disclosure of all clinical trial information and results for marketed products. We believe that this is consistent with public health needs. For unapproved products we do not believe it is necessary to disclose trial information and results. Whilst some argue that these trials should be equally transparent, the public health argument is not as compelling when contrasted with the likelihood of introducing more information noise into the lay press and public and publicizing company know-how, strategies, and confidential information.

On Eli Lilly's clinical trial registry (Lillytrials.com), summaries of all the studies on the marketed drugs—Phases I through IV—are posted when the drug becomes available, so that every clinical trial conducted on a drug that goes to market will be posted, according to Dr. Breier.

Harold Sox, Editor of *Annals of Internal Medicine*, explained the ICMJE position, which defines two types of trials. Clinically directive trials, which are intended to influence clinical policy and are typically large trials of agents that have already gone through preliminary testing, "should be registered—period, no argument." Exploratory trials, which precede clinically directive trials, have been the subject of the most discussion between industry and the editors. The ICMJE excludes Phase I trials, which are designed to study major unknown toxicity or determine pharmacokinetics, but notes: "Between those two extremes are some clinical trials whose prespecified goal is to investigate the biology of disease or to provide preliminary data that may lead to larger, clinically directive trials."

Dr. Sox said the ICMJE has changed its position regarding those intermediate trials. Recognizing that requiring public registration might slow the forces that drive innovation, each journal editor will decide on a case-by-case basis about reviewing unregistered trials in this category. Authors whose trial is unregistered will have to convince the editor that they had a sound rationale when they decided not to register their trial. Editors plan to get together after 2 or 3 years of experience to come up with a body of "case law" that editors could apply more generally.

DELAYED DISCLOSURE OF INFORMATION AVAILABLE AT THE INITIATION OF TRIALS

Fields 1 through 13 in the IOM background material (see Table 4-1) are also common to the ICMJE requirements, the voluntary commitment made by the pharmaceutical industry, and the WHO project. Fields 14 through 17 in Table 4-1 are the elements for which there are disagreements between the pharmaceutical industry's proposed elements and the elements used by WHO and accepted by the ICMJE. Therefore, these elements were the focus of the discussion at the June 27 meeting. For the most part, the elements that needed further discussion corresponded with elements in the WHO list (Table 3-3) labeled "sensitive" for commercial reasons, except for one. WHO considered target sample size (Field 17) as a sensitive element, but that corresponds with Field 13 in the IOM list, which was not at issue.

TABLE 4-1 Clinical Trial Registry Data Fields Discussed at IOM Meetings

	Information to be registered when a clinical trial is initiated
	Information to be registered for completed clinical trials

#	Clinical Trial Data Field Description—to be registered prior to the first patient visit in a study
1.	Unique Trial Identification Number
2.	Name of Sponsor
3.	Brief Title
4.	Trial Description in Lay Terminology
5.	Trial Phase
6.	Trial Type (e.g., interventional)
7.	Trial Status (e.g., enrolling, completed)
8.	Intervention Type (e.g., drug, vaccine)
9.	Condition or Disease
10.	Key Eligibility Criteria (including gender and age)
11.	Location of Clinical Trial
12.	Contact Information*
13.	Estimated Target Number of Subjects

#	Clinical Trial Data Field Description—to be registered prior to the first patient visit in a study
	Clinical Trial Data Fields Requiring Further Discussion
14.	Hypothesis Statement: Statement of Intervention(s) and Comparison(s) Studied
15.	Definition of Primary and Secondary Outcome Measures
16.	Key Trial Dates: Registration Date, Trial Start Date (anticipated or actual), Projected Year of Trial Completion (= last patient, last visit)
17. ***Results***	*a. Once a drug is marketed and commercially available in at least one country, summary results of all clinical trials other than exploratory will be posted, either by linking to a peer-reviewed publication or by providing the summary results in a common, nonpromotional format.*
	b. Summary exploratory results will be posted if deemed to have significant medical importance.
	c. If results are published, a citation or link to the journal article will be posted in the registry and/or a summary of the results will be provided in a standardized format, such as ICH E3.

*Some large-scale clinical trials have numerous investigators on different continents. In addition, many investigator sites are not equipped with the personnel to field numerous phone calls inquiring about a clinical trial. A possible solution is inclusion of a toll-free number that allows a central call line to direct patients and health care providers to the appropriate and most convenient clinical trial site. This central number also would allow the health care community to identify and contact the individual directly responsible for the conduct of the trial, if necessary.

On certain occasions, the trial sponsor may consider some information in Data Fields 14 through 16 to be highly proprietary and consequently may want to delay public disclosure. Specifically:

- A hypothesis statement describes the nature of the trial, so that anyone reading it will know what is being tested in the trial and specifically which disease is of concern. For serious and life-threatening diseases, this information is already required and is typically posted in the "Trial Description" data field on ClinicalTrials.gov (Item 14).
- Industry has offered to register the intervention type (e.g., drug, vaccine), but on certain occasions, the sponsor may want to keep the intervention and/or comparator confidential (Item 14).
- The sponsor may want primary and secondary outcome measures to remain confidential in cases when such disclosure could put

an entire research program at risk of being unfairly copied by others who have not invested to develop the necessary expertise (see U.S. DHHS, 1998). The hypothesis and outcome measures in a clinical trial protocol describe the specifics of the sponsoring entity's product development plan (Item 15).

- Generally the projected year of trial completion is acceptable; however, industry representatives indicated there may be circumstances in which this information is considered proprietary. For publicly held companies, stock market analysts carefully monitor the development of a product. Accordingly, projecting a year of clinical trial completion and subsequently missing that date—which can occur due to multiple, uncontrollable factors—could have a significant negative impact on a company's shareholder value, especially for a small biotech company whose portfolio only consists of a compound or two (Item 16).

The physicians working on the clinical trial also have full access to the hypothesis being tested, the intervention and comparison arms, the protocol-specific hypothesis statement, and a complete listing of primary and secondary outcome measures as part of the detailed clinical trial protocol. However, these physicians are required to keep the protocol information confidential as a result of a confidentiality agreement signed with the trial sponsor. The confidentiality agreement protects against unauthorized disclosure of the research that is being invested in by the clinical trial's sponsor.

Comments on Delayed Disclosure of Information Available at Trial Initiation

"There is a legitimacy to confidentiality," Dr. Breier stated. "Confidentiality spurs innovation, it gives it a competition that speeds things to market. If we remove all aspects of confidentiality of the innovation, the energy and some of the speed to market could get lost." He gave examples of confidentiality that are embraced by the research community: peer review of scientific papers and NIH grant review. In both cases, the reviews are confidential to encourage the most thoughtful reviews of the research and its presentation. He provided a case example of the importance of confidentiality:

> A drug called a selective estrogen receptor modulator is in Phase III testing; it has a 6-year Phase III plan. It will cost more than $100 million for the Phase III program, and there are multiple ways to design the clinical plan and different indications. Posting the full clinical plan at the inception, when the drug will not be on the market for over 6 years, will not benefit patients or prescribing physicians. The drug is not available. However, it will allow other companies to mimic the clinical plan and potentially be first to market. That could discourage innovation if all of the key aspects of this clinical plan were made available 6 years before the first prescription could be written, and I would argue that if we put the patient at the center, that's not critical to the patient, but it is to the business model.

Jeffrey Drazen, Editor-in-Chief of the *New England Journal of Medicine*, countered that competitors could not come up with a trial design that gave the answer in less time. "The competitor will always be behind."

Dr. Sox voiced concern that concealing the content of a field in a trial registry for 6 years or more is too long. People who are trying to summarize a body of evidence should be able to know about uncompleted trials so they can at least make a guess as to how an ongoing trial might affect the body of evidence of which it will eventually become a part.

Dr. Breier responded that information would be available to important selected parties—journal editors should have access to the blinded data and the non-blinded data any time they are looking at a manuscript.

Annetta Beauregard, from Eli Lilly and Company, clarified that for the majority of cases, all the fields—the intervention, the primary and secondary outcome measures—will be on the Web before the first patient is enrolled. Delayed disclosure will be sought in a minority of cases.

Frank Rockhold, Senior Vice President and Director, Biomedical Data Sciences at GlaxoSmithKline (GSK) Pharmaceuticals Research and Development, said that if the purpose is to get as many trials as possible onto a registry, "don't get hung up on the few trials that need to have their data masked until the end of the trial."

The FDA's Robert Temple stated that any registry, if it is to facilitate understanding of what is planned and, when looking at the results, what was planned, needs to provide a complete description of the trial and any changes. "You really need to see the whole protocol, the statistical analysis plan, and any amendments to the protocol."

Dr. Drazen noted that the data that are in contention—the drug or intervention that is being used, the outcome that is being measured—are major points. "In our discussions with a number of commercial sponsors of clinical trials, the idea has come up to place the details of clinical trials in a so-called 'lockbox,' which would be a way of assuring that the trials were carried out the way that they had been proposed, but that the detailed information wasn't going to be widely available at the time the trial was either planned or completed," he said. He asked the patient representatives in particular what they thought of this approach.

The public/patient representatives were generally in favor of some limited form of data shielding in order to ensure continued development of innovative treatments. Ms. Terry said she thought "the lockbox concept is one that allows the commercial sponsor to feel safe as it evolves, whatever it has to go through in terms of drug development or device development, but also for people to get some information as that process goes. But since the information is banked somewhere, it also allows making sure that the trial was conducted in the way that it should have been." She later added this qualifier: "I think the public will trust if the system is more healthy and more transparent and that a great deal has to remain outside the lockbox. And that ultimately it should be all outside, but I don't think we can jump today to a tomorrow when everything is transparent."

Myrl Weinberg, Health Sciences Policy Board member and President of the National Health Council, suggested the word "lockbox" be replaced. "That is not a positive word that would make me feel particularly trusting. We really need to be careful from the beginning and then clarify exactly what would be held back and at what point would it be released."

Dr. Speers added, "There's going to be a tradeoff. If the goal is to get good participation and to have carrots rather than sticks, which I support as well, then there's got to be some support or recognition that some information is proprietary."

Patty Delaney, of the FDA's Cancer Liaison Program, speaking as a former participant in a clinical trial, stated that trial sponsors are deluding themselves if they think they can keep their trial's endpoints a secret. For example, patients entering a trial are told everything going on in that trial as part of the informed consent process. Therefore, there is no secret. The patient is free to tell anyone they want, including going to an Internet chat room to discuss the trial's objective and endpoint. "In this day and age I'm going to go to the Internet. I'm going to go to the International Myeloma Foundation and say here's the trial I entered, here's what's

going on, because people like me consider ourselves to be at the top of the pyramid of information and we want everybody to know about the trial. So that secret is blown at that point. Whether the trial is in the registry or not, everybody's going to find out because patients are getting smarter and smarter."

Deborah Zarin, Director of ClinicalTrials.gov for the National Library of Medicine (NLM), stated that secondary endpoints are important. She used the example of the selective serotonin reuptake inhibitors (SSRIs) and suicidality. "If suicidality was always a secondary outcome measure, never a primary outcome measure, and you're a systematic reviewer and you want to look at Paxil and suicidality but you had no idea how many trials ever looked at that, you'd be in the same conundrum that we've talked about. Now suppose you're the parent of a child and you're thinking of enrolling her in a study of SSRIs for depression, you might want to know if, in fact, someone had looked at the link between SSRIs and suicidality. What if you were the parent of a child who had committed suicide in such a trial? You might feel like you want someone to know about that, you want someone to have the opportunity to learn about that."

Dr. Sandrock commented that "a registry that does not include primary and key secondary outcome measures would ring hollow to me and probably to the public as well." He continued:

> If a company chooses to employ a novel outcome in a Phase II or exploratory trial, that outcome could be listed in the registry in enough detail to give the reader an accurate view of what is being measured but not specific enough for others to emulate. For example, an outcome measure in a neurodegenerative disease trial could be listed as the 12-month change in regional brain atrophy as measured by magnetic resonance imaging (MRI). It does not detail how the MRIs are actually acquired, what segmentation parameters are being used, and how the data are being analyzed. A competitor would not readily be able to do its own trial with the same endpoint without that additional information. But a journal editor, a patient or a physician, will still have a good idea of what is being measured in such a trial. Phase III endpoints are typically standard endpoints such as survival, or are endpoints that have been extensively validated and sanctioned by regulatory agencies—hardly a trade secret. In fact I would argue that there are precious few secrets in this business. My belief is that

companies that participate fully in the registry can and will continue to find ways of being innovative.

Sherry Marts, Vice President for Scientific Affairs at the Society for Women's Health Research, suggested that a registry include a notation of whether subgroup analyses are being done. "From a patient perspective, if I as a woman or a minority am looking at three different trials for my condition and only one of them is going to break the data out by sex, that will be the one I sign up for. That's a crucial bit of information that patients are going to need."

TIMING AND CONTENT FOR REPORTING RESULTS OF TRIALS

To provide accountability as well as transparency, both WHO and the pharmaceutical industry call for results to be reported. WHO calls for results to be reported upon trial completion, and the Joint Position of the pharmaceutical industry limits results reporting to products approved for marketing in any country in the world. The ICMJE does not call for the posting of results. The June 27 discussion covered the function of results reporting, what the content of results reporting should be, and when results should be posted.

Comments on the Timing and Content for Reporting Results of Trials

The journal editors explained why the ICMJE did not call for describing the results of trials in a trial registry. Dr. Sox stated that they are more concerned with recording the existence of a trial and some basic data. He continued, "Seeing how many clinical trials are simply unworthy of publication after going through the peer review process, I have to worry about making publicly accessible the results of trials that have not gone through that process." Dr. Drazen added that, if you know about a trial, you have the opportunity to query what happened with the trial. "We can't deal with results reporting until we can get the trial existence part right." The editors also expressed concern that showing the results of poorly done clinical trials is a disservice to the public. Posting results that have not gone through peer review may be dangerous.

Dr. Speers warned that data are not the same as information. Item 17, results of clinical trials, is most problematic because results are data, not information:

> I cannot imagine the type of results or the level of detail that could be included in a registry that would provide truly valuable information about clinical trials for the public. The proposal is to provide summary results. What does that mean? One suggestion is to link to a peer-reviewed publication. However, a single peer-reviewed publication will not put the results in a form where the public can easily interpret them. I ask the IOM to think very carefully about the purpose of providing results and to ask whether results can be provided in a way that would be truly meaningful to the public.

She also stated that the registry should not get in the way of the doctor–patient relationship.

Ms. Delaney stated that "patients should absolutely be given results of the trials they are in."

Ms. Terry went further to say that a comprehensive database could redefine the patient's relationship with the system. "Patients can handle a great deal of information with the right systems in place to support that integration of data to information. Don't keep information from them." She also added that the publication of negative data or failed endpoints will improve research and clinical practice.

Giving patients more rather than less information is the direction to take, Ms. Ireland said. "I've simply been amazed at the sophistication of patients, the amount that they know and understand and want to know about their own care and the care of their loved ones." She added that results should be included, unless it could be proven that there would be a serious competitive disadvantage.

"Negative results and toxicities need to be part of a registry," said Dr. Pizzo. Ms. Terry made the same point, stating that knowing negative data and failed endpoints is helpful.

Dr. Temple stated that a registry should provide results. "If they don't do that, they miss a large fraction of the concern that's driving interest in unpublished data, which is that you're not telling me all the studies that there are. Now how exactly to do this properly is not a trivial question. Who writes it? It's not peer reviewed and the FDA is worried about the potential for promotional reports. Nonetheless, if data don't become available, one could ask what all this is for."

Dr. O'Rourke, representing academic medical centers, expressed concern about databases that include data regarding trials open to enrollment and trial results. "These two types of databases have different goals, different audiences, and require different rules of operation. Realistic goals and rules for those two quite different types of information need to be looked at very seriously."

The most important issue, according to Dr. Breier, is ensuring that all relevant clinical trial results are available in a comprehensive, objective, and unbiased manner when a prescribing decision is made. "It's an issue of WHEN, not IF. If a drug is in early development and it is not on the market and it is not available for a prescribing decision, the importance of that information is less so to the patient. The patient cares when the doctor has to make the prescribing decision and he wants all of the relevant information available in order to make the best prescribing decision." Dr. Breier stated that results reporting is the way to address the file-drawer phenomenon, or failure to report negative results.

GSK Pharmaceuticals has a registry that posts results once a product is approved, on the assumption that disclosing results on a register does not preclude publication, according to Dr. Rockhold. Before the end of the year there will be well over 1,000 trials in the GSK registry. Currently 28 products and more than 500 trials are posted. "I feel strongly that whatever the strategy is, it needs to include the results."

NLM's Dr. Zarin noted that NIH is working on a proposal to enhance access to a wider range of information on NIH-supported clinical trials—with positive, neutral, or negative results. They see challenges, though, in reporting results, including verification of results and problems with misinterpretation.

5

Implementation Issues

The various proposals for creating a clinical trial registry agree that such a registry is needed on the national or international level to benefit public health. They agree on most of the specific elements and that uniform standards for data disclosure should apply to all entities conducting human clinical trials, whether publicly or privately funded. In addition, a number of process issues need to be addressed, as follows:

1. Process for Selection of Uniform Standards
2. Balanced Process for Determining What Information Should Be Protected
3. Mechanism to Ensure Compliance and Protect Against Promotion of Unauthorized Use of a Drug in Registry Postings
4. Responsibility for Developing and Managing the Registry

PROCESS FOR SELECTION OF UNIFORM STANDARDS

Uniform standards are needed for the following:

- Define *what clinical trials* would be posted at inception.
- Define the *required data fields* to be posted when a clinical trial is initiated.
- Define *what clinical trial results information* will be posted to a registry for completed clinical trials.

Such standards should apply to public and private funders of research and should provide a uniform template for presentation of results (e.g., the ICH E3 template—currently utilized globally to summarize results for global regulatory agencies). Much of Chapter 4 of this report documented discussions aimed toward reaching a common understanding of what those standards should be.

BALANCED PROCESS FOR DETERMINING WHAT INFORMATION SHOULD BE PROTECTED

A process to protect confidential and proprietary research, yet provide a mechanism for public disclosure as needed, already exists and is familiar to the U.S. Department of Health and Human Services in the area of public health information disclosures—the Freedom of Information Act (FOIA). FOIA exemptions for commercial information and trade secrets, and the consequent process for adjudication, potentially could be adapted for a clinical trial registry. Confidentiality protections are the cornerstone of the National Institutes of Health (NIH) grant submission process. Pending NIH grant applications and unfunded new and competing continuations and competing supplemental applications are withheld, as is "information which, if released, would adversely affect the competitive position of the person or organization." These rules govern NIH basic and clinical research, including clinical trials.

For reasons similar to those motivating the need to create broad clinical trial registries, FOIA was created in 1966 to give the public expansive access to the records and information in the possession and control of U.S. government agencies. There is a clear public interest in allowing the public access to this information, supported by many of the same reasons cited in support of mandatory clinical trial registries. However, Congress realized that the data in the government's possession will, in a minority of cases, be very sensitive, and if forcibly made public, could create powerful disincentives for investigators or industry to innovate or share important information with the government. For this reason, Congress created some exemptions from forced disclosure of information in the government's possession, but also created a process to guard against abuses.

In most situations, the research entity will not be harmed by disclosing primary and secondary endpoints at the initiation of the clinical trial.

However, when there is no patent or no data package exclusivity or where a research entity is conducting research in a novel area subject to intense competition, then some of the research data of the innovator will need to be protected. This protection will need to be similar to the mechanism FOIA uses to regulate the protection of data included in New Drug Applications submitted to the Food and Drug Administration (FDA) or in grant proposals submitted to NIH.

Some of the FOIA definitions and parts of the process might be applicable to the registry context, especially if a central registry is created and managed by a federal government entity such as the National Library of Medicine (NLM), which manages ClinicalTrials.gov. The utility and practicality of using FOIA in relation to the clinical trial registry needs further discussion.

Comments on Balanced Process for Determining What Information Should Be Protected

Jeanne Ireland, Director of Public Policy for the Elizabeth Glaser Pediatric AIDS Foundation, commented, "I'm no FOIA expert so I can't comment too specifically, but I would say it does seem useful to build on an existing process so that there is clarity both on the part of the trial sponsors and on the part of the patients."

Dr. Deborah Zarin, Director of Clinical Trials.gov for NLM's Lister Hill National Center for Biomedical Communications, stated that NLM did look into the FOIA issue. But rather than having the research sponsor enter the data in the fields, which would then have to be withheld from the public, NLM considered getting the protocol, keeping it in a non-public file, and having the fields filled in by the sponsor when they were ready. NLM would always have a way of saying "yes that's consistent with the initial protocol" or "no it's not." But Dr. Zarin has not been able to get a clear reading as to whether those protocols could be obtained through FOIA until there is a test case. "There's a fair amount of uncertainty about how that would work and what would actually happen."

Gail Cassell, Vice President of Scientific Affairs of Eli Lilly and a member of the Board on Health Sciences Policy (HSP), noted that in publicly funded research, it is common for proprietary information—not just intellectual property information—to be protected. The Freedom of Information Act system has been in place for nearly two decades and has

"worked effectively in favor of the public who funds that research," she noted.

MECHANISMS TO ENSURE COMPLIANCE AND PROTECT AGAINST PROMOTION OF UNAUTHORIZED USE OF A DRUG IN REGISTRY POSTINGS

A purely voluntary system would not protect against the selective disclosures objected to in the past. Therefore it seems evident that a deterrent is needed to protect against failure to post required clinical trial information to a central registry and against promoting unauthorized uses of a drug in the registry. Mechanisms to ensure compliance are necessary to maintain the integrity and reliability of the clinical trial registry. Possible mechanisms include:

- *Institutional Review Board (IRB) Checkpoint*
  Posting to a central registry such as ClinicalTrials.gov could be made a condition of approval by the IRB. In such a case, the failure to post a clinical trial at inception would result in the inability of the study to begin because IRB approval is required for patient enrollment.

- *Broader Role for FDA Audits*
  To ensure that completed trial results are disclosed, the manager of the database could periodically audit the results data posted against the information that was posted when a clinical trial was initiated.

- *Remedial Action: A Tiered Approach*
  One approach that might provide an effective deterrent against real abuses but not penalize inadvertent missed disclosures would be to adopt a tiered approach to remedial action. In such a system, if noncompliance were found, the database manager for the registry could send a warning letter to the sponsor. This is the procedure that the FDA's Division of Drug Marketing, Advertising, and Communications (DDMAC) currently follows for perceived violations of the agency's rules on promotion of marketing and advertising of pharmaceuticals. As with DDMAC, the database manager would give the entity in noncompliance a

defined period of time to rectify the posting omission. If, for example, after 30 days the entity responsible for posting to the registry continues to be noncompliant, the warning letter could be turned into a public notice of noncompliance (i.e., a kind of "scarlet letter") by posting it on the registry. If the entity responsible for posting the data still fails to do so, then the database manager could turn to the Department of Justice to negotiate a Consent decree, again like the process currently used by DDMAC. The New York Attorney General recently used the same mechanism in several high-profile cases involving the pharmaceutical and other industries. Of course, failure to register the clinical trial would also likely preclude publication of the data in a leading medical journal.

The advantage of adopting this tiered approach to ensuring registry compliance is that it, like the FOIA application, builds on already existing and successful processes. Certainly the process used by the FDA to protect the public against violation of the agency's promotional rules should be adequate to protect the integrity of a central clinical trial registry. Any remedial actions that would go beyond those used by DDMAC in its regulation of pharmaceutical advertising would likely be excessive. On the same note, a middle-tier step—between the notice of noncompliance and the costly and more severe move of turning to the Department of Justice—may be advisable. These suggestions are for compliance mechanisms in the United States. Assuring compliance for a global registry would pose a more daunting challenge.

The FDA's Role in Preventing Promotion of Unauthorized Use of a Drug

No new processes need be created to guard against attempts to post registry information for purposes of promoting unauthorized uses of a drug by the drug's manufacturer or marketer. Nor does the database manager for the registry need to be accountable for this oversight. The FDA's DDMAC already is required by law to perform this duty. DDMAC authority extends to all attempts by drug sponsors to promote their products. Registry postings are legally no different from dissemination of marketing detail pieces in terms of whether DDMAC can regulate

them for off-label promotion. In fact, the FDA participants in these Institute of Medicine registry discussions confirmed that DDMAC has and will use this authority when registries are implemented. However, regulations outside the United States would need to be considered to ensure protection against commercialization on a global basis.

Comments on Mechanisms to Ensure Compliance and Protect Against Promotion of Unauthorized Use of a Drug in Registry Postings

Dr. Alan Breier, Vice President, Medical and Chief Medical Officer of Eli Lilly and Company, suggested two ways to ensure compliance while protecting proprietary information: (1) The study protocol and related amendments could be placed in a secure repository managed by an independent third party and the study summary could be matched to the protocol; or (2) in a slightly less complicated approach, study initiation templates could be used, such as an ICH E3 template, with confidential fields for proprietary information that become automatically available to the public when the drug is approved. "Let's enter all of the important methodology at the initiation of the trial. We could then blind certain key proprietary fields, but the information is there. When the drug is then on the market and that important prescribing decision has to be made, it's automatically unblinded. Then you've got all the methodology. You've then got the result piece that you amend to its methodology all on the same template," Dr. Breier explained.

Dr. Alfred Sandrock, Vice President, Medical Research-Neurology for Biogen Idec, added that the scientists in his company want to publish in the top journals in the world, a move that he believes is incentive enough to be as compliant as possible. In terms of making sure that all the fields are properly filled out, the National Library of Medicine has staff who check the ClinicalTrials.gov database to make sure all the fields are appropriately entered. Many companies have staff who have been trained to do this and to interface with the NLM staff. That model is workable. The strong incentive of wanting to publish in the top journals is enough incentive to register completely and honestly.

Regarding an IRB checkpoint, Ms. Ireland stated that conditioning IRB approval on registration of a trial was a useful approach. She suggested that the IRBs not play an enforcement role. Rather, they would act

as a checkpoint, notifying whatever agency is playing the enforcement role, if a trial about to start is not registered.

Dr. Marjorie Speers, Executive Director of the Association for the Accreditation of Human Research Protection Programs, noted that IRBs already feel overburdened and that she would be very cautious about having them assume this role. She also predicted redundancy in the case of multisite studies with multiple IRBs.

John Schneider, Chair of the Council on Scientific Affairs of the American Medical Association, stated that using IRBs makes sense if their only job is to look for a unique identifier, indicating the trial has been registered. If it's not there, the IRBs bounce it back. Dr. Breier echoed his statement.

Suanna Bruinooge, representing the American Society of Clinical Oncology, suggested that planners contact some IRBs to further discuss feasibility.

Dr. P. Pearl O'Rourke, Director of Human Research Affairs at Partners HealthCare System, Inc., stated that IRBs will need more clarity about what trials are included before signing on as a decision node.

Several participants asked whether the FDA should be given a stronger role in a clinical trial registry. Ms. Ireland suggested that the FDA become part of the approval checkpoints. Could the FDA be given an auditing function to ensure veracity, if additional resources were provided?

Dr. Speers added that registration should be a requirement to get an IND from the FDA.

Sharon Terry, President and Chief Executive Officer of Genetic Alliance, noted that the FDA should have greater oversight. She was striving to show the benefit for industry. Perhaps by registering, industry would have an easier time with FDA processes.

Sue Levi-Pearl, with the Tourette Syndrome Association, asked whether the FDA should play a critical role in the development of such a broad-based clinical database because the FDA has all the data, which are often proprietary.

HSP Board Member Lynn Goldman of the Johns Hopkins Bloomberg School of Public Health noted that much of this information is submitted to the FDA. Much more goes to the FDA than would ever be on a registry. Could there be efficiency in having a component of what is submitted to the FDA transferred to a clinical trial registry?

William Vaughan of Consumers Union submitted the following comment: "We believe that the FDA needs a number of additional au-

thorities and resources to give more emphasis to safety in the process of pre- and post-market approval of pharmaceuticals."

Regarding audits, Dr. Breier stated: "We've got to be able to audit posting commitments as well as accuracy, objectivity of summaries. Who will do it and how? And who will pay for it? It will be a very large task. What are the implications for compliance lapses? How are we going to put some teeth into the compliance checking?"

Dr. Zarin described a pilot study going on at ClinicalTrials.gov in which staff are trying to reach IRB contacts and health authorities for non-U.S. trials to try to understand how much help they can provide in verifying that they, in fact, approve a trial in question, and whether they could actually verify more detailed information because the IRB has seen the protocol. She also noted that avoiding duplications is a big task, as is updating, for example, recruitment status.

Ms. Ireland called for "reasonable financial penalties" for those who do not comply. Ms. Terry asked if there were a way to "incentivize" compliance.

Lindsey Johnson from U.S. PIRG said that a "scarlet letter" for those who do not comply is not enough. "We need penalties that will resonate with the public, if we expect the public to trust the database."

RESPONSIBILITY FOR DEVELOPING AND MANAGING THE REGISTRY

Different workshop participants suggested that a national registry might be managed by either a nonprofit organization or a trusted government agency. Expansion of the National Library of Medicine's responsibility for ClinicalTrials.gov to include more trials and more information might be a logical way to build on existing programs. It was also noted that the FDA has some of the data that would be needed by a clinical trial registry.

6

Conclusion and Next Steps

The Institute of Medicine (IOM) brought together many diverse entities to express their views on the content, purposes, and implementation of a clinical trial registry. A summary of these views has been attempted here, and there have been clear signs of convergence and momentum since the discussions that were convened by the IOM began.

Most of the possible content fields for a clinical trial registry are not being debated. The discussions at the workshop centered on the following five concepts:

- ***Purpose.*** There was little or no controversy over whether a registry should track the status of individual clinical trials and provide a complete record of all trials to aid in doing systematic reviews of the evidence. There appeared not to be agreement on whether the same registry could or should be used for patient recruitment, whether the registry should include the results of the trials, and if it did include the results, when those results should be posted.

- ***Which Trials to Include.*** There was little controversy over the desirability of expanding the information currently collected by ClinicalTrials.gov beyond serious or life-threatening diseases and conditions. There was no agreement, however, over the inclusion of exploratory trials in a registry. The line between exploratory and confirmatory trials is not a bright one, and although some participants thought these trials should be included for the sake of completeness, others did not, citing proprietary interest and the lack of applicability to policy and health care decisions. More work is needed to come to agreement on this.

- ***Delayed Disclosure Mechanism.*** For proprietary reasons, speakers from industry argued for the delayed disclosure of certain fields (i.e., at project initiation, not disclosing the hypothesis statement, primary and secondary outcome measures, and projected year of trial completion) for a minority of trials. However, the workshop did not discuss implementation questions such as what is meant by "delay" (in terms of time or staging in the marketing process) or whether there should be objective criteria for when industry would invoke such a delay. More work is needed to reach agreement on whether delayed disclosure is an acceptable approach and, if so, to define processes for authorizing these delays. An option that might accompany delayed disclosure is to store the data in a non-public part of the registry.

- ***Reporting Results of Completed Trials.*** The International Committee of Medical Journal Editors (ICMJE) does not call for results to be reported. The World Health Organization (WHO) calls for the reporting of results once a trial is completed. The Joint Position of the pharmaceutical industry calls for reporting of results for products that are brought to market in any country. As the interested parties continue to discuss and seek a resolution to the issue of reporting results, the other purposes of a clinical trial registry can be met.

- ***Compliance.*** Incentives for complying and consequences for not complying with registry requirements would seem necessary for a registry to be comprehensive. Possible roles for Institutional Review Boards, the Food and Drug Administration, and others were discussed, but this is still a controversial topic.

Activities toward a comprehensive, publicly accessible clinical trial registry continued after the workshop. Depending on when a clinical trial started, it has to be registered before enrolling the first patient or (for trials initiated before July 1, 2005) before submitting an article to an ICMJE journal. The international pharmaceutical industry working with the National Library of Medicine (NLM) has begun registering all but exploratory clinical trials on ClinicalTrials.gov, and providing the results of clinical trials on marketed products on ClinicalStudyResults.gov, an Internet database launched in September 2004 by the Pharmaceutical Research and Manufacturers of America. These new efforts are being monitored closely on the pages of the medical journals. Zarin and col-

leagues at NLM (2005) noted that, between May and October 2005, there was a large increase (73 percent) in the number of clinical trial registrations on ClinicalTrials.gov, an increase that staff attribute to enactment of the ICMJE policy. They note, however, that completeness of registration information varies, indicating differing levels of discomfort with full disclosure, as expressed at the IOM workshop. In an accompanying editorial, Drazen and Wood (2005) note that a handful of commercial entities are still using meaningless entries for the Intervention Name field and for the Primary Outcome field. They point to the fact that several other pharmaceutical firms are in full compliance, "undercutting any argument that this failure reflects a commercial imperative." Finally, several of the individuals involved in this IOM workshop have moved into advisory roles on the WHO project. WHO is in the process of establishing norms and standards for international clinical trial registration.

References

AMA (American Medical Association). 2004, June 15. *AMA Recommends That DHHS Establish a Registry for All U.S. Clinical Trials.* [Online]. Available: http://www.ama-assn.org/ama/pub/category/13934.html [accessed May 9, 2005].

Brownlee S. 2004. Doctors without borders: Why you can't trust medical journals anymore. *Washington Monthly.* [Online]. Available: http://www.washingtonmonthly.com/features/2004/0404.brownlee.html [accessed May 9, 2005].

Chan A-W, Hrobjartsson A, Haahr MT, Gotzsche PC, Altman DG. 2004. Empirical evidence for selective reporting of outcomes in randomized trials. Comparison of protocols to published articles. *Journal of the American Medical Association* 291(20):2457–2465.

De Angelis CD, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, Kotzin S, Laine C, Marusic A, Overbeke AJ, Schroeder TV, Sox HC, Van Der Weyden MB. 2004. Clinical trial registration: A statement from the International Committee of Medical Journal Editors. *Journal of the American Medical Association* 292(11):1363–1364.

De Angelis CD, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, Kotzin S, Laine C, Marusic A, Overbeke AJ, Schroeder TV, Sox HC, Van Der Weyden MB. 2005. Is this clinical trial fully registered? A statement from the International Committee of Medical Journal Editors. *Annals of Internal Medicine* 143(2):146–148.

Drazen JM, Wood AJJ. 2005. Trial registration report card. *New England Journal of Medicine* 353:2809–2811.

European Federation of Pharmaceutical Industries and Associations. 2005. *Joint Position on the Disclosure of Clinical Trial Information Via Clinical Trial Registries and Databases*. [Online]. Available: http://www.efpia.org/4_pos/sci_regu/Clinicaltrials2005.pdf [accessed August 3, 2005].

Fair Access to Clinical Trials Act of 2005, H.R. 3196 and companion bill S. 470. [Online]. Available: http://thomas.loc.gov/cgi-bin/query/z?c109:S.470 [accessed August 3, 2005].

The "file drawer phenomenon": Suppressing clinical evidence. 2004. *Canadian Medical Association Journal* 170(4):437, 439.

ICH Harmonised Tripartite Guideline: Statistical Principles for Clinical Trials. 1998 (February 5). The ICH Steering Committee. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

Kennedy D. 2004. Clinical trials and public trust. *Science* 306(5702):1649.

Public Welfare and Human Service Act. Title 45, Volume 1, Parts 1 to 199 NIH Grants Policy Statement. Terms and Conditions of NIH Grant Awards.

Santana S. 2004, August. Call for clinical trials registry gaining momentum. *AAMC Reporter*. [Online]. Available: http://www.aamc.org/newsroom/reporter/aug04/clinicaltrials.htm [accessed August 3, 2005].

U.S. DHHS (U.S. Department of Health and Human Services). 1998. *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*. [Online]. Available: http://www.fda.gov/cder/guidance/1397fnl.pdf [accessed May 9, 2005].

U.S. DHHS. 2002. Section 113. Information Program on Clinical Trials for Serious or Life-Threatening Diseases.

Whittington CJ, Kendall T, Fonagy P, Cottrell D, Cotgrove A, Boddington E. 2004. Selective serotonin reuptake inhibitors in childhood depression: Systematic review of published versus unpublished data. *Lancet* 363(9418):1341–1345.

WHO (World Health Organization). 2005. *WHO International Clinical Trials Registry Platform.* [Online]. Available: http://www.who.int/ictrp/en/ [accessed December 10, 2005].

Zarin DA, Tse T, Ide N. 2005. Trial registration at ClinicalTrials.gov between May and October 2005. *New England Journal of Medicine* 353:2779–2787.

A

Participants and Invited Experts Between December 1, 2004, and June 27, 2005

Participants
December 1, 2004

Alan Breier
Vice President, Medical, and Chief Medical Officer
Eli Lilly and Company

Catherine D. DeAngelis
Editor-in-Chief
Journal of the American Medical Association

Jeffrey M. Drazen
Editor-in-Chief
New England Journal of Medicine

Lawrence Hirsch
Executive Director, Medical Communications
Merck Research Laboratories

Richard Kingham
Partner
Covington & Burling

Ronald Krall
Senior Vice President, World Wide Development, GlaxoSmithKline Pharmaceuticals

Alexa McCray
Director, Lister Hill National Center for Biomedical Communications
National Library of Medicine

Lana Skirboll (via phone)
Associate Director of Science Policy
Office of the Director
National Institutes of Health

Harold C. Sox
Editor
Annals of Internal Medicine

Melvyn L. Sterling
Chair, Council on Scientific Affairs
American Medical Association

Robert Temple (via phone)
Director, Office of Medical Policy
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Elias Zerhouni (via phone)
Director
National Institutes of Health

Invited Experts
Between December 1, 2004, and June 27, 2005

Alan Breier
Vice President, Medical and Chief Medical Officer
Eli Lilly and Company

Catherine D. DeAngelis
Editor-in-Chief
Journal of the American Medical Association

Jeffrey M. Drazen
Editor-in-Chief
New England Journal of Medicine

Lawrence Hirsch
Executive Director, Medical Communications
Merck Research Laboratories

John Hoey
Editor
Canadian Medical Association Journal

Christine Laine
Executive Secretary
Annals of Internal Medicine

Justin McCarthy
General Counsel, Pfizer Global Research and Development
Pfizer, Inc.

Frank Rockhold
Senior Vice President and Director, Biomedical Data Sciences
GlaxoSmithKline Pharmaceuticals Research and Development

Alfred Sandrock
Vice President, Medical Research-Neurology
Biogen Idec

Ralph Smalling
Vice President, Global Research and Development Policy Analysis
Amgen

Harold Sox
Editor
Annals of Internal Medicine

B

Workshop Agenda, Speakers, Panelists, and Participants: June 27, 2005

Workshop Agenda

8:30 **WELCOME AND OPENING REMARKS**

Philip A. Pizzo
Chair, IOM Board on Health Sciences Policy
Dean, Stanford University School of Medicine

Gail Cassell
Member, IOM Council and Board on Health Sciences Policy
Vice President, Scientific Affairs and Distinguished Lilly Research Scholar for Infectious Diseases
Eli Lilly and Company

OVERVIEW & BACKGROUND

8:45 **KEYNOTE: IMPORTANCE OF THE PUBLIC TRUST**

The Honorable John Porter
Partner
Hogan & Hartson, LLP

9:15 **STATUS OF IOM BOARD ACTIVITY**

Philip A. Pizzo
Chair, IOM Board on Health Sciences Policy
Dean, Stanford University School of Medicine

PANEL 1: PATIENT/PUBLIC/JOURNAL EDITORS PERSPECTIVE

9:45 **PATIENT/PUBLIC NEEDS**

Marjorie Speers
Executive Director
Association for the Accreditation of Human Research Protection Programs

DISCUSSANTS:
Miriam O'Day
Senior Director of Public Policy
Alpha-1 Foundation

Sharon Terry
President and CEO
Genetic Alliance

Jeanne Ireland
Director of Public Policy
Elizabeth Glaser Pediatric AIDS Foundation

10:00 **DISCUSSION**

10:15 **CLINICAL TRIAL REGISTRY REQUIREMENTS: INTERNATIONAL COMMITTEE OF MEDICAL JOURNAL EDITORS**

Harold Sox
Editor
Annals of Internal Medicine

DISCUSSANTS:
Catherine DeAngelis
Editor-in-Chief
JAMA

Jeffrey Drazen
Editor-in-Chief
NEJM

10:30 **DISCUSSION**

10:45 **BREAK**

PANEL 2: CURRENT REGISTRY ACTIVITIES

11:00 **INDUSTRY PERSPECTIVE**

Alan Breier
Vice President, Medical and Chief Medical Officer
Eli Lilly and Company

DISCUSSANTS:
Alfred Sandrock
Vice President, Medical Research-Neurology
Biogen Idec

Frank Rockhold
Senior Vice President and Director, Biomedical Data Sciences
GlaxoSmithKline Pharmaceuticals Research and Development

11:15 **DISCUSSION**

11:30 **U.S. FOOD AND DRUG ADMINISTRATION**

Robert Temple
Director, Office of Medical Policy
Center for Drug Evaluation and Research (CDER)
U.S. Food and Drug Administration

11:45 **DISCUSSION**

12:00 **LUNCH**

1:00 **PERSPECTIVES FROM NIH**
AND
SURVEY OF DATA IN CLINICALTRIALS.GOV

Deborah Zarin
Director, ClinicalTrials.gov
Lister Hill National Center for Biomedical Communications
National Library of Medicine

1:15 **DISCUSSION**

1:30 **WORLD HEALTH ORGANIZATION CLINICAL TRIAL REGISTRY PROJECT**

Metin Gulmezoglu
Scientist
World Health Organization

1:45 **DISCUSSION**

PANEL 3: ACADEMIC PERSPECTIVES

2:00 **PRESENTER:**
P. Pearl O'Rourke
Director, Human Research Affairs
Partners HealthCare System, Inc.

DISCUSSANTS:
John Schneider
Chair, Council on Scientific Affairs
American Medical Association

Hugh Tilson
Chair, National Steering Committee
Centers for Education and Research on Therapeutics (CERTs)

2:15 **DISCUSSION**

3:00 **BREAK**

PANEL 4: CONGRESSIONAL PERSPECTIVE

3:30 **PRESENTER:**
Kate Reinhalter
Legislative Assistant
Office of Congressman Ed Markey
U.S. House of Representatives

Rachel Sher
Health Counsel
Office of Congressman Henry Waxman
U.S. House of Representatives

3:45 **DISCUSSION**

4:00 **GENERAL DISCUSSION/AUDIENCE PARTICIPATION**

5:00 **ADJOURN TO RECEPTION**

Speakers and Panelists

Alan Breier
Vice President, Medical and Chief Medical Officer
Eli Lilly and Company

Catherine DeAngelis Editor-in-Chief
JAMA

Jeffrey Drazen
Editor-in-Chief
NEJM

Metin Gulmezoglu
Scientist
World Health Organization

Jeanne Ireland
Director of Public Policy
Elizabeth Glaser Pediatric AIDS Foundation

Miriam O'Day
Senior Director of Public Policy
Alpha-1 Foundation

P. Pearl O'Rourke
Director, Human Research Affairs
Partners HealthCare System, Inc.

The Honorable John Porter
Partner
Hogan & Hartson, LLP

Kate Reinhalter
Legislative Assistant
Office of Congressman Ed Markey
U.S. House of Representatives

Frank Rockhold
Senior Vice President and Director
Biomedical Data Sciences
GlaxoSmithKline Pharmaceuticals R&D

Alfred Sandrock
Vice President
Medical Research-Neurology
Biogen Idec

John Schneider
Chair, Council on Scientific Affairs
American Medical Association

Rachel Sher
Health Counsel
Office of Congressman Henry Waxman
U.S. House of Representatives

Harold Sox
Editor
Annals of Internal Medicine

Marjorie Speers
Executive Director
Association for the Accreditation of Human Research Protection Programs

Robert Temple
Director, Office of Medical Policy
Center for Drug Evaluation and Research (CDER)
U.S. Food and Drug Administration

Sharon Terry
President and CEO
Genetic Alliance

Hugh Tilson
Chair, National Steering Committee
Centers for Education and Research on Therapeutics (CERTs)

Registered Workshop Participants

Margaret Anderson
FasterCures

Debra Aronson
BIO

Naomi Aronson
Blue Cross Blue Shield Association

Angela Bates
NIH

Peggy Beat
Cleveland VA

Annetta Beauregard
Eli Lilly and Company

Lisa Begg
DHHS/NIH

Mario Belledonne
Biolab Research

Douglas Boenning
Children's National Medical Center

Michele Boisse
American Society for Clinical Pharmacology & Therapeutics

Claire Bornstein
Elizabeth Glaser Pediatric AIDS Foundation

Lizbet Boroughs
American Psychiatric Association

Lynn Bosco
AHRQ

Laquitta Bowers
Self-Employed

Steven Brotman
Wyeth Pharmaceuticals

Voncelia Brown
Salisbury University

Mario Browne
University of Pittsburgh Graduate School of Public Health

Suanna Bruinooge
American Society of Clinical Oncology

Kristin Butterfield
American Academy of Pediatrics

Ronald Califre
Novartis Pharmaceuticals Corporation

Scott Campbell
American Diabetes Association

Dolph Chianchiano
National Kidney Foundation, Inc.

Yen-pin Chiang
AHRQ

Anita Cicero
Gardner, Carton & Douglas

Michelle Cissell
JDRF

Mickey Clarke
Washington University

Elaine Collier
National Center for Research Resources

Sarah Comley
International Observers

Christina Copty
Aspen Systems Corporation

Jennifer Couzin
Science Magazine

Tyler C. Cymet, DO
C/O Sinai Hospital of Baltimore

MaryAnn D'Alessandro
NPPTL

Kevin Davis
National Cancer Institute

Patty Delaney
Cancer Liaison Program, FDA

Don Detmer
American Medical Informatics Association

Jeffrey Dickey
Spriggs & Hollingsworth

Barry Dickinson
American Medical Association

Wei Du
Adolor Corporation

Brenda Evelyn
Food and Drug Administration

Brian Feit
DHHS/HRSA/HAB/DCBP

Lorraine Fitzsimmons
National Institute on Aging

Yolanda Fleming
National Medical Association

MaryAnn Foote
Amgen

Robert Fulcher
American Society of Nephrology

Barbara Galen
Cancer Imaging Program/NCI/NIH

Roger Garceau
Sanofi-Aventis

Edward Garcia
Washington Health Advocates

Kathryn Goettge
NLM Clinical Information Services

Alan Goldhammer
PhRMA

Jennifer Gorman
Office of the Director, NIH

Lakshmi Grama
National Cancer Institute

David Grandison
Meharry Medical College

Donald Greene
Veritas Medicine

Jeffrey Grossi
Johns Hopkins Medicine

Mary Hager
American Dietetic Association

Kimberly Harris
Education to Advance Cancer Clinical Trials

Lynne Haverkos
National Institute of Child Health and Human Development

Anthony Hayward
NIH

Katerina Herodotou
Novo Nordisk, Inc.

Susan Herold
Consumers Union

Lauren Hetrick
Abbott Laboratories

Nick Ide
National Library of Medicine

Heather Jameson
Research!America

Lindsey Johnson
U.S. PIRG

Nicole Johnson Baker
Director's Council of Public Representatives, NIH

Cheryl Karol
Hoffmann-LaRoche Inc.

Kenneth Katz
University of Pennsylvania

Mahin Khatami
NIH/NCI

Felix Khin-Maung-Gyi
Chesapeake Research Review, Inc.

Gary Kline
FASEB

Yosuke Komatsu
Otsuka America Pharmaceutical, Inc.

Kristin Kroeger Ptakowski
American Academy of Child and Adolescent Psychiatry

Steven Krosnick
NIH

Michel Krumenacker
Sanofi-Aventis

Selma Kunitz
KAI Research, Inc.

Theresa Lawrence
Department of Health and Human Services

Sue Levi-Pearl
Tourette Syndrome Association, Inc.

Tola Life
Health Resources and Services Administration

Caroline Loew
PhRMA

Laura Lyman Rodriguez
NIH

Nancy Maher
Department of Veterans Affairs

Michael Manganiello
National Institutes of Health

Richard Manrow
National Cancer Institute

Sherry Marts
Society for Women's Health Research

Debra McCoy
Arthritis Foundation

Christopher McGowen
Novo Nordisk, Inc.

Paul Meade
Clear Point Health

David Miller
GlaxoSmithKline

Nancy Miller
NIH

Abdulaziz Mohamed
Manchester Health Department

Richard Mowery
National Institute of Dental and Craniofacial Research

Esther Myers
American Dietetic Association

Nancy Myers
PhRMA

John Neylan
Wyeth Research

Martha Nolan
Society for Women's Health Research

Susan Norris
AHRQ

Laura Nufire
Self-Employed

Joanne Odenkirchen
NIH/NINDS

Sharon Olmstead
Schering Plough

Paul Parry
Abigail Alliance for Access to Clinical Trials

Carol Payne
Department of Housing and Urban Development

JoNell Potter
University of Miami

Karla Price
Epilepsy Foundation

Kate Reinhalter
U.S. House of Representatives

Stephen Rose
Foundation Fighting Blindness

Marcel Salive
DHHS/Centers for Medicare & Medicaid Services

Susan Schiffner
Veterans Affairs

Jeff Schomisch
Thompson Publishing Group

Nanette Schwann
Lehigh Valley Medical Center

Yvette Seger
FasterCures

Katie Senauer
RTI

Clarissa Agee Shavers
Michigan State University

J.C. Shay
Department of Housing and Urban Development

Sam Shekar
Center for Quality, HRSA

Rachel Sher
U.S. House of Representatives

Juliette Shih
Genzyme

David Silk
Avalere Health

Paul Sirovatka
American Psychiatric Association

Douglas Sporn
Abbott Laboratories

Linda Temple
Regulatory Affairs Professionals Society

Sona Thakkar
Office of Education and Special Initiatives

Roni Thaler
The Center for Information & Study on Clinical Research Participation

Susan Thaul
Congressional Research Service

Phil Thevenet
GlaxoSmithKline

Stephen Thomas
University of Pittsburgh

Terry Toigo
FDA

Cathy Tran
Science Magazine

Tony Tse
ClinicalTrials.gov, National Library of Medicine

Judith Vaitukaitis
NIH

William Vaughan
Consumers Union

Paula Squire Waterman
Office of Research Oversight, Veterans Affairs

Jill Wechsler
Applied Clinical Trials Magazine

Beat Widler
Roche Products Limited

Erin Williams
Congressional Research Service

Reginald Williams
Avalere Health

Marcel Willner
Bristol-Myers Squibb

Marsha Wilson
Gynecologic Cancer Foundation

Kim Witherspoon
National Cancer Institute

Jerome Yates
American Cancer Society

C

Section 113 of the Food and Drug Administration Modernization Act of 1997 and Guidance for Industry: Information Programs on Clinical Trials for Serious or Life-Threatening Diseases and Conditions. U.S. Department of Health and Human Services. March 2002

SECTION 113. INFORMATION PROGRAM ON CLINICAL TRIALS FOR SERIOUS OR LIFE- THREATENING DISEASES

(a) In General.--Section 402 of the Public Health Service Act (42 U.S.C. 282) is amended--

(1) by redesignating subsections (j) and (k) as subsections (k) and (l), respectively; and

[[Page 111 STAT. 2311]]

(2) by inserting after subsection (i) the following:

<<NOTE: Establishment.>> ``(j)(1)(A) The Secretary, acting through the Director of NIH, shall establish, maintain, and operate a data bank of information on clinical trials for drugs for serious or life-threatening diseases and conditions (in this subsection referred to as the 'data bank'). The activities of the data bank shall be integrated and coordinated with related activities of other agencies of the

Department of Health and Human Services, and to the extent practicable, coordinated with other data banks containing similar information.

"(B) The Secretary shall establish the data bank after consultation with the Commissioner of Food and Drugs, the directors of the appropriate agencies of the National Institutes of Health (including the National Library of Medicine), and the Director of the Centers for Disease Control and Prevention.

"(2) In carrying out paragraph (1), the Secretary shall collect, catalog, store, and disseminate the information described in such paragraph. The Secretary shall disseminate such information through information systems, which shall include toll-free telephone communications, available to individuals with serious or life-threatening diseases and conditions, to other members of the public, to health care providers, and to researchers.

"(3) The data bank shall include the following:

"(A) A registry of clinical trials (whether federally or privately funded) of experimental treatments for serious or life-threatening diseases and conditions under regulations promulgated pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act, which provides a description of the purpose of each experimental drug, either with the consent of the protocol sponsor, or when a trial to test effectiveness begins. Information provided shall consist of eligibility criteria for participation in the clinical trials, a description of the location of trial sites, and a point of contact for those wanting to enroll in the trial, and shall be in a form that can be readily understood by members of the public. Such information shall be forwarded to the data bank by the sponsor of the trial not later than 21 days after the approval of the protocol.

"(B) Information pertaining to experimental treatments for serious or life-threatening diseases and conditions that may be available--

"(i) under a treatment investigational new drug application that has been submitted to the Secretary under section 561(c) of the Federal Food, Drug, and Cosmetic Act; or

"(ii) as a Group C cancer drug (as defined by the National Cancer Institute).

The data bank may also include information pertaining to the

results of clinical trials of such treatments, with the consent of the sponsor, including information concerning potential toxicities or adverse effects associated with the use or administration of such experimental treatments.

"(4) The data bank shall not include information relating to an investigation if the sponsor has provided a detailed certification to the Secretary that disclosure of such information would substantially interfere with the timely enrollment of subjects in the investigation, unless the Secretary, after the receipt of the certification, provides the sponsor with a detailed written determination that such disclosure would not substantially interfere with such enrollment.

<<NOTE: Appropriation authorization.>> ``(5) For the purpose of carrying out this subsection, there are authorized to be appropriated such sums as may be necessary. Fees collected under section 736 of the Federal Food, Drug, and Cosmetic Act shall not be used in carrying out this subsection.".

<<NOTE: 42 U.S.C. 282 note.>> (b) Collaboration and Report.--

(1) In general.--The Secretary of Health and Human Services, the Director of the National Institutes of Health, and the Commissioner of Food and Drugs shall collaborate to determine the feasibility of including device investigations within the scope of the data bank under section 402(j) of the Public Health Service Act.

(2) Report.--Not later than two years after the date of enactment of this section, the Secretary of Health and Human Services shall prepare and submit to the Committee on Labor and Human Resources of the Senate and the Committee on Commerce of the House of Representatives a report--

(A) of the public health need, if any, for inclusion of device investigations within the scope of the data bank under section 402(j) of the Public Health Service Act;

(B) on the adverse impact, if any, on device innovation and research in the United States if information relating to such device investigations is required to be publicly disclosed; and

(C) on such other issues relating to such section 402(j) as the Secretary determines to be appropriate.

Guidance for Industry:

Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions

Additional copies are available from: Office of Training and Communication Division of Drug Information, HFD-240 Center for Drug Evaluation and Research Food and Drug Administration, 5600 Fishers Lane Rockville, MD 20857, (Tel) 301-827-4573 http://www.fda.gov/cder/guidance/index.htm

Or

Office of Communication, Training and Manufacturers Assistance, HFM-40 Center for Biologics Evaluation and Research Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448, http://www.fda.gov/cber/guidelines.htm. Fax: 1-888-CBERFAX or 301-827-3844 (Tel) Voice Information System at 800-835-4709 or 301-827-1800

U.S. Department of Health and Human Services
Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER)

March 2002

Procedural
TABLE OF CONTENTS

H. What happens to the information submitted to the Clinical Trials Data Bank?

I. Can I submit other information to the Clinical Trials Data Bank?

J. Should I continue submitting information to the ACTIS and PDQ databases?

K. Are there exemptions for submitting clinical trials information?

L. Is Institutional Review Board preapproval of the protocol listing required?

M. Will FDA monitor compliance?

Guidance for Industry:[1] Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

This guidance is intended to assist sponsors who will be submitting information to the Clinical Trials Data Bank. The data bank was established as required under section 113 of the Food and Drug Administration Modernization Act of 1997 (Modernization Act). This guidance combines the statutory and procedural issues discussed in two previously published draft guidances on this topic. It was finalized after considering comments received on the two draft guidances.

II. BACKGROUND

Section 113 of the Modernization Act creates a public resource for information on studies of drugs, including biological drug products, to treat serious or life-threatening diseases and conditions conducted under FDA's investigational new drug (IND) regulations (21 CFR part 312). Section 113 of the Modernization Act, enacted November 21, 1997, amends section 402 of the Public Health Service Act (42 U.S.C. 282). It directs the Secretary of Health and Human Services, acting through the Director of NIH, to establish, maintain, and operate a data bank of information on clinical trials for drugs to treat serious or life-threatening diseases and conditions.

[1] This guidance has been prepared by the Implementation Team for section 113 of the Food and Drug Administration Modernization Act of 1997, including individuals from the Office of the Commissioner, the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Center for Devices and Radiological Health (CDRH), at the Food and Drug Administration.

The Clinical Trials Data Bank is intended to be a central resource, providing current information on clinical trials to individuals with serious or life-threatening diseases or conditions, to other members of the public, and to health care providers and researchers. Specifically, section 113 of the Modernization Act requires that the Clinical Trials Data Bank contain (1) information about Federally and privately funded clinical trials for experimental treatments (drug and biological products) for patients with serious or life-threatening diseases or conditions, (2) a description of the purpose of each experimental drug, (3) patient eligibility criteria, (4) a description of the location of clinical trial sites, and (5) a point of contact for patients wanting to enroll in the trial. Section 113 of the Modernization Act requires that information provided through the Clinical Trials Data Bank be in a form that can be readily understood by the public. 42 U.S.C. 282(j)(3)(A).

The National Institutes of Health (NIH), through its National Library of Medicine (NLM) and with input from the FDA and others, developed the Clinical Trials Data Bank. The first version of the Clinical Trials Data Bank was made available to the public on February 29, 2000, on the Internet.[2] At that time, the data bank included primarily NIH-sponsored trials.

On March 29, 2000, FDA made available in the *Federal Register* a draft guidance entitled *Information Program on Clinical Trials for Serious or Life-Threatening Diseases: Establishment of a Data Bank*.[3] The draft guidance provided recommendations for industry on the submission of protocol information to the Clinical Trials Data Bank. It included information about the types of clinical trials for which submissions are required under section 113 of the Modernization Act, as well as the content of those submissions.

FDA made available a second draft guidance entitled *Information Program on Clinical Trials for Serious or Life-Threatening Diseases: Implementation Plan,* in the *Federal Register* on July 9, 2001.[4] The

---

[2] See http://clinicaltrials.gov.

[3] See 65 FR 16620 and http://www.fda.gov/cder/guidance/3585dft.htm.

[4] See 66 FR 35798 and http://www.fda.gov/cder/guidance/4602dft.htm.
Section 113 of the Modernization Act requires that you submit a description of the purpose of each experimental drug, patient eligibility criteria for participation in the trial,

second draft guidance addressed procedural issues, including how to submit required and voluntary protocol information to the Clinical Trials Data Bank, as well as issues related to submitting certification to the Secretary that disclosure of information for a particular protocol would substantially interfere with the timely enrollment of subjects in the clinical investigation. The second draft guidance also proposed a time frame for submitting the information. This final guidance combines the two draft guidances into a single guidance.

III. REQUIREMENTS UNDER SECTION 113 OF THE MODERNIZATION ACT FOR IND SPONSORS

A. What information must I submit to the Clinical Trials Data Bank?

Section 113 of the Modernization Act requires you to submit information to the data bank about a clinical trial conducted under an investigational new drug (IND) application if it is for a drug to treat a serious or life-threatening disease or condition and it is a trial to test effectiveness (42 U.S.C. 282(j)(3)(A)). If you wish, you can also provide information on non-effectiveness trials or for drugs to treat conditions not considered serious or life-threatening.

Section 113 requires that the data bank provide this information in a form that can be readily understood by members of the public (42 U.S.C. 282(j)(3)(A)).

To ensure that information available through the Clinical Trials Data Bank is in a form that is readily understood, we have established four data elements, which are listed below. The data elements are made up of the following data fields: (1) descriptive information, (2) recruitment information, (3) location and contact information, and (4) administrative data. We have established the Protocol Registration System (PRS), a Web-based data processing program, to facilitate collection of this information for the data bank. The four data elements, which are listed below, as well as definitions applicable to the PRS, can be viewed at http://prsinfo.clinicaltrials.gov/.

---

a description of the location of clinical trial sites, and a point of contact for those wanting to enroll in the trial.

1. Descriptive Information

Brief Title (in lay language)
Brief Summary (in lay language)
Study Design/Study Phase/Study Type
Condition or Disease
Intervention

2. Recruitment Information

Study Status Information, Including:

- Overall Study Status (e.g., recruiting, no longer recruiting)
- Individual Site Status
- Eligibility Criteria/Gender/Age

3. Location and Contact Information

Location of Trial Contact Information (includes an option to list a central contact person for all trial sites)

4. Administrative Data

Unique Protocol ID Number
Study Sponsor
Verification Date

To verify the existence of an IND and to assist in administrative tracking, we ask that you also include in your submission the IND number and serial number and designate whether the IND is located in the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER). This administrative information is in a separate data field and will not be made public.

B. When should I begin submitting clinical trial information?

Section 113 of the Modernization Act requires that sponsors submit information no later than 21 days after the trial is opened for enrollment[5] (42 U.S.C. 282(j)(3)). Section 113 does not specify when sponsors must submit information about clinical trials that are existing and ongoing. To provide a transitional period for sponsors of clinical trials that are currently ongoing and expected to continue enrolling patients for more than 45 days, we ask that you submit information within 45 days after this guidance is made available through the *Federal Register*. We encourage you to submit information through the PRS for inclusion in the data bank as soon as possible.[6]

C. Can I submit my information at specified intervals rather than on a rolling basis?

As discussed above, you must submit information about new protocols open for enrollment within 21 days after the trial is open for enrollment (42 U.S.C. 282(j)(3)), and we request that you submit information about existing ongoing trials within 45 days after this guidance is published. Supplemental information can be submitted at 30-day intervals. Such information includes amendments to the protocol with respect to one of the data elements, or interruptions, continuations, or completion of enrollment for a study. Protocol changes related to eligibility or status information, such as routine opening and closing of trial sites, can be made at 30-day intervals. FDA strongly encourages you to update information about trials that are unexpectedly closed (e.g., clinical hold) within 10 days after the closing or sooner if possible. To ensure that the information available through the data bank is timely and accurate, FDA also encourages you to review, verify, and update all active protocol records on a semi-annual basis, at a minimum.

---

[5] Section 113 says "not later than 21 days after the approval of the protocol. Because the Agency does not approve protocols, we have interpreted this to mean within 21 days after the trial is open for enrollment.

[6] See http://prsinfo.clinicaltrials.gov.

D. What is a trial for a serious or life-threatening disease or condition?

FDA has defined serious and life-threatening diseases and conditions in previous documents. Most recently, FDA discussed issues related to products intended to treat serious or life-threatening diseases and conditions in the guidance for industry on *Fast Track Drug Development Programs—Designation, Development, and Application Review* (November 1998).[7] In that guidance, we stated that all conditions meeting the definition of life-threatening, as set forth at 21 CFR 312.81(a), would also be serious conditions. The term *life-threatening* is defined as (1) diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and (2) diseases or conditions with potentially fatal outcomes, where the endpoint of clinical trial analysis is survival (21 CFR 312.81(a)). All references in this document to serious diseases or conditions include life-threatening diseases and conditions.

As FDA reiterated in the *Fast Track Guidance*, the seriousness of a disease is a matter of judgment, but generally is based on such factors as survival, day-to-day functioning, and the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one. For example, acquired immunodeficiency syndrome (AIDS), all other stages of human immunodeficiency virus (HIV) infection, Alzheimer's disease, angina pectoris, heart failure, cancer, and many other diseases are clearly serious in their full manifestations. Furthermore, many chronic illnesses that are generally well managed by available therapy can have serious outcomes. For example, inflammatory bowel disease, asthma, rheumatoid arthritis, diabetes mellitus, systemic lupus erythematosus, depression, psychoses, and many other diseases can be serious in some or all of their phases or for certain populations.

Any investigational drug that has received fast track designation would be considered a drug to treat a serious disease or condition.[8] Information on effectiveness trials for drugs that have received fast

[7] CDER guidances are available at http://www.fda.gov/cder/guidance/index.htm.

[8] That a drug is intended to treat a serious or life-threatening disease or condition, however, does not mean that it fills an unmet medical need and qualifies for fast track designation under section 506 of the Food, Drug and Cosmetic Act (21 U.S.C. 356).

track designation would qualify for submission to the Clinical Trials Data Bank.

E. What is a trial to test effectiveness?

Not all trials carried out under 21 CFR part 312 are trials to test effectiveness. FDA considers all phase 2, phase 3, and phase 4 trials with efficacy endpoints as trials to test effectiveness.[9]

F. Which trials are provided to the public through the Clinical Trials Data Bank?

Section 113 of the Modernization Act requires sponsors to submit information about clinical trials of experimental treatments for serious diseases and conditions when conducted under the IND regulations. 42 U.S.C. 282(j)(3)(A). Such information can be submitted at any time with the consent of the protocol sponsor, and must be submitted within 21 days after a trial to test effectiveness begins. In addition, section 113 of the Modernization Act states that information on all treatment IND protocols and all Group C protocols[10] must be included in the Clinical Trials Data Bank.

Although it is not specifically discussed in section 113 of the Modernization Act, there are situations in which there may be a significant number of patients with the disease or condition for which the drug is being developed who are not adequately treated by existing therapy, who do not meet the eligibility criteria for enrollment, or who are otherwise unable to participate in a controlled clinical study. In these situations, sponsors may have initiated one or more expanded access protocols that include such patients. In such cases, FDA

---

[9] Listing a trial in the Clinical Trials Data Bank is not a guarantee that the trial design is considered adequate to support approval of a drug, nor does it reflect any judgment on the conduct, analysis, or outcome of the study.

[10] "Group C protocols" refers to investigational drugs designated by FDA for the treatment of specific cancers. These drugs have reproducible efficacy in one or more specific tumor types. Such a drug (Q: change to plural? See previous sentence) has altered or is likely to alter the pattern of treatment of disease and can be safely administered by properly trained physicians without specialized supportive care facilities. See National Cancer Institute Handbook for Investigators, Appendix XV, "Policy for Group C Drug Distribution," http://ctep.info.nih.gov/HandbookText/Appendix_XV.htm#Proc_Mgmt_GrpC_Prot.

strongly recommends that sponsors also consider submitting information to the Clinical Trials Data Bank about the availability of any expanded access protocol for treatment use in addition to required submissions.

For protocols not specifically mentioned above, sponsors should review each protocol submitted to an IND to determine if the protocol is for a serious disease or condition and if it is a trial to test effectiveness. If the protocol meets these criteria, the sponsor must submit information about the trial to the Clinical Trials Data Bank, ***unless*** the sponsor provides detailed certification to FDA that such a disclosure would substantially interfere with the timely enrollment of subjects in the investigation (42 U.S.C. 282(j)(3) and (j)(4)). Sponsors with questions on whether protocols meet the criteria for submission to the Clinical Trials Data Bank are encouraged to contact the appropriate review division for additional guidance.

G. Must I include information about foreign trial sites?

Yes, you must include information about foreign trials when those trials are conducted under an IND submitted to FDA and the trial meets the criteria for submission to the Clinical Trials Data Bank. Section 113 of the Modernization Act requires sponsors to submit information about specified clinical trials that are "under regulations promulgated pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act," which are FDA's IND regulations (42 U.S.C. 282(j)(3)). Sponsors may voluntarily conduct a foreign trial under the IND regulations. Sponsors are not required to submit information to the Clinical Trials Data Bank when a foreign trial is not conducted under an IND.

IV. IMPLEMENTATION ISSUES

A. How do I submit information to the Clinical Trials Data Bank?

To facilitate the submission process, we have established the Web-based PRS at ClinicalTrials.gov. The system allows for entry of required and voluntary information about clinical trials. You or your designee can initiate submission of clinical trial information to ClinicalTrials.gov by completing a registration form at http://prsinfo.clinicaltrials.gov/.

After you have entered the data, the PRS generates a receipt for use by sponsors. An electronic copy of the receipt will be sent to the FDA.

B. What information about trial sites must be included?

Section 113 of the Modernization Act requires sponsors to submit a description of the location of trial sites and a point of contact. To ensure an adequate description, we recommend that you provide for each individual trial site the full name of the organization, city, state, postal code, and country where the protocol is being conducted; and a central contact name and phone number. You can also provide the names and phone numbers of individual site contacts.

C. How long does it take for information to be made available on ClinicalTrials.gov?

Studies will be made available to the public through ClinicalTrials.gov within two to five days after submission by the sponsor.

D. How long will information about studies remain available through ClinicalTrials.gov?

NLM intends to maintain the Data Bank as a long-term registry of clinical trials. Therefore, in addition to information about open trials, information about closed trials will also be available through ClinicalTrials.gov, even after accrual and analysis are completed and the product is approved.

E. Can information be transferred from a sponsor computer to the PRS?

Yes. Information can be transferred according to the format specified by the PRS. The PRS has a mechanism for uploading and downloading XML-formatted protocol records. Instructions for transferring information are provided at http://prsinfo.clinicaltrials.gov/.

F. Can intermediaries acting on behalf of a sponsor submit data?

Yes. For example, in some cases a sponsor might want to contract with an information management company to serve as an intermediary in preparing data for inclusion in ClinicalTrials.gov. The information management company, when authorized by the sponsor, could act on behalf of the sponsor for this purpose.

G. Can sponsors designate multiple individuals to be data providers?

Yes. When sponsors register to become a PRS data provider, they will be given information, including instructions, for creating additional users for their accounts. A sponsor can control access to the account by designating users and administrators for the account.

H. What happens to the information submitted to the Clinical Trials Data Bank?

Except for the IND number, serial number, and FDA center designation, all information submitted through the PRS is made available to the public at http://clinicaltrials.gov.

I. Can I submit other information to the Clinical Trials Data Bank?

Yes. PRS is designed to permit you to submit more detailed information about a protocol. Additional data fields (e.g., projected enrollment) and their definitions are included in the PRS. You also can submit protocol information about other clinical trials under IND, including trials for a disease or condition that is not serious or any trial that is not designed to test effectiveness.

Finally, you can submit information about results of a trial. This information, which, according to the structure of the Clinical Trials Data Bank, must come from the published literature, should be linked by including the unique MEDLINE identifier for citations of publications.

You can use the link section provided to allow pointers to Web pages directly relevant to the protocol. If you link to other Web pages from your entries, you should ensure that the links do not misbrand your products, for example, by promoting the products before the product or

an indication is approved. (See 21 U.S.C. 321(n), 331(a)(b)(c)(d), 352(a)(n), http://www.fda.gov/opacom/laws/fdcact/fdcact1.htm.) When inputting links to other Web pages, the database will instruct you that the links should be directly relevant to the protocol, and that you should not link to sites whose primary goal is to advertise or sell commercial products or services.

J. Should I continue submitting information to the ACTIS and PDQ databases?

No. All information for AIDS and cancer protocols that meet the requirements of section 113 of the Modernization Act must now be submitted to ClinicalTrials.gov through the PRS. Data from the current AIDS Clinical Trials Information System (ACTIS) and Physician's Data Query (PDQ) databases are included in ClinicalTrials.gov. Information from the Rare Diseases and National Institute of Aging Databases is also included in ClinicalTrials.gov.

K. Are there exemptions for submitting clinical trials information?

Information about an investigation will not be included in the data bank if you provide a detailed certification to the Secretary of Health and Human Services that disclosure of such information would substantially interfere with timely enrollment of subjects in the clinical trial and the Secretary does not disagree. If there is disagreement, the Secretary will provide a detailed written determination that such disclosure would not substantially interfere with such enrollment (42 U.S.C. 282(j)(4)).

FDA has not identified specific instances when disclosure of information would substantially interfere with enrollment of subjects in a clinical investigation. We solicited comments on this topic for the purpose of including a listing of acceptable reasons for certification in the final guidance. We received no comments. Therefore, if you identify a specific instance when disclosure of information would interfere with enrollment of subjects in a clinical investigation, FDA will consider your request on a case-by-case-basis.

All requests for exemption should be forwarded to Director, Office of Special Health Issues, Office of Communications and Constituent Relations, Office of the Commissioner, HF-12, 5600 Fishers Lane,

Rockville, MD 20857, or by email at 113trials@oc.fda.gov, or by fax at 301-443-4555.

L. Is Institutional Review Board preapproval of the protocol listing required?

No. Section 113 of the Modernization Act does not require prior IRB approval when submitting this information to the Clinical Trials Data Bank. Current FDA guidance recommends that IRB review of listings need not occur when, as here, the system format limits the information provided to basic information, such as title, purpose of the study, protocol summary, basic eligibility criteria, study site locations, and how to contact the site for further information.[11]

M. Will FDA monitor compliance?

A copy of the protocol listing in ClinicalTrials.gov will be sent to the FDA. FDA's Office of Special Health Issues intends to initiate a one-year pilot educational program in 2002 that will include a component to evaluate compliance. The primary objective of the pilot program is to educate sponsors about the existence of the guidance document and the availability of the online PRS data entry tool. The secondary objective of the pilot program is to evaluate the success of the educational initiative. The pilot, which will measure the number of protocols (voluntary and required) made available through the ClinicalTrials.gov database, will provide FDA with compliance information.

[11] The 1998 update of *Information Sheets: Guidance for Institutional Review Boards and Clinical Investigators* provides guidance on IRB review and approval of listings of clinical trials on the Internet. See http://www.fda.gov/oc/ohrt/irbs/toc4.html#recruiting.

D

Published Journal Editorials

Clinical Trial Registration: A Statement from the International Committee of Medical Journal Editors

Altruism and trust lie at the heart of research on human subjects. Altruistic individuals volunteer for research because they trust that their participation will contribute to improved health for others and that researchers will minimize risks to participants. In return for the altruism and trust that make clinical research possible, the research enterprise has an obligation to conduct research ethically and to report it honestly. Honest reporting begins with revealing the existence of all clinical studies, even those that reflect unfavorably on a research sponsor's product.

Unfortunately, selective reporting of trials does occur, and it distorts the body of evidence available for clinical decision making. Researchers (and journal editors) are generally most enthusiastic about the publication of trials that show either a large effect of a new treatment (positive trials) or equivalence of two approaches to treatment (noninferiority trials). Researchers (and journals) typically are less excited about trials that show that a new treatment is inferior to standard treatment (negative trials) and even less interested in trials that are neither clearly positive nor clearly negative, since inconclusive trials will not in themselves change practice. Irrespective of their scientific interest, trial results that place financial interests at risk are particularly likely to remain unpublished and hidden from public view. The interests of the sponsor or authors notwithstanding, anyone should be able to learn of any trial's existence and its important characteristics.

The case against selective reporting is particularly compelling for research that tests interventions that could enter mainstream clinical practice. Rather than a single trial, it is usually a body of evidence, consisting of many studies, that changes medical practice. When research sponsors or investigators conceal the presence of selected trials, these studies cannot influence the thinking of patients, clinicians, other researchers, and experts who write practice guidelines or decide on insurance-coverage policy. If all trials are registered in a public repository at their inception, every trial's existence is part of the public record and the many stakeholders in clinical research can explore the full range of clinical evi-

dence. We are far from this ideal at present, since trial registration is largely voluntary, registry data sets and public access to them vary, and registries contain only a small proportion of trials. In this editorial, published simultaneously in all member journals, the International Committee of Medical Journal Editors (ICMJE) proposes comprehensive trials registration as a solution to the problem of selective awareness and announces that all 11 ICMJE member journals will adopt a trials-registration policy to promote this goal.

The ICMJE member journals will require, as a condition of consideration for publication, registration in a public trials registry. Trials must register at or before the onset of patient enrollment. This policy applies to any clinical trial starting enrollment after July 1, 2005. For trials that began enrollment prior to this date, the ICMJE member journals will require registration by September 13, 2005, before considering the trial for publication. We speak only for ourselves, but we encourage editors of other biomedical journals to adopt similar policies. For this purpose, the ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Studies designed for other purposes, such as to study pharmacokinetics or major toxicity (for example, phase I trials), would be exempt.

The ICMJE does not advocate one particular registry, but its member journals will require authors to register their trial in a registry that meets several criteria. The registry must be accessible to the public at no charge. It must be open to all prospective registrants and managed by a not-for-profit organization. There must be a mechanism to ensure the validity of the registration data, and the registry should be electronically searchable. An acceptable registry must include at minimum the following information: a unique identifying number, a statement of the intervention (or interventions) and comparison (or comparisons) studied, a statement of the study hypothesis, definitions of the primary and secondary outcome measures, eligibility criteria, key trial dates (registration date, anticipated or actual start date, anticipated or actual date of last follow-up, planned or actual date of closure to data entry, and date trial data considered complete), target number of subjects, funding source, and contact information for the principal investigator. To our knowledge, at present, only www.clinicaltrials.gov, sponsored by the United States National Library of Medicine, meets these requirements; there may be other registries, now or in the future, that meet all these requirements.

Registration is only part of the means to an end; that end is full transparency with respect to performance and reporting of clinical trials. Research sponsors may argue that public registration of clinical trials will result in unnecessary bureaucratic delays and destroy their competitive edge by allowing competitors full access to their research plans. We argue that enhanced public confidence in the research enterprise will compensate for the costs of full disclosure. Patients who volunteer to participate in clinical trials deserve to know that their contribution to improving human health will be available to inform health care decisions. The knowledge made possible by their collective altruism must be accessible to everyone. Required trial registration will advance this goal.

Catherine De Angelis, MD, MPH Editor-in-Chief, *Journal of the American Medical Association*
Jeffrey M. Drazen, MD Editor-in-Chief, *New England Journal of Medicine*
Frank A. Frizelle, MB, ChB, MMedSc, FRACS Editor, *The New Zealand Medical Journal*
Charlotte Haug, MD, PhD, MSc Editor-in-Chief, *Norwegian Medical Journal*
John Hoey, MD Editor, *Canadian Medical Association Journal*
Richard Horton, FRCP Editor, *The Lancet*
Sheldon Kotzin, MLS Executive Editor, MEDLINE, National Library of Medicine
Christine Laine, MD, MPH Senior Deputy Editor, *Annals of Internal Medicine*
Ana Marusic, MD, PhD Editor, *Croatian Medical Journal*
A. John P.M. Overbeke, MD, PhD Executive Editor, *Nederlands Tijdschrift voor Geneeskunde (Dutch Journal of Medicine)*
Torben V. Schroeder, MD, DMSc Editor, *Journal of the Danish Medical Association*
Harold C. Sox, MD Editor, *Annals of Internal Medicine*
Martin B. Van Der Weyden, MD Editor, *The Medical Journal of Australia*

Original editorial available at www.ICMJE.com.

Is This Clinical Trial Fully Registered?—A Statement from the International Committee of Medical Journal Editors

Catherine D. De Angelis, M.D., M.P.H., Jeffrey M. Drazen, M.D., Frank A. Frizelle, M.B.,Ch.B., M.Med.Sc., F.R.A.C.S., Charlotte Haug, M.D., Ph.D., M.Sc., John Hoey, M.D., Richard Horton, F.R.C.P., Sheldon Kotzin, M.L.S., Christine Laine, M.D., M.P.H., Ana Marusic, M.D., Ph.D., A. John P.M. Overbeke, M.D., Ph.D., Torben V. Schroeder, M.D., D.M.Sc., Harold C. Sox, M.D., and Martin B. Van Der Weyden, M.D.

In September 2004, the members of the International Committee of Medical Journal Editors (ICMJE) published a joint editorial aimed at promoting registration of all clinical trials (De Angelis et al., 2004). We stated that we will consider a trial for publication only if it has been registered before the enrollment of the first patient. This policy applies to trials that start recruiting on or after July 1, 2005. Because many ongoing trials were not registered at inception, we will consider for publication ongoing trials that are registered before September 13, 2005. Our goal then and now is to foster a comprehensive, publicly available database of clinical trials. A complete registry of trials would be a fitting way to thank the thousands of participants who have placed themselves at risk by volunteering for clinical trials. They deserve to know that the information that accrues from their altruism is part of the public record, where it is available to guide decisions about patient care, and deserve to know that decisions about their care rest on all of the evidence, not just the trials that authors decided to report and that journal editors decided to publish.

We are not alone in pursuing this goal. The World Health Organization (WHO), through meetings in New York, Mexico City, and Geneva, has brought us close to the goal of a single worldwide standard for the information that trial authors must disclose. Around the world, governments are beginning to legislate mandatory disclosure of all trials. For example, among the bodies considering new legislation is the U.S. Congress, where the proposed Fair Access to Clinical Trials (FACT) Act would expand the current mandate for registration of clinical trials. Many other journals have adopted our policy of requiring trial registration. These initiatives show that trial registration has become a public issue. But, as our deadline for registration approaches, trial authors and spon-

sors want to be sure that they understand our requirements, so that reports of their research will be eligible for editorial review. The purpose of this joint and simultaneously published editorial is to answer questions about the ICMJE initiative and to bring our position into harmony with that of others who are working toward the same end.

Our definition of a clinical trial remains essentially the same as in our September 2004 editorial: "Any research project that prospectively assigns human subjects to intervention and comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome." By "medical intervention" we mean any intervention used to modify a health outcome. This definition includes drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. We update our 2004 editorial to state that a trial must have at least one prospectively assigned *concurrent* control or comparison group in order to trigger the requirement for registration.

Among the trials that meet this definition, which need to be registered? The ICMJE wants to ensure public access to all "clinically directive" trials—trials that test a clinical hypothesis about health outcomes (e.g., "Is drug X as effective as drug Y in treating heart failure?"). We have excluded trials from our registration requirement if their primary goal is to assess major unknown toxicity or determine pharmacokinetics (phase 1 trials). In contrast, we think the public deserves to know about trials that could shape the body of evidence about clinical effectiveness or adverse effects. Therefore, we require registration of all trials whose primary purpose is to affect clinical practice (phase 3 trials). Between these two extremes are some clinical trials whose prespecified goal is to investigate the biology of disease or to provide preliminary data that may lead to larger, clinically directive trials.

We recognize that requiring public registration of trials whose prespecified goal is to investigate the biology of disease or to direct further research might slow the forces that drive innovation. Therefore, each journal editor will decide on a case-by-case basis about reviewing unregistered trials in this category. Authors whose trial is unregistered will have to convince the editor that they had a sound rationale when they decided not to register their trial. The ICMJE will maintain this policy for the next two years. We will then review our experience.

Our September 2004 editorial specified the information that we would require for trial registration. Attendees at a recent meeting of the WHO registration advisory group identified a minimal registration data set of 20 items (Table D-1). The WHO-mandated items collectively ad-

dress every key requirement that we established in our September 2004 editorial. The ICMJE supports the WHO minimal data set and has adopted it as the ICMJE's requirement: we will consider a trial for publication if the authors register it at inception by completing all 20 fields in the WHO minimal data set. As individual editors, we will review the data in the registration fields when we decide whether to consider the trial for publication. We will consider a registration data set inadequate if it has missing fields or fields that contain uninformative terminology. If an investigator has already registered a clinical trial in a publicly owned, publicly accessible registry using the data fields that we specified in our 2004 editorial, we will consider that registration to be complete as long as each field contains useful information.

TABLE D-1
Minimal Registration Data Set*

Item	Comment
1.	Unique trial number The unique trial number will be established be the primary registering entity (the registry).
2.	Trial registration date The date of registration will be established by the primary registering entity.
3.	Secondary IDs May be assigned by sponsors or other interested parties (there may be none).
4.	Funding source(s) Name of the organization(s) that provided funding for the study.
5.	Primary sponsor The main entity responsible for performing the research.
6.	Secondary sponsor(s) The secondary entities, if any, responsible for performing the research.
7.	Responsible contact person Public contact person for the trial, for patients interested in participating.
8.	Research contact person Person to contact for scientific inquiries about the trial.

9. Title of the study
   Brief title chosen by the research group (can be omitted if the researchers wish).

10. Official scientific title of the study
    This title must include the name of the intervention, the condition being studied, and the outcome (e.g., The International Study of Digoxin and Death from Congestive Heart Failure).

11. Research ethics review
    Has the study at the time of registration received appropriate ethics committee approval (yes/no)? (It is assumed that all registered trials will be approved by an ethics board before commencing.)

12. Condition
    The medical condition being studied (e.g., asthma, myocardial infarction, depression).

13. Intervention(s)
    A description of the study and comparison/control intervention(s) (for a drug or other product registered for public sale anywhere in the world, this is the generic name; for an unregistered drug the generic name or company serial number is acceptable). The duration of the intervention(s) must be specified.

14. Key inclusion and exclusion criteria
    Key patient characteristics that determine eligibility for participation in the study.

15. Study type
    Database should provide drop-down lists for selection. This would include choices for randomized vs. non-randomized, type of masking (e.g., double-blind, single-blind), type of controls (e.g., placebo, active), and group assignment, (e.g., parallel, crossover, factorial).

16. Anticipated trial start date
    Estimated enrollment date of the first participant.

17. Target sample size
    The total number of subjects the investigators plan to enroll before closing the trial to new participants.

18. Recruitment status
    Is this information available (yes/no) (if yes, link to information).

19. Primary outcome
    The primary outcome that the study was designed to evaluate. Description should include the time at which the outcome is measured (e.g., blood pressure at 12 months).

20. Key secondary outcomes
The secondary outcomes specified in the protocol. Description should include time of measurement (e.g., creatinine clearance at 6 months).

*The data fields were specified at a meeting convened by the WHO in April 2004; the explanatory comments are largely from the ICMJE.

Acceptable completion of data fields is an important concern. It shouldn't be, but it is. Many entries in the publicly accessible clinicaltrials.gov database do not provide meaningful information in some key data fields. A search conducted on May 4, 2005 (Zarin D.: personal communication) indicates that certain pharmaceutical-company entries list a meaningless phrase (e.g., "investigational drug") in place of the actual name of the drug, even though a U.S. law requires trial registrants to provide "intervention name" (www.fda.gov/cder/guidance/4856fnl.htm). Many companies and other entities are completing the data fields in a meaningful fashion. Data entries must include information that will be of value to patients and health professionals; the intervention name is needed if one is to search on that intervention.

We recognize that clinical trial registries have many uses, but whatever the use, a worldwide uniform standard for a minimal database is necessary. We have participated in the WHO effort to establish a clinically meaningful trial registration process. The ICMJE supports this ongoing project. When it is complete we will evaluate the process, and if it meets our primary objectives, we will adopt it.

We stated our requirements for an acceptable trial registry in the September 2004 editorial, and they remain the same. The registry must be electronically searchable and accessible to the public at no charge. It must be open to all registrants and not for profit. It must have a mechanism to ensure the validity of the registration data.

The purpose of a clinical trials registry is to promote the public good by ensuring that everyone can find key information about every clinical trial whose principal aim is to shape medical decision making. We will do what we can to help reach this goal. We urge all parties to register new and ongoing clinical trials. If in doubt about whether a trial is "clinically directive," register it. Don't use meaningless phrases to describe key information. Every trial participant and every investigator should be asking, "Is this clinical trial fully registered?"

Catherine D. De Angelis, M.D., M.P.H.
Editor-in-Chief, Journal of the American Medical Association

Jeffrey M. Drazen, M.D.
Editor-in-Chief, New England Journal of Medicine

Frank A. Frizelle, M.B., Ch.B., M.Med.Sc., F.R.A.C.S. *Editor, The New Zealand Medical Journal*

Charlotte Haug, M.D., Ph.D., M.Sc.
Editor-in-Chief, Norwegian Medical Journal

John Hoey, M.D.
Editor, Canadian Medical Association Journal

Richard Horton, F.R.C.P.
Editor, The Lancet

Sheldon Kotzin, M.L.S.
Executive Editor, MEDLINE, National Library of Medicine

Christine Laine, M.D., M.P.H.
Senior Deputy Editor, Annals of Internal Medicine

Ana Marusic, M.D., Ph.D.
Editor, Croatian Medical Journal

A. John P.M. Overbeke, M.D., Ph.D.
Executive Editor, Nederlands Tijdschrift voor Geneeskunde (Dutch Journal of Medicine)

Torben V. Schroeder, M.D., D.M.Sc.
Editor, Journal of the Danish Medical Association

Harold C. Sox, M.D.
Editor, Annals of Internal Medicine

Martin B. Van Der Weyden, M.D.
Editor, The Medical Journal of Australia

REFERENCE

De Angelis C, Drazen JM, Frizelle FA, et al. 2004. Clinical trial registration: A statement from the International Committee of Medical Journal Editors. *New England Journal of Medicine* 351:1250–1251.

Original editorial available at www.ICMJE.com.

E

Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases[1]

The innovative pharmaceutical industry, which is represented worldwide by the European Federation of Pharmaceutical Industries and Associations (EFPIA), the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), the Japanese Pharmaceutical Manufacturers Association (JPMA), and the Pharmaceutical Research and Manufacturers of America (PhRMA), is committed to increasing the transparency of the clinical trials our member companies sponsor. We recognize that there are important public health benefits associated with making clinical trial information more widely available to health care practitioners, patients, and others. Such disclosure, however, must maintain protections for individual privacy, intellectual property, and contract rights, as well as conform to the regulations in relevant countries. We thus commit to the following principles regarding the disclosure of information relating to clinical trials we sponsor and appeal to all sponsors of clinical trials to commit to keeping these registries accurate and up to date.

Clinical Trial Registry

A clinical trial registry serves as a repository for information on ongoing clinical trials. The innovative pharmaceutical industry commits to make the following information available on ongoing clinical trials we sponsor involving pharmaceutical products:

[1]A number of different terms are in current usage to describe electronic repositories for various types of clinical trial information. This position uses the term "registry" for information on ongoing clinical studies, and "database" for the results of completed clinical studies. However, the term "database" has been applied elsewhere for information on ongoing clinical studies, and the term "register"' for the results of completed clinical studies.

- All clinical trials, other than exploratory trials,[2] should be submitted for listing in a free, publicly accessible clinical trial registry within 21 days of the initiation of patient enrollment, unless there are alternative national requirements.
- The registry should contain basic information about each trial sufficient to inform interested subjects (and their health care practitioners) about how to enroll in the trial. This would include, at a minimum, the following information: brief title; trial description in lay terminology; trial phase; trial type (e.g., interventional); trial status; trial purpose (e.g., treatment, diagnosis, prevention); intervention type (e.g., drug, vaccine); condition or disease; key eligibility criteria, including gender and age; the location of the trial; and contact information. Industry is also prepared to explore the concept of placing additional protocol information in a secure, non-public, third-party electronic repository[3] for subsequent disclosure to medical journals when publication is sought.
- Each trial listed in the registry should be given a unique identifier to ensure transparency of clinical trial results. The unique identifier should permit registry users to track the trial through multiple databases, including clinical trial results databases.
- Registration of clinical trials on any one of a number of internet-based registries may achieve these objectives. The clinical trial registry maintained by the National Library of Medicine in the US at www.clinicaltrials.gov is already in place and can be used for this purpose, regardless of where the trial is conducted.

Clinical Trial Results Database

A clinical trial results database serves as a repository for the summary results of completed clinical trials. The innovative pharmaceutical

[2]Throughout this document the phrase "all clinical trials, other than exploratory trials" is intended to have the same meaning as the terms "hypothesis-testing clinical trials," also known as "confirmatory clinical trials" as defined in the ICH Harmonised Tripartite Guideline E9. Statistical Principles for Clinical Trials. Stats Med 1999; 18:1905-42. Whereas exploratory trials serve to set direction (i.e., to generate hypotheses) for possible future studies, "hypothesis-testing trials" serve to examine pre-stated questions (i.e., to test hypotheses) using statistically valid plans for data analysis and provide firm evidence of safety and/or efficacy to support product claims.

[3]An example exists in Europe where recent legislation set up a database, "EudraCT," containing information on all interventional clinical trials of medicines initiated in the Community from 1 May 2004. "EudraCT" is accessible to European Regulatory Authorities from the time of data submission (i.e., trial initiation). Some data fields will subsequently be made publicly accessible once the product is approved.

industry commits to make the following information available on completed clinical trials:

- The results of all clinical trials, other than exploratory trials,[2] conducted on a drug that is approved for marketing and is commercially available in at least one country should be publicly disclosed on a free, publicly accessible, clinical trial results database, regardless of outcome. Trial results from exploratory trials also should be publicly disclosed if they are deemed to have significant medical importance and may have an impact on a marketed product's labeling.
- This disclosure policy applies to drug products that have been approved for marketing and are commercially available in at least one country. However, if trial results for an investigational product that has failed in development have significant medical importance, study sponsors are encouraged to post the results if possible. In all cases disclosure should be undertaken in a manner consistent with applicable local laws.
- If trial results are published in a peer-reviewed medical journal, the database should include a citation to or link to the journal article and/or a summary of the results in a standard, nonpromotional format, such as the ICH E-3 summary format, that includes a description of the trial design and methodology, results of the primary and secondary outcome measures, and safety results. If trials results are not published in a journal, the results should be posted on the database in the ICH E-3 summary format.
- The results should include the unique identifier used to register the trial at inception.
- The results generally should be posted within one year after the drug is first approved and commercially available in any country or, for trials completed after this initial approval, within one year of trial completion, unless such posting would compromise publication in a peer-reviewed medical journal or contravene national laws or regulations.
- Publication of clinical trials on any one of a number of internet-based databases may achieve these objectives. We also support the use of an industry-wide clinical trial results database, including, to the extent appropriate and feasible, the PhRMA Clinical Study Results Database available at www.clinicalstudyresults.org, as well as company-specific databases.

Implementation Dates

- Trials initiated on or after July 1, 2005, and meeting the above requirements should be included in a clinical trial registry.
- Ongoing clinical trials meeting the above requirements should be included in a clinical trial registry by September 13, 2005.
- With respect to the posting of clinical trial results, this proposal applies to clinical trials meeting the above requirements that have been completed since the publication date of this joint position statement.

Compliance

- Companies subscribing to the joint position should establish a process of verification for both the clinical trial registry and the clinical trial database. Companies are encouraged to make public how they will adhere to these standards.

Original article available at www.ifpma.org.

F

Illustrative Data Fields for the Results Summary (based on ICH E3 template*)

These results are supplied for informational purposes only. Prescribing decisions should be made based on the approved package insert.		
Proprietary drug name:	Generic drug name:	Therapeutic area and FDA-approved indications:
Name of sponsor/company:		
Title of study:		
Principal study investigators:		
Study Center(s):		
Publication (reference, if applicable):		
Studied period (years): (date of first enrollment): (date of last completed):		Phase of development:
Objectives:		
Methodology:		
Number of patients (planned and analyzed):		
Diagnosis and main criteria for inclusion:		

Test product, dose and mode of administration, batch number:
Duration of treatment:
Reference therapy, dose and mode of administration, batch number:
Criteria for evaluation: Efficacy: Safety:
Statistical methods:
SUMMARY CONCLUSIONS Efficacy results: Safety results: Conclusion: Date of the report:

*Based on the ICH E3 template in the Food and Drug Administration (FDA) report, *Guideline for Industry Structure and Content of Clinical Study Reports*, July 1996.

G

Biographical Sketches of Committee Members

PHILIP PIZZO (Chair) is dean of the Stanford University School of Medicine where he is also Professor of Pediatrics and of Microbiology and immunology. Dr. Pizzo has previously served as the physician-in-chief and Chairman of the Department of Medicine at Children's Hospital Boston and professor and Chair of Pediatrics at Harvard Medical School. Dr. Pizzo's research efforts have focused on the treatment of childhood cancers and on the diagnosis, management, and prevention of infectious complications in immunocompromised hosts. He and his colleagues pioneered the development of new treatments for children with symptomatic HIV infection and changed the process of drug development for children with catastrophic disease. Positions he has held within the government include: pediatric oncology investigator at the National Institutes of Health, clinical associate with the National Cancer Institute (NCI),Chief of Pediatrics and Head of the Infectious Disease Section at NCI, and Acting Scientific Director of NCI's Division of Clinical Sciences. Dr. Pizzo is a member of both the Institute of Medicine, and the National Academy of Sciences.

GAIL H. CASSELL is Vice President, Scientific Affairs, Distinguished Lilly Research Scholar for Infectious Diseases, Eli Lilly & Company. Previously, she was the Charles H. McCauley Professor and (since 1987) Chair, Department of Microbiology, University of Alabama Schools of Medicine and Dentistry at Birmingham, a department which, under her leadership, has ranked first in research funding from the National Institutes of Health since 1989. She is a member of the Director’s Advisory Committee of the Centers for Disease Control and Prevention. Dr. Cassell is past president of the American Society for Microbiology (ASM) and is serving her third three-year term as chairman of the Public

and Scientific Affairs Board of ASM. She is a former member of the National Institutes of Health Director's Advisory Committee and a former member of the Advisory Council of the National Institute of Allergy and Infectious Diseases. She has also served as an advisor on infectious diseases and indirect costs of research to the White House Office on Science and Technology and was previously chair of the Board of Scientific Counselors of the National Center for Infectious Diseases, Centers for Disease Control and Prevention. Dr. Cassell served eight years on the Bacteriology-Mycology-II Study Section and served as its chair for three years. She serves on the editorial boards of several prestigious scientific journals and has authored over 275 articles and book chapters. She has been intimately involved in the establishment of science policy and legislation related to biomedical research and public health. Dr. Cassell has received several national and international awards and an honorary degree for her research on infectious diseases.

ELLEN WRIGHT CLAYTON is one of the preeminent scholars in the field of law and genetics. She joined the Vanderbilt faculty in 1988 and holds appointments in both the Medical School and Law School. She has numerous publications in books, medical journals, interdisciplinary journals, and law journals on the intersection of law, medicine, and public health. Professor Clayton has collaborated with faculty in the Law School, Medical School, and Sociology Department in producing interdisciplinary research. She has been an active participant in policy debates advising the National Human Genome Research Institute as well as numerous bodies concerned with the ethical conduct of research involving human subjects for many years. In addition to teaching in the Law School and Medical School, Professor Clayton is a practicing pediatrician at the Vanderbilt Medical Center. Recently she was appointed Director of the Genetics and Health Policy Center, and holds the Rosalind E. Franklin Chair in Genetics and Health Policy. Dr. Clayton obtained her undergraduate degree from Duke University, earned her M.D. from Stanford and her J.D. from Yale.

DAVID COX is Chief Scientific Officer of Perlegen Sciences Inc. Dr. Cox is an active participant in the Human Genome Project while carrying out research involving the molecular basis of human genetic disease. After receiving his B.A. and M.S. degrees from Brown University in Rhode Island, Dr. Cox obtained his M.D. and Ph.D. degrees from the University of Washington, Seattle. He then completed his Pediatric Residency at the

Yale-New Haven Hospital in New Haven, Connecticut and was a Fellow in both genetics and pediatrics at the University of California San Francisco. From 1980 to 1993, Dr. Cox held faculty positions in the Departments of Pediatrics, Biochemistry and Psychiatry at the University of California San Francisco. In 1993, he accepted a position as a Professor of Genetics and Pediatrics at the Stanford University School of Medicine as well as the Co-director of the Stanford Genome Center. In October of 2000, Dr. Cox took a leave of absence from his position at Stanford University to become the Chief Scientific Officer of Perlegen Sciences, Inc. Dr. Cox is certified by both the American Board of Pediatrics and the American Board of Medical Genetics. He has served on several international and national councils and commissions including the Council of the Human Genome Organization (HUGO) and the National Bioethics Advisory Commission (NBAC). He presently serves as a member of the Health Sciences Policy Board of the Institute of Medicine. Dr. Cox's honors include election to the Institute of Medicine of the National Academy of Sciences.

NANCY DUBLER is the Director of the Division of Bioethics, Montefiore Medical Center and Professor of Epidemiology and Population Health at the Albert Einstein College of Medicine. She received her B.A. from Barnard College and her LL.B. from the Harvard Law School. Ms. Dubler has founded the Bioethics Consultation Service at Montefiore Medical Center in 1978, as a support for analysis of difficult cases presenting ethical issues in the health care setting. She lectures extensively and is the author of numerous articles and books on termination of care, home care and long-term care, geriatrics, prison and jail health care, research with human subjects and AIDS. She is Co-Director of the Certificate Program in Bioethics and the Medical Humanities, conducted jointly by Montefiore Medical Center, Albert Einstein College of Medicine with The Hartford Institute of Geriatric Nursing at New York University. Her most recent books are: Ethics On Call: Taking Charge of Life and Death Choices in Today's Health Care System, published by Vintage in 1993 and Mediating Bioethical Disputes, published in 1994 by the United Hospital Fund in New York City. The Ethics and Regulation of Research with Human Subject (Coleman, Menikoff, Goldner and Dubler) will be published in Spring 2005 by Anderson Press. She consults often with federal agencies, national working groups and bioethics centers.

ROBERT GIBBONS is Professor of Biostatistics and Director of the Center for Health Statistics at the University of Illinois at Chicago. He received his doctorate in statistics and psychometrics from the University of Chicago in 1981. In 1985 he received a Young Scientist Award from the Office of Naval Research, which funded his statistical research in the areas of the analysis of multivariate binary data and the analysis of longitudinal data. Dr. Gibbons has also received additional grant support from the National Institutes of Health and the John D. and Catherine T. MacArthur Foundation, including a Research Scientist Award from the National Institutes of Health. Applications of Dr. Gibbons' work are widespread in the general areas of health and environmental sciences. Dr. Gibbons has authored more than 150 peer-reviewed scientific papers and three books. He has served on several IOM committees including the Committee on Halcion: An Assessment of Data Adequacy and Confidence as well as the Committee on Organ Procurement and Transplantation Policy. Dr. Gibbons is a member of the Institute of Medicine of the National Academy of Sciences.

LYNN R. GOLDMAN is a pediatrician and an epidemiologist. She is a Professor at the Johns Hopkins University Bloomberg School of Public Health, where her areas of focus are environmental health policy and children's environmental health. In 1993, Dr. Goldman was appointed by the President and confirmed by the Senate to serve as Assistant Administrator for the EPA's Office of Prevention, Pesticides and Toxic Substances (OPPTS). In that position, she was responsible for the nation's pesticide, toxic substances and pollution prevention laws. Under her watch, EPA expanded right-to-know under the Toxics Release Inventory and overhauled the nation's pesticides laws. Dr. Goldman made significant progress on the issues of testing high volume industrial chemicals and identification of chemicals that disrupt endocrine systems. At the EPA she was successful in promoting children's health issues and furthering the international agenda for global chemical safety. Prior to joining the EPA, Dr. Goldman served in several positions at the California Department of Health Services, most recently as head of the Division of Environmental and Occupational Disease Control. She has conducted public health investigations on pesticides, childhood lead poisoning and other environmental hazards. She has a B.S. in Conservation of Natural Resources from the University of California, Berkeley, an M.P.H. from the Johns Hopkins University School of Public Health, and an M.D. from

the University of California, San Francisco. Dr. Goldman completed pediatric training at Children's Hospital, Oakland, California.

BERNARD GOLDSTEIN is Dean of the University of Pittsburgh Graduate School of Public Health. Previously he served as the Director of the Environmental and Occupational Health Sciences Institute, a joint program of Rutgers, the State University of New Jersey and the University of Medicine and Dentistry of New Jersey (UMDNJ) - Robert Wood Johnson Medical School. He was also Principal Investigator of the Consortium of Risk Evaluation with Stakeholder Participation (CRESP). Dr. Goldstein was Assistant Administrator for Research and Development, U.S. Environmental Protection Agency, 1983-1985. His past activities include Member and Chairman of the NIH Toxicology Study Section and EPA's Clear Air Scientific Advisory Committee; Chair of the Institute of Medicine Committee on the Role of the Physician in Occupational and Environmental Medicine, the National Research Council Committees on Biomarkers in Environmental Health Research and Risk Assessment Methodology and the Industry Panel of the World Health Organization Commission on Health and Environment. He is a member of the Institute of Medicine where he has chaired the Section on Public, Biostatistics, and Epidemiology.

MARTHA N. HILL is Dean and professor at the Johns Hopkins University School of Nursing. She holds joint appointments in the Bloomberg School of Public Health and the School of Medicine. Dr. Hill, the 1997-1998 president of the American Heart Association, is a Fellow in the American Academy of Nursing and a member of the Institute of Medicine of the National Academy of Sciences. She serves on the IOM Board on Health Sciences Policy and was the Co-vice chair of the IOM Report Unequal Treatment: Confronting Ethnic and Racial Disparities in Health Care. Dr. Hill received her Bachelor of Science degree in nursing from Johns Hopkins University, her masters degree from the University of Pennsylvania, and her doctoral degree in behavioral sciences from the Johns Hopkins University School of Public Health. Dr. Hill is internationally known for her work and research in preventing and treating hypertension and its complications among underserved blacks, particularly among young, urban black men. She is an active investigator and consultant on several NIH funded clinical trials. She has published extensively and serves on numerous review panels, editorial boards, and advisory committees including. Dr. Hill has also consulted on hyperten-

sion and other cardiovascular-related issues outside of the U.S. including South Africa, Scotland, Israel, and Australia.

ALAN LESHNER is Chief Executive Officer of the American Association for the Advancement of Science (AAAS) and Executive Publisher of *Science* magazine. From 1994-2001, he was Director of the National Institute on Drug Abuse at NIH, and from 1988-1994 he was Deputy Director and Acting Director of the National Institute of Mental Health. Prior to that, he spent nine years at the National Science Foundation, where he held a variety of senior positions, focusing on basic research in the biological, behavioral and social sciences, and on science education. He began his career at Bucknell University, where he was Professor of Psychology. His research has focused on the biological bases of behavior, particularly the role of hormones in the control of behavior. Dr. Leshner is a member of the Institute of Medicine and a fellow of AAAS and many other professional societies. He has received numerous awards form both professional and lay groups for his national leadership in science, mental illness and mental health, and substance abuse and addiction.

DANIEL MASYS is Professor and Chair of the Department of Biomedical Informatics at Vanderbilt University Medical Center. An honors graduate of Princeton University and the Ohio State University College of Medicine, he completed postgraduate training in Internal Medicine, Hematology and Medical Oncology at the University of California, San Diego, and the Naval Regional Medical Center, San Diego. Previously, he served as Director of Biomedical Informatics and Adjunct Professor of Medicine at the University of California, San Diego School of Medicine. Prior to that, he served as Chief of the International Cancer Research Data Bank of the National Cancer Institute, National Institutes of Health, and from 1986 through 1994 was Director of the Lister Hill National Center for Biomedical Communications. In this capacity, Dr. Masys served as the chief program architect and first director of the National Center for Biotechnology Information (NCBI) that was established within the National Library of Medicine in 1987 to support molecular databases and computational tools. NCBI is home to GenBank, the national DNA sequence database, and a growing variety of bioinformatics resources. Dr. Masys is a Diplomate of the American Board of Internal Medicine in Medicine, Hematology, and Medical Oncology. He is a Fellow of the American College of Physicians, and a Fellow of the Ameri-

can College of Medical Informatics. He is a founding associate editor of the *Journal of the American Medical Informatics Association*, and has received numerous awards including the NIH Director's Award, Public Health Service Outstanding Service Medal, and the US Surgeon General's Exemplary Service Medal.

JONATHAN MORENO is the Emily Davie and Joseph S. Kornfeld Professor of Biomedical Ethics at the University of Virginia where he is also Director of the Center for Biomedical Ethics. Dr. Moreno is a member of the National Human Research Protection Advisory Committee, a bioethics consultant for the Howard Hughes Medical Institute, a Senior Research Fellow at the Kennedy Institute of Ethics at Georgetown University, and a Fellow of the Hastings Center. During 1995-96 he was Senior Policy and Research Analyst for the President's Advisory Committee on Human Radiation Experiments.

E. ALBERT REECE is Vice Chancellor and Dean of the University of Arkansas College of Medicine. Dr. Reece received his undergraduate degree from Long Island University, his M.D. from New York University, his Ph.D. degree in biochemistry from the University of the West Indies, and his M.B.A. degree from the Fox School of Business and Management of Temple University. He completed a residency in OB/GYN at Columbia University - Presbyterian Hospital, and a fellowship in maternal-fetal medicine at Yale University School of Medicine. He served on the faculty at Yale for 10 year and was the Chairman of the Department of Obstetrics, Gynecology and Reproductive Sciences at Temple University. Dr. Reece has published over 400 journal articles, papers, book chapters, and abstracts and 9 textbooks including Diabetes in Pregnancy; Medicine of the Fetus & Mother; and Fundamentals of Ultrasound in Obstetrics & Gynecology. He is an editor for the Journal of Maternal-Fetal Medicine and a reviewer for several other scientific journals. His research focuses on diabetes in pregnancy, birth defects and prenatal diagnosis. Dr. Reece is a member of the Institute of Medicine.

MYRL WEINBERG is President of the National Health Council, an umbrella organization encompassing more than 100 national health-related groups. Previously, Ms. Weinberg served as Vice President for Corporate Relations and Public Affairs for the American Diabetes Association and was in charge of government relations, public relations, and

corporate marketing. Ms. Weinberg has a long history of board and committee service, including work with the National Chronic Care Consortium's National Resource Center, the American Medical Association's Ethical FORCE initiative, the American Society of Association Executives' Ethics Committee, the Funding First Program, the Foundation for Accountability, the National Legal Center for the Medically Dependent and Disabled, Inc., and the Accreditation for Services for Mentally Retarded and Other Developmentally Disabled Persons. She holds an M.A. in special education from George Peabody College and a B.A. in psychology from the University of Arkansas.

MICHAEL WELCH is Professor of Radiology, Co-Director of the Division of Radiology Sciences of The Edward Mallinckrodt Institute of Radiology, and is Professor of Molecular Biology and Pharmacology at Washington University School of Medicine. He received his B.A. and M.A. degrees in Natural Sciences from Cambridge University and his Ph.D. degree in Radiochemistry at the University of London. Dr. Welch has published several books, numerous journal articles, and book chapters in the area of radiology. Dr. Welch is a member of the Institute of Medicine.

MARY WOOLLEY is the President of Research!America, a non-profit, membership supported grassroots public education and advocacy organization committed to making health-related research a much higher national priority. Ms. Woolley serves on the University of California, Berkeley, School of Public Health Dean's Council, the Lovelace Respiratory Research Institute and is a Founding Member of the Board of Associates of the Whitehead Institute for Biomedical Research. For her work on behalf of medical research, she has been awarded the Distinguished Contribution to Research Administration Award from the Society for Research Administrators; the American Hospital Association Silver Touchstone Award for Public Affairs Programming; the Columbia University College of Physicians and Surgeons Dean's Award for Distinguished Service; the Federation of American Societies for Experimental Biology (FASEB) Special Award for Science Advocacy and the Friends of the National Institute for Nursing Research's Health Advocacy Award. She is a member of the Institute of Medicine and a fellow of the American Association for the Advancement of Science (AAAS).