FORUM ON DRUG DISCOVERY, DEVELOPMENT, AND TRANSLATION

TRANSFORMING CLINICAL RESEARCH IN THE UNITED STATES

CHALLENGES AND OPPORTUNITIES

WORKSHOP SUMMARY

Rebecca A. English, Yeonwoo Lebovitz, and Robert B. Giffin, *Rapporteurs*

Forum on Drug Discovery, Development, and Translation
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.

This project was supported by the Department of Health and Human Services (Contract Nos. N01-OD-4-2139 and 223001003T), the American Diabetes Association, the American Society for Microbiology, Amgen Inc., the Association of American Medical Colleges, AstraZeneca Pharmaceuticals, the Burroughs-Wellcome Fund, Celtic Therapeutics, LLLP, the Critical Path Institute, the Doris Duke Charitable Foundation, Eli Lilly & Co., Entelos Inc., Genentech, GlaxoSmithKline, Johnson & Johnson, Novartis Pharmaceuticals Corporation, and Pfizer Inc. Any opinions, findings, conclusions, or recommendations 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.

International Standard Book Number-13: 978-0-309-15332-4
International Standard Book Number-10: 0-309-15332-8

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.

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Suggested citation: IOM (Institute of Medicine). 2010. *Transforming Clinical Research in the United States: Challenges and Opportunities: Workshop Summary.* Washington, DC: The National Academies Press.

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

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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 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 process. We wish to thank the following individuals for their review of this report:

Timothy Coetzee, Fast Forward, LLC, National Multiple Sclerosis Society
Marlene E. Haffner, Haffner Associates, LLC
Steven E. Kahn, Division of Metabolism, Endocrinology, and Nutrition, Seattle VA Puget Sound Health Care System
Michael S. Lauer, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute, National Institutes of Health

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 **Alastair J.J. Wood,** Symphony Capital, LLC. Appointed by the Institute of Medicine, he was 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 considered. Responsibility for the final content of this report rests entirely with the authors and the institution.

Preface

Clinical trials are the way the medical field tests whether a new therapeutic product performs as expected and actually makes a difference in treating disease. Hundreds of innovative therapies are generated in laboratories, but few survive early development to reach the point of human testing. Clinical trials in patients suffering from a specific condition represent the crucial link between scientific discovery and medical utility.

To plan and execute a clinical trial today can take years and cost hundreds of millions of dollars. In the past, the United States was considered the best place to conduct clinical trials because of the right mix of clinical and scientific expertise and an understanding of the research process. However, many believe that the clinical research enterprise in the United States has failed to keep pace with that in the rest of the world because of this time and cost burden. To evaluate the state of clinical research in the United States and identify strategies for enhancing the effectiveness and efficiency of clinical trials, the Institute of Medicine's Forum on Drug Discovery, Development, and Translation convened a public workshop on October 7–8, 2009, titled Transforming Clinical Research in the United States. Clinical trial experts from academic research centers, pharmaceutical companies, contract research organizations, government, nonprofit research networks, and patient advocacy groups came together to discuss their clinical trial successes and failures, the challenges they face in conducting clinical research, and strategies for improving the efficiency of clinical trials while maintaining the highest standards for the data generated.

The intent of the workshop was to engage stakeholders in an honest discussion of the state of clinical trials today and to gain an understanding

of what has and has not worked in planning and executing trials. The workshop was focused on four disease areas: cardiovascular disease, depression, cancer, and diabetes. Although "clinical research" is a generic term, a clinical trial in breast cancer, with 5-, 10-, or 15-year outcomes, is quite different from a clinical trial in cardiovascular disease, where the outcome of interest may occur in a month or less. The disease being studied also affects the kind of patients needed and how they are recruited and retained. Gaining an appreciation of the differences in clinical trials by disease helped generate ideas for improving the clinical research enterprise as a whole.

This workshop is part of a broader initiative of the Forum addressing different aspects of clinical research. Future Forum plans include the following: further examining regulatory, administrative, and structural barriers to the effective conduct of clinical research; developing a vision for a stable, continuously funded clinical research infrastructure in the United States; and considering strategies and collaborative activities to facilitate more robust public engagement in the clinical research enterprise.

As the starting point for the Forum's work in the area of clinical research, it is our hope that this workshop summary will serve as a resource for all organizations and individuals seeking a greater understanding of how the clinical research enterprise works and how it can improve. The workshop showcased the best examples from clinical research conducted to date and developed novel ideas for organizing and conducting clinical trials. Ultimately, as the health care system moves forward, we hope our work can serve as a source of information and inspiration to those involved in clinical research as sponsors, investigators, clinicians, patients, and policy makers.

Jeffrey M. Drazen, *Co-Chair*
Forum on Drug Discovery, Development, and Translation

Contents

Tables, Figures, and Boxes

TABLES

FIGURES

BOXES

Acronyms

ACS	acute coronary syndromes
ADA	American Diabetes Association
ADOPT	A Diabetes Outcome Progression Trial
AHA	American Heart Association
AHRQ	Agency for Healthcare Research and Quality
ARO	academic research organization
ARRA	American Recovery and Reinvestment Act of 2009
caBIG	Cancer Biomedical Informatics Grid
CDER	Center for Drug Evaluation and Research
CEC	clinical events committee
CER	comparative effectiveness research
CMS	Centers for Medicare and Medicaid Services
CNS	central nervous system
CRF	case report form
CRN	clinical research network
CRO	contract research organization
CTA	clinical trial agreement
CTEP	Cancer Therapy Evaluation Program
CTSA	Clinical and Translational Science Awards
CTTI	Clinical Trials Transformation Initiative
DBSA	Depression and Bipolar Support Alliance
DCRI	Duke Clinical Research Institute
DMC	data monitoring committee

DPP	diabetes prevention program
DSMB	data safety monitoring board
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	U.S. Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDAMA	Food and Drug Administration Modernization Act of 1997
HAM-D	Hamilton Depression Rating Scale
HHS	U.S. Department of Health and Human Services
HIPAA	Health Information Portability and Accountability Act
ICMJE	International Committee of Medical Journal Editors
IECRN	Inventory and Evaluation of Clinical Research Networks
IOM	Institute of Medicine
IRB	Institutional Review Board
ISIS	International Study of Infarct Survival
JDRF	Juvenile Diabetes Research Foundation
MI	myocardial infarction
MTA	material transfer agreement
NCI	National Cancer Institute
NCRR	National Center for Research Resources
NDA	New Drug Application
NHLBI	National Heart, Lung, and Blood Institute
NIA	National Institute on Aging
NIAID	National Institute of Allergy and Infectious Diseases
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NLM	National Library of Medicine
OAT	occluded artery trial
OPEN	oncology patient enrollment network
PBRN	Practice-Based Research Network
PCI	percutaneous intervention

PCORI	Patient-Centered Outcomes Research Institute
PhRMA	Pharmaceutical Research and Manufacturers of America
PI	principal investigator
RCT	randomized controlled trial
RFA	Request for Applications
SSRI	selective serotonin reuptake inhibitor
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
STEMI	ST segment elevation myocardial infarction
TIMI	Thrombolysis in Myocardial Infarction Study Group
VA	U.S. Department of Veterans Affairs
WHO	World Health Organization

1

Introduction

Efficiently generating medical evidence and translating it into practice implies a "learning health care system" in which the divide between clinical practice and research is diminished and ultimately eliminated. Such a system relies on efficiently generating timely, accurate evidence to deliver on its promise of diminishing the divide between clinical practice and research. There are growing indications, however, that the current health care system and the clinical research that guides medical decisions in the United States falls far short of this vision. The process of generating medical evidence through clinical trials in the United States is expensive and lengthy, includes a number of regulatory hurdles, and is based on a limited infrastructure. The link between clinical research and medical progress is also frequently misunderstood or unsupported by both patients and providers.

Generating relevant medical evidence is an ongoing process subject to the dynamic nature of health care. The focus of clinical research changes as diseases emerge and new treatments create cures for old conditions. As diseases evolve, the ultimate goal remains to speed new and improved medical treatments to patients throughout the world. To keep pace with rapidly changing health care demands, clinical research resources need to be organized and on hand to address the numerous health care questions that continually emerge. Improving the overall capacity of the clinical research enterprise will depend on ensuring that there is an adequate infrastructure in place to support the investigators who conduct research, the patients with real diseases who volunteer to participate in experimental research, and the institutions that organize and carry out the trials.

To address these issues and better understand the current state of clinical research in the United States, the Institute of Medicine's (IOM's) Forum on Drug Discovery, Development, and Translation (the "Drug Forum") held a 2-day workshop on October 7–8, 2009, titled Transforming Clinical Research in the United States. This workshop laid the foundation for a broader initiative of the Forum addressing different aspects of clinical research. Future Forum plans include the following: further examining regulatory, administrative, and structural barriers to the effective conduct of clinical research; developing a vision for a stable, continuously funded clinical research infrastructure in the United States; and considering strategies and collaborative activities to facilitate more robust public engagement in the clinical research enterprise.

This report builds on a body of related IOM work. Focused on the national objective of achieving the best health outcome for each patient, the IOM Roundtable on Value & Science-Driven Health Care explores the need for a learning health care system in the United States and possible ways such a system can create value in health care interactions. Reports based on the Roundtable's recent workshops include The Healthcare Imperative: Lowering Costs and Improving Outcomes (IOM, 2009a) and Value in Health Care: Accounting for Cost, Quality, Safety, Outcomes, and Innovation (IOM, 2010). The IOM's National Cancer Policy Forum is discussing strategies for improving cancer clinical trials and the National Cancer Institute's (NCI's) Cooperative Group program. That Forum's recent reports include *Multi-Center Phase III Clinical Trials and NCI Cooperative Groups* (IOM, 2009b) and *Improving the Quality of Cancer Clinical Trials* (IOM, 2008).

THE CLINICAL TRIALS PROCESS

The focus of the workshop was clinical trials—a type of clinical research that prospectively evaluates the risks and benefits of a drug, device, behavioral intervention, or other form of treatment. The materials and resources (human capital, financial support, patient participants, and institutional commitment) available to conduct such research can vary by research sponsor, disease area being studied, and type of research question being asked. Once a research question has been posed and the concept for a study has been defined, funding must be secured to continue the process. The study protocol, which is an extensive blueprint for the trial and how it will be conducted, is also required to be submitted to the relevant institutions and organizations that provide ethical and regulatory approval.

All clinical trials are designed to answer one or more specific questions. They can vary by the study population chosen (number of subjects, as well as criteria to enter the study) and the type of question(s) posed. For

example, clinical trials to gain U.S. Food and Drug Administration (FDA) approval for a new drug are designed to show its safety and efficacy over the course of a few years. These trials seek to answer narrowly defined questions related to safety and efficacy in a carefully selected group of study participants most likely to experience the intended effects of the drug. Clinical trials conducted without the goal of regulatory approval (e.g., government sponsored) might test a drug or intervention in a diverse group of study participants, include a long time frame for follow-up of study subjects, and address a broader set of questions. The workshop examined a variety of clinical trials, including those sponsored by industry and government, but the focus was on large, multicenter trials.

The clinical trials process for gaining regulatory approval of a new drug has traditionally been described in five discrete phases. Each phase seeks to answer a different set of questions. An increasing number of volunteers are included in each phase as the trial progresses and attempts to build a case that an experimental drug or treatment is safe and effective against the disease or condition it is intended to treat.

Phase 0 trials are exploratory, first-in-human studies designed to determine whether a drug affects the human body as expected from earlier preclinical, animal studies. These trials involve a small number of people (10–15) who receive a low, nontherapeutic dose of the investigational drug. These preliminary trials help companies rank a number of different drug candidates in their pipeline and make decisions about which candidates should be developed.

Phase I clinical trials test an experimental drug or treatment for the first time in a small group of people (20–80) over the course of a few weeks or a month. Their goals are to assess the safety of the drug or treatment, find a safe dosage range, and identify any side effects.

In phase II trials, a larger group of people (100–300) receives the experimental drug to determine whether it is effective and further evaluate its safety. These trials involve subjects with the target disease and usually last months.

Once preliminary evidence from phase II reveals that a treatment is effective, phase III trials are designed to fully examine the risk/benefit profile of an experimental drug or treatment and test it over a longer period of time in a broader population (1,000–3,000). Because these trials are the last phase in the preapproval process, they are often referred to as "pivotal" trials.

Phase IV, or post-marketing, trials take place after a drug has been approved. They provide additional evidence on the risks and benefits of the drug or treatment and how it can be used optimally.

As a new drug progresses through the development pipeline, costs rise with each phase. Phase III clinical trials have become extraordinarily expen-

sive. One study found that on average, drug development costs for an approved compound were $15.2 million in phase I, $41.7 million in phase II, and $115.2 million in phase III (Di Masi et al., 2003, p. 171). As reported in Chapter 3, a large, global clinical trial involving 14,000 patients and 300 research sites can cost approximately $300 million. Also contributing to the already high-risk and high-cost drug development process, patient enrollment and physician participation in clinical trials are considered by many to be inadequate to sustain a vigorous drug development pipeline, and clinical research is increasingly shifting overseas (see Chapter 3).

WORKSHOP SCOPE AND OBJECTIVES

Workshop participants included clinical trial experts from academia, government, industry, and patient advocacy groups. The workshop focused primarily on large, multisite, phase III clinical trials. NIH trials that were not designed to gain regulatory approval, but address clinically important issues, were also presented. In addition, examples of post-marketing studies resulting from federal requirements were also presented during the workshop. Presentations highlighted clinical trials in four disease areas: cardiovascular disease (acute myocardial infarction and heart failure), depression, cancer, and diabetes. These four areas were chosen because they represent a range of diseases: acute life-threatening conditions (acute myocardial infarction); chronic life-threatening conditions (heart failure and cancer); and chronic, not acutely life-threatening conditions (depression and diabetes). Clinical trials vary across the conditions being studied. For instance, trials in breast cancer require long-term patient follow-up to capture outcomes that are 5 to 15 years into the future. Conversely, trials treating acute myocardial infarction (heart attack) measure short-term patient outcomes within hours, days, or weeks. For each disease being treated in a clinical trial, the patient population varies as do the methods used by investigators to locate, classify, recruit, and retain patients. Fundamental differences in clinical practice and what is viewed as appropriate exist across each of the diseases chosen as the focus of the workshop. The workshop sought to examine how trials are being conducted in these four areas and draw lessons from each that can be applied more broadly. The workshop also focused primarily on the randomized controlled trial (RCT), which although labor-intensive and expensive to conduct, is the gold standard for producing high-quality evidence.

The workshop had three main objectives:

- to examine the state of clinical research in the United States;
- to identify areas of strength and weakness in the current clinical trial enterprise by examining trials in the above four disease areas; and

- to consider transformative strategies for enhancing the way clinical research is organized and conducted.

Through a series of case studies and stakeholder perspectives, workshop participants examined clinical research networks and clinical trials in the four disease areas. Using the presentations and discussion from day one as a starting point, four breakout groups, each focused on one of the four disease areas, produced observations and insights relevant to the workshop objectives.

ORGANIZATION OF THE REPORT

This report is intended to provide a faithful summary of the presentations and discussions that took place during the workshop, although remarks have been substantially abbreviated and reorganized to improve the report's readability and usefulness. It should be noted that although a number of presenters and participants expressed opinions and recommendations that were summarized in this report, these should in no way be interpreted as attributable to the IOM Drug Forum or the IOM.

The remainder of the report provides a comprehensive summary of the presentations and discussions that occurred during the workshop. Chapter 2 gives an overview of the state of clinical research in the United States today, including new research on the subject commissioned for the workshop. Chapter 3 describes the broad challenges that are faced in conducting clinical trials today. Chapters 4, 5, 6, and 7, respectively, summarize workshop presentations and discussions regarding the strengths and weaknesses of various clinical trial models in the above four disease areas and the usefulness of clinical trial results for informing clinical practice in each area. Chapter 8 describes efforts currently under way to improve clinical trials, summarizes the breakout session discussions regarding strategies for advancing clinical research in the identified disease areas, and presents a vision for a sustainable clinical trials infrastructure in the United States.

It should be noted that, while the Drug Forum conceived the idea for this workshop, its planning was the responsibility of an independently appointed committee. That committee's role was limited to advance planning; this summary was prepared by the rapporteurs as a factual summary of what occurred at the workshop.

2

The State of Clinical Research in the United States: An Overview

The Institute of Medicine (IOM) reports *To Err Is Human: Building a Safer Health System* (IOM, 2000) and *Crossing the Quality Chasm: A New Health System for the 21st Century* (IOM, 2001a), focused the nation's attention on concerns about the quality of health care in the United States. Since those reports were published, efforts have accelerated to develop a health care system that systematically measures and improves the quality of care delivered. Essential to such a system is a systematic approach for assessing which clinical approaches do and do not work and then ensuring that this knowledge is utilized in clinical decision making. This approach is what is often referred to as a learning health care system.

Many different kinds of evidence can inform the policies and practices of a health care system. Clinical trials, a type of clinical research, are one of the most robust sources of this knowledge. A number of workshop speakers from many backgrounds—clinical investigators, research sponsors, practitioners, and patients—expressed the view that the current clinical research enterprise[1] in the United States is unable to produce the high-quality, timely, and actionable evidence needed to support a learning health care system. They identified numerous obstacles to producing this evidence, including the length of time and high financial cost involved in conducting clinical trials, delays associated with navigating the many regulatory and ethical

[1]The clinical research enterprise is a broad term that encompasses the full spectrum of clinical research and its applications. It includes early-stage, laboratory research and the processes, institutions, and individuals that eventually apply research to patient care (IOM, 2002).

requirements of studies involving human subjects (e.g., Institutional Review Board [IRB] approval), difficulties in recruiting and retaining the appropriate patient population, and the generally fragmented way clinical research is prioritized and undertaken to advance medical care in the United States.

As noted in Chapter 1, the workshop focused on the randomized controlled trial (RCT), the gold standard in clinical research. Many consider the RCT to be unsustainable as an approach to addressing the large number of research questions that need to be answered because of the time and expense involved. Yet alternative approaches have limitations with respect to producing high-quality data. Christopher Cannon, senior investigator in the Thrombolysis in Myocardial Infarction (TIMI) Study Group, for example, discussed the use of registries, which are large databases that provide extensive observational data on current clinical practice. He commented that while registry data are of good quality and less expensive to obtain compared with data from RCTs, confounding (i.e., why an individual received one therapy versus another) is a significant problem. Because it is difficult to attribute trends in registry data to particular therapies, registries do not provide the conclusive evidence necessary to change clinical practice. Instead, registries generate hypotheses that can then be tested in an RCT. Therefore, while patient registries and other research tools exist, the workshop focused primarily on RCTs.

Results of thousands of RCTs are published each year, yet clinical decision making frequently is not based on the evidence created by these results. A key issue informing the workshop discussions, then, was how RCTs can be conducted in an efficient, timely manner to answer all of the questions and meet all of the needs of a learning health care system. A logical first step in addressing this issue is to examine the clinical research enterprise as it operates in the United States today.

This chapter describes various aspects of clinical research in the United States, beginning with clinical research networks (CRNs). Research commissioned for the workshop from Ronald Krall, former Chief Medical Officer, GlaxoSmithKline, is then presented, addressing tools available for assessing clinical research in the United States; volume and type of clinical trials conducted; the clinical investigator workforce; and the overall capacity of the clinical research enterprise.

CLINICAL RESEARCH NETWORKS

CRNs have been developed to pool resources and expertise in conducting clinical research. They include clinical sites and investigators usually organized around a specific disease area and can be accessed by many different research stakeholders for the conduct of clinical research.

The National Institutes of Health's (NIH's) Roadmap for Medical

Research points specifically to CRNs and their ability to rapidly conduct high-quality studies as a way to improve the efficiency and productivity of the clinical research enterprise. In this vein, NIH's National Center for Research Resources (NCRR) manages the Inventory and Evaluation of Clinical Research Networks (IECRN) project to survey active networks and characterize best practices that could potentially be implemented in other networks or clinical trial settings. Although the exact structures vary, the NIH project defines a CRN as an organization of clinical sites and investigators that conducts or intends to conduct multiple collaborative research protocols. CRNs can carry out a number of different types of studies, including clinical trials, and the organization of sites and investigators can be formal or informal as long as the collaborative accomplishments of the group are clear. For instance, a group of researchers that conducts a single trial and subsequently disbands is not considered to be a network (NCRR, 2006).

By pooling the resources of multiple entities, CRNs can realize efficiencies in implementing and conducting clinical trials. They create a supportive infrastructure for investigators and can facilitate the rapid conduct of trials to answer important research questions. For instance, CRNs organized around a particular disease often have access to patients with that disease who can serve as study participants. The in-house scientific leadership of CRNs can also streamline the protocol development process and create uniformity in clinical trials across the network or disease area. When clinical trials from a particular network generate consistent results, this can also accelerate the drug development pipeline for the disease studied.

TOOLS FOR ASSESSING CLINICAL RESEARCH IN THE UNITED STATES[2]

Krall obtained information on the current state of clinical trials in the United States from various public and private sources. A key source was data on submissions to clinicaltrials.gov, a federally sponsored, publicly available registry of clinical trials. Information was also obtained from the Tufts Center for the Study of Drug Development, KMR Group, Citeline, and individual pharmaceutical companies. The Tufts Center and KMR collect data from pharmaceutical companies for the purpose of providing benchmarking data and proprietary analyses. Citeline is a proprietary data source that draws from a number of resources (literature, advertising, and clinicaltrials.gov) to create a comprehensive database of clinical research and the global investigator workforce.

[2]The remainder of this chapter is based on the presentation of Dr. Krall.

Clinicaltrials.gov

The Food and Drug Administration Modernization Act (FDAMA) of 1997 mandated the creation of the clinicaltrials.gov registry for efficacy trials in serious and life-threatening conditions and interventions regulated by the FDA. Developed by NIH's National Library of Medicine (NLM) in 2000, it allows interested parties to find information on both completed and ongoing clinical trials. The database includes federally and privately supported clinical trials, and study sponsors are responsible for submitting timely and accurate information about their studies.

The database registered a modest number of clinical trials in its initial years (Figure 2-1). A dramatic increase in trial registration came in 2005 in response to the newly introduced International Committee of Medical Journal Editors' (ICMJE's) requirement that studies published in their journals be registered in clinicaltrials.gov or other equivalent publicly available registries. The Food and Drug Administration Amendments Act (FDAAA) of 2007 created a legal requirement for the registration of trials of drugs, biologics, and devices, generating a modest increase in the registration of

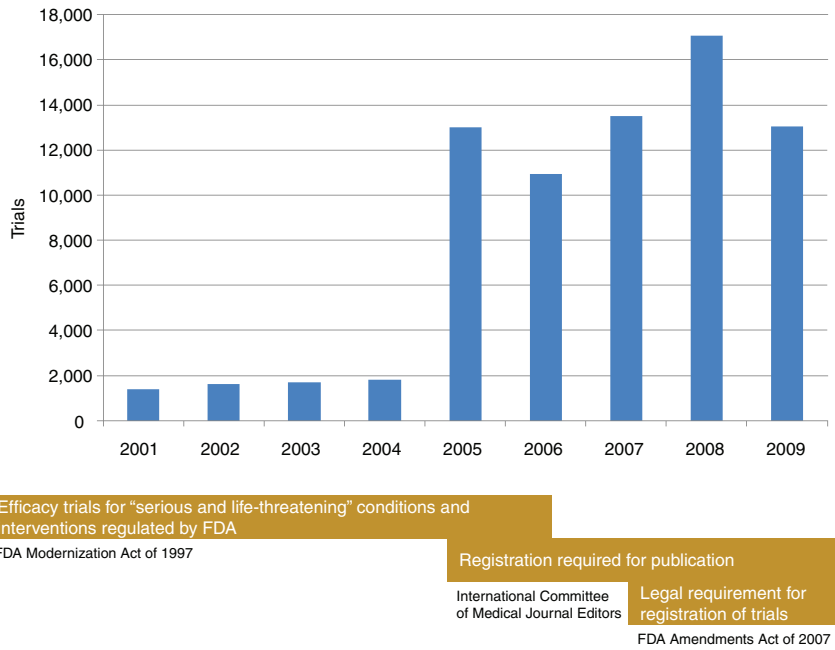


FIGURE 2-1 Timeline reflecting the number of clinical trials registered on clinicaltrials.gov and regulatory changes affecting the database registration from 2001 to 2009.
SOURCE: Krall, 2009. Reprinted with permission from Ronald Krall 2009.

trials over what had been seen in 2005. Given the increasing number of trials registered on clinicaltrials.gov over time, the database encompasses a broad spectrum of research organized by study sponsor (industry, government, and nonprofit), disease and treatment being studied, and trial design.

Data Limitations

The information gathered by Krall to inform the workshop discussions of the state of the U.S. clinical research enterprise was not intended to provide an exhaustive analysis of the impact of every role and action of the broad range of research stakeholders involved. Rather, the goal was to highlight the productivity of one aspect of the clinical research enterprise—clinical trials. The data gathered reflect not the "effectiveness" of trials in terms of how well they answer the study questions, but how efficiently they are conducted. The commissioned research was designed to meet the needs of the workshop, however, the topics covered and issues raised by Krall's analysis could be informative for other areas of the clinical research enterprise as well.

The data collected have some limitations. With respect to certain industry information, individual pharmaceutical company data can vary significantly depending on how the various elements and costs of clinical trials are measured. Also, although NLM reviews information submitted to the clinicaltrials.gov database, neither the accuracy of the data nor the scientific relevance of the study is guaranteed. Thus, while the information gathered on the number and type of clinical trials being conducted today is revealing, it would be incorrect to assume that it reflects the quality or relevance of those trials. Krall also noted that some types of clinical trials do not need to be reported to the database, and that there are concerns about the timeliness and accuracy of the data that are submitted. Variability in the reporting and classification of certain data elements in clinicaltrials.gov (e.g., drugs vs. biologics, phases of research, reporting no funding source, and currency of investigator site information) is another concern. Yet while clinicaltrials.gov is not without limitations, Krall suggested that its creation is undoubtedly a positive step toward developing a clearer picture of the state of clinical research in the United States.

VOLUME AND TYPE OF CLINICAL TRIALS CONDUCTED

In RCTs, investigators control which participants receive the study treatment by assigning them at random to a particular experimental study group. Observational, non-experimental studies occur in natural settings and involve no manipulation of the interventions or treatments study par-

ticipants receive. Because RCTs were the focus of the workshop, observational studies were excluded from Krall's analysis.

Krall reported that as of August 16, 2009, there were 10,974 ongoing, interventional clinical trials with at least one U.S. center. The 10,974 ongoing trials collectively are seeking to enroll 2.8 million subjects. As Figure 2-2 indicates, the majority of trials (59 percent) are testing drugs. A distant second and third to drug interventions are behavioral trials (10 percent) and those testing biologics (9 percent), respectively.

Clinical Trials by Phase of Research

The phase of clinical trials (i.e., phases 0–IV; see Chapter 1) is considered by some to be a marker of innovation, reported Krall. An analysis of clinical research by phase of experimental clinical trials can indicate the degree to which innovative new therapies are being developed and tested. It takes 10–15 years for a typical drug to be developed successfully from discovery to registration with the FDA. In the earlier phases of research, the chance of a drug reaching patients is small—approximately 1 in 10. In phase III research, however, the odds of registering a new product improve. About two-thirds of drugs that reach pivotal phase III trials will make it to the market (IOM, 2009c, p. 85).

To characterize trials by phase more precisely, Krall narrowed the focus of his research to trials for FDA-regulated interventions (drugs, biologics, devices, and dietary supplements). In these FDA-regulated categories, there are 8,386 trials recruiting 1.9 million subjects. As shown in Figure 2-3, among clinical trials for FDA-regulated products, phase II research is the largest category, followed closely by phase IV. Also referring to Figure 2-3, although there are larger numbers of phase II and III trials, phase III trials by design involve the largest number of participants; thus it makes sense that 52 percent of all subjects are enrolled in these pivotal trials.

Clinical Trials by Disease

Krall described ongoing clinical trials in the four disease areas of focus at the workshop—cardiovascular disease, depression, cancer, and diabetes. Figure 2-4 indicates that approximately half of the 10,974 trials being conducted today are in cancer; however, each such trial involves a relatively small number of participants. Figure 2-4 also reveals that cardiovascular disease trials are seeking more than 300,000 participants—10 percent of all clinical trial participants being recruited and far more than the number of participants sought for cancer, diabetes, or depression trials. Recruiting a large number of subjects per trial is a trademark of cardiovascular disease studies: on average, 275 patients are sought per cardiovascular trial, as

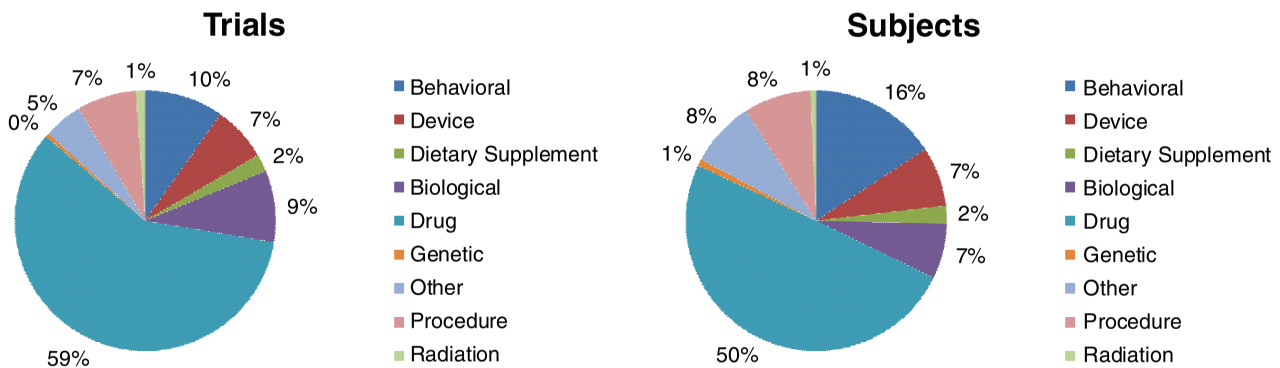


FIGURE 2-2 Percentage of the 10,974 ongoing clinical trials and 2.8 million study subjects being sought by intervention being tested.
SOURCE: Krall, 2009. Reprinted with permission from Ronald Krall 2009.

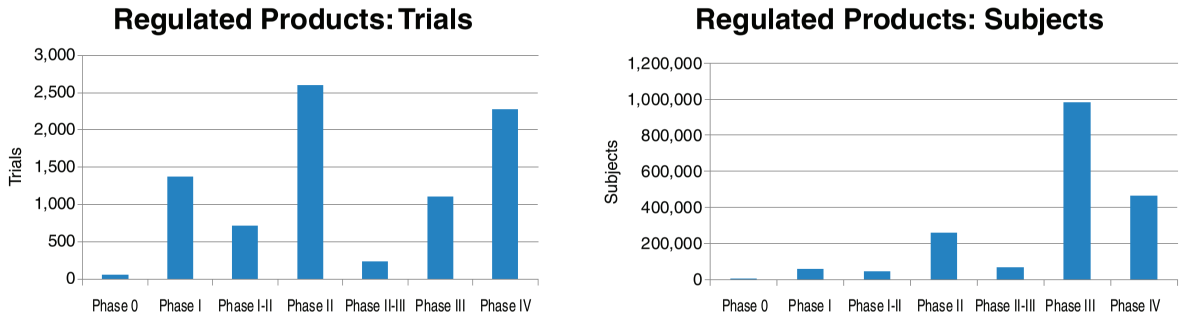


FIGURE 2-3 Number of the 8,386 clinical trials involving FDA-regulated products and 1.9 million study subjects being sought for these trials by phase of research.
SOURCE: Krall, 2009. Reprinted with permission from Ronald Krall 2009.

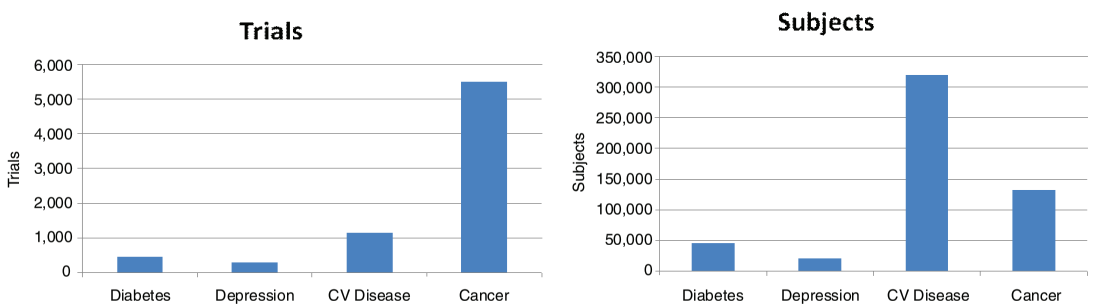


FIGURE 2-4 Number of the 10,974 ongoing clinical trials and 2.8 million study subjects being sought by disease being studied.
NOTE: CV Disease = cardiovascular disease.
SOURCE: Krall, 2009. Reprinted with permission from Ronald Krall 2009.

compared with 20 patients per cancer trial, 70 patients per depression trial, and 100 per diabetes trial.

THE CLINICAL INVESTIGATOR WORKFORCE

Annual surveys from the Tufts Center for the Study of Drug Development indicate a consistently high turnover rate in the clinical investigator community. Investigators conducting a clinical trial to support a New Drug Application (NDA) or a change in labeling are required to complete FDA's Form 1527. In 2007, 26,000 investigators registered this form with the FDA, 85 percent of whom participated in only one clinical trial. The issues facing clinical investigators were discussed throughout the workshop, and many participants echoed the theme of the Tufts data—it is difficult to conduct clinical trials in the United States and establish a career as a clinical investigator. While opportunities in clinical investigation can vary depending on whether or not an investigator is working in private practice or academia, for example, the challenges to successfully conducting a clinical trial in the United States are substantial. Making clinical investigation an attractive career option for academics and professionals was mentioned by a number of participants as an important component of any approach to improving the capacity of the clinical trials enterprise in the United States.

Globalization

In addition to high turnover, the U.S. clinical investigator workforce is subject to an absolute decrease in its ranks. While there has been an annual decline of 3.5 percent in U.S.-based investigators since 2001, there has been an increase in investigators outside the United States. Figure 2-5 reveals that investigators from the rest of the world increased steadily between 1997 and 2007, making up for the decline in North American investigators over the same period. As of 2007, U.S. investigators constituted 57 percent of the global investigator workforce, a decrease from approximately 85 percent in 1997. According to the Tufts data, there are an estimated 14,000 U.S. investigators, compared with an estimated 12,000 investigators outside the United States. Currently, 8.5 percent of investigators are from Central and Eastern Europe, 5.5 percent from Asia, and 5.5 percent from Latin America.

Finally, Krall noted the difference between the role of a clinical investigator (i.e., the person who establishes the hypotheses to test, designs the trial, analyses and reports the results) and that of the individual who finds patients to participate in a trial and collects information about them. The latter role is essential to the ability to carry out research and should be recognized, rewarded, and developed to a greater degree, according to

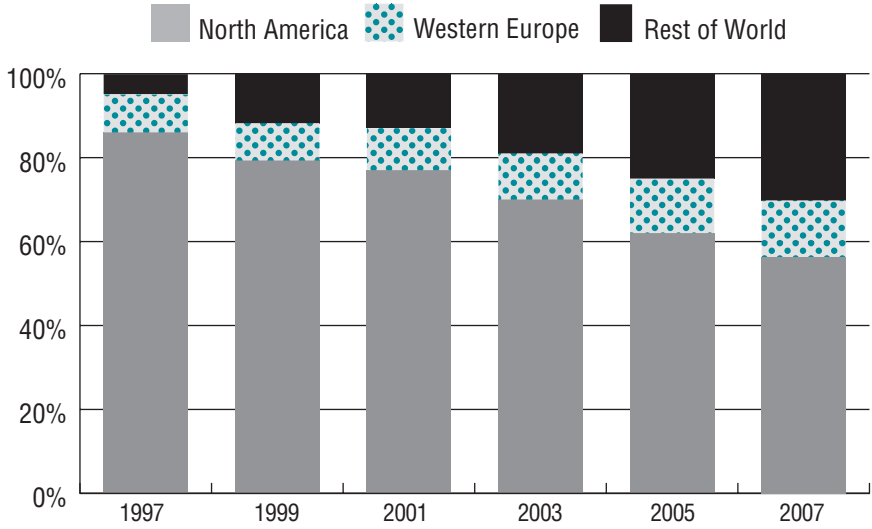


FIGURE 2-5 The proportion of clinical investigators from North America has decreased since 1997, while the proportion of investigators from Western Europe and the rest of the world has increased.
SOURCE: Tufts Center for the Study of Drug Development. 2009. Impact Report Jan/Feb; Current Investigator Landscape Poses a Growing Challenge for Sponsors. 11(1):2. Reprinted with permission from Kenneth Kaitin.

Krall. Workshop presenters and participants echoed Krall's sentiment later in the day by discussing the many different levels of staff, in addition to the principal investigator, that ultimately make a clinical trial successful.

CAPACITY OF THE CLINICAL RESEARCH ENTERPRISE

KMR data from 2006 for the 15 largest pharmaceutical companies show that the majority of patient visits associated with an industry-sponsored clinical trial occur outside the United States. According to Krall, this statistic speaks to the costs and difficulty associated with conducting clinical research in the United States. In terms of cost-effectiveness, 860 patient visits occur in the United States per $1 million spent on clinical operations, whereas for the same cost, 902 patient visits occur outside of the United States. Thus, by the measure of cost per patient visit, U.S.-based clinical trials are not as cost-effective as those in the rest of the world. Krall urged caution in interpreting these data, however, given the high degree of variability among pharmaceutical companies in patient visit and cost measures.

U.S. investigators enroll two-thirds as many subjects into clinical trials as investigators in the rest of the world. Among U.S. investigators participating in a clinical trial, 27 percent fail to enroll any subjects, compared with 19 percent of investigators elsewhere. Investigator performance in the United States and the rest of the world is similar in that 75 percent of investigators fail to enroll the target number of subjects; also, 90 percent of all clinical trials worldwide fail to enroll patients within the target amount of time and must extend their enrollment period. Krall commented that these data on patient enrollment are from one pharmaceutical company but that, based on his industry experience and conversations with colleagues from other companies, he believes the data are generally consistent with the pharmaceutical industry as a whole.

According to clinicaltrials.gov data, clinical trials today call for the enrollment of 1 in every 200 Americans as study participants. Because this is such a remarkable undertaking, Krall questioned whether this high level of human participation is being put to the best use possible—that is, are the right questions being asked through the thousands of clinical trials being conducted today?

3

Challenges in Clinical Research

Cooperation among a diverse group of stakeholders—including research sponsors (industry, academia, government, nonprofit organizations, and patient advocates), clinical investigators, patients, payers, physicians, and regulators—is necessary in conducting a clinical trial today. Each stakeholder offers a different set of tools to support the essential components of a clinical trial. These resources form the infrastructure that currently supports clinical research in the United States. Time, money, personnel, materials (e.g., medical supplies), support systems (informatics as well as manpower), and a clear plan for completing the necessary steps in a trial are all part of the clinical research infrastructure. A number of workshop participants lamented that most clinical trials are conducted in a "one-off" manner.[1] Significant time, energy, and money are spent on bringing the disparate resources for each trial together. Some workshop attendees suggested that efficiencies could be gained by streamlining the clinical trials infrastructure so that those investigating new research questions could quickly draw on resources already in place instead of reinventing the wheel for each trial.

This chapter summarizes workshop presentations and discussions focused on the challenges facing clinical research today. The first three challenges reflect broad, systemic issues in clinical research: (1) prioritizing of clinical research questions, (2) the divide between clinical research and

[1]The term "one-off" alludes to the current situation in which the necessary components of a trial (usually a single coordinating center and multiple research sites) are brought together for a discrete period of time and disbanded once the trial is completed.

clinical practice, and (3) the globalization of clinical trials. Issues of paying for clinical trials and the narrow incentives for practitioners to participate in clinical research are then discussed. Finally, the chapter turns to the challenges of a shrinking clinical research workforce, the difficulties of navigating administrative and regulatory requirements, and the recruitment and retention of patients.

PRIORITIZING OF CLINICAL RESEARCH QUESTIONS

Fewer than half of all the medical treatments delivered today are supported by evidence (IOM, 2007), yet the United States lacks a clear prioritization of the gaps in medical evidence and an allocation of clinical research resources to efficiently and effectively fill these evidence gaps. The federal government, industry, academic institutions, patient advocacy organizations, voluntary health organizations, and payers each have incentives to develop research questions that suit their unique interests. The value of a particular research effort is judged by stakeholders according to their own cost–benefit calculation. Reflecting the diversity of stakeholder value judgments, and in the absence of a broad national agenda, clinical trials are conducted in a "one-off," narrowly focused fashion.

Because clinical trials are necessary to obtain regulatory approval in the United States, they are a high priority to companies. It was noted by a number of workshop participants that the prioritization of clinical research questions by companies seeking regulatory approval is distinctly different from the priorities of society in general, which may prioritize the comparison of two commonly used therapies. This divergence between the priorities of society and industry is notable as the nation discusses how to address the current gaps in clinical research and medical decision making.

As an example, in investigator-initiated research, academic investigators seek federal funding (primarily from the National Institutes of Health [NIH]) to conduct research they deem important to advancing science and/or medical practice. But James McNulty, Vice President of Peer Support for the Depression and Bipolar Support Alliance (DBSA), believes the NIH peer review process for research grants is inherently conservative and fails to reward innovative research into areas about which little is known. McNulty believes this conservative approach has contributed to serious gaps in knowledge in the area of mental health, specifically in schizophrenia, depression, and bipolar disorder. In terms of formulating relevant research hypotheses, the U.S. Department of Veterans Affairs (VA) was cited as one example of a health system that successfully engages practicing physicians in noting potential research questions that arise in the day-to-day care of patients. The VA Cooperative Studies Program works to ultimately take physicians' questions into the clinical trial setting.

Industry-sponsored trials are conducted largely to gain U.S. Food and Drug Administration (FDA) approval to market a new drug or a previously approved drug for a new indication. Preapproval trials include a simple protocol (i.e., ask a limited number of questions) and test a drug in a highly selected patient group designed to provide the most robust evidence on the drug's benefits and risks. Conversely, the federal government conducts large clinical trials to answer medical questions unrelated to gaining regulatory approval for a new drug or therapy. These studies can involve a wide range of patients and seek to answer a number of relevant clinical questions at once. Several presenters in the diabetes session of the workshop suggested that government-funded clinical trials for diabetes would not be conducted by industry or other sectors. New therapies for type 1 diabetes are often of limited interest to pharmaceutical companies because of the small patient population, whereas drugs for the exponentially larger type 2 diabetes population are avidly pursued.

The beginnings of a coordinated prioritization of research needs can be seen in the recent increased interest in comparative effectiveness research (CER). To enhance the ability of clinical research to generate knowledge that can better inform clinical practice, Congress included in the American Recovery and Reinvestment Act (ARRA) of 2009 an allocation of $1.1 billion for federal agencies (the Agency for Healthcare Research and Quality [AHRQ], NIH, and the Department of Health and Human Services [HHS]) to jumpstart the national CER effort. CER seeks to identify what works for which patients under what circumstances, providing evidence about the costs and benefits of different medical options. One-third of ARRA funds ($400 million) were designated as discretionary spending by the Secretary of HHS to accelerate CER efforts. The Institute of Medicine (IOM) was tasked with recommending national CER priorities to be supported with these discretionary funds and to guide the nation's creation of a long-term, sustainable national CER enterprise.[2] Recently enacted health care reform legislation (Patient Protection and Affordable Care Act passed in March 2010) created the Patient-Centered Outcomes Research Institute (PCORI)—a nonprofit institution positioned outside the federal government to define and execute comparative effectiveness research methods.

Several speakers and workshop participants raised questions about the ability of the current clinical trials system, which is already showing signs of strain, to absorb a substantial amount of the anticipated CER studies. Many voiced concern regarding the overall organization of clinical research in the United States: how it is prioritized, where it is conducted, who oversees it, how it is funded, who participates, and who staffs it. Presenters and

[2]A list of initial national priorities for CER recommended by the IOM in 2009 can be found at http://www.iom.edu/Reports/2009/ComparativeEffectivenessResearchPriorities.aspx.

participants also described the diminished capacity of the current clinical trials system. These observations, and proposed solutions, informed the discussion over the course of the 2-day workshop.

THE DIVIDE BETWEEN CLINICAL RESEARCH AND CLINICAL PRACTICE

Janet Woodcock, Director of the FDA's Center for Drug Evaluation and Research (CDER), identified bridging the divide between research and the clinical practice of medicine as one of the most critical needs facing the clinical research enterprise today. The limited involvement of community physicians in clinical research reduces physician referrals of patients to clinical research studies, as well as the total number of investigators available to conduct the research (see the discussion of narrow incentives for physician participation in clinical trials below). Furthermore, the findings of research conducted in academic medical centers rather than in community settings are less likely to be adopted by physicians in their daily practice. The poor rate of adoption of effective clinical practices is reflected in one study that examined adherence to 439 indicators of health care quality for 30 acute and chronic conditions and preventive care. Results indicated that American adults receive on average only 54.9 percent of recommended care (McGlynn et al., 2003).

Woodcock stressed that, to generate relevant research based in clinical practice, community practitioners must be actively involved in the clinical trial process. She suggested it is not surprising that the uptake of evidence-based practices is slow when practitioners are not engaged in the research that supports the changes. In many instances, the characteristics of the study population, their comorbidities and therapeutic regimens, and the setting and conditions under which the trial is conducted bear little resemblance to typical community practice. Indeed, the outcomes are often quite different as well. It is little wonder that community physicians may be hesitant to modify their treatment practices to reflect clinical findings developed in this manner. According to Woodcock, the divergence between physicians conducting research and those in community practice is one of the greatest barriers to successfully translating study results into clinical practice. She argued that, to develop a truly learning health care system capable of self-evaluation and improvement, the currently separate systems of clinical research and practice must converge.

Challenges Facing Investigators in Academic Health Centers

Woodcock discussed a number of important obstacles facing investigators conducting research using the current infrastructure. Clinical investi-

gators, those who lead a research idea through the clinical trial process, face multiple small obstacles that together can appear insurmountable. These obstacles include locating funding, responding to multiple review cycles, obtaining Institutional Review Board (IRB) approvals, establishing clinical trial and material transfer agreements with sponsors and medical centers, recruiting patients, administering complicated informed consent agreements, securing protected research time from medical school departments, and completing large amounts of associated paperwork. As a result of these challenges, many who try their hand at clinical investigation drop out after their first trial. Especially in the case of investigator-initiated trials, where an individual's idea and desire to explore a research question are the primary force behind the trial, the complex task of seeing a clinical trial through from beginning to end is making the clinical research career path unattractive for many young scientists and clinicians. Woodcock noted that in her experience, successful clinical investigators represent a select subset of clinicians—highly tenacious and persistent individuals with exceptional motivation to complete the clinical trial process.

According to Robert Califf, Vice Chancellor for Clinical Research and Director of the Duke Translational Medicine Institute, some of the challenges to participating in clinical research mentioned by clinical cardiovascular investigators include

- the time and financial demands of clinical practice;
- the overall shortage of cardiovascular specialists;
- the increasing complexity of regulations;
- the increasing complexity of contracts;
- the lack of local supportive infrastructure;
- inadequate research training;
- less enjoyment from participation (e.g., increasing business aspects, contract research organization pressures); and
- data collection challenges (medical records, reimbursement, quality control, pay for performance).

Califf noted that most of these challenges do not involve the actual conduct of a clinical trial and that many investigators say it is not difficult to get patients to participate in trials as long as the critical physician–patient interaction takes place. Investigators also cite the importance of support for research efforts from their home institution.

Challenges Confronting Community Physicians

Practitioners face a number of challenges to their involvement in clinical research. Busy patient practices and the associated billing and reporting

requirements leave them with limited time for research. A further barrier is the lack of a supportive clinical research infrastructure, especially in the form of administrative and financial support. For practitioners who become engaged in running a clinical trial and recruiting patients, their financial reimbursement per patient can, in some cases, be less than they would receive from regular practice. In addition, there is a financial disincentive for physicians to refer their patients to clinical trials. Physicians who do so must often refer those patients away from their care; thus each patient referred represents a lost revenue stream.

Challenges Facing Patients

Patients also face challenges to participating in clinical research. Many workshop participants noted that patients often are unaware of the possibility of enrolling in a clinical trial. If they are aware of this opportunity, it is often difficult for them to locate a trial. Patients may reside far from study centers; even the largest multicenter trials can pose geographic challenges for those wishing to participate. Moreover, depending on the number of clinic visits required by the study protocol, significant travel and time costs may be associated with participation. In addition, trials designed with narrow eligibility criteria for participation purposely eliminate many patients who might have the disease being studied but are ineligible because of other characteristics (e.g., age, level of disease progression, exposure to certain medicines).

As noted, trials often require patients to temporarily leave the care of their regular doctor and receive services from unfamiliar providers. In addition to confronting potentially undesirable interruptions in care, it is understandably difficult for many patients to justify the physical and emotional strain of leaving their regular provider to volunteer for a clinical trial. If a patient reaches the point of enrolling in a clinical trial, the extensive paperwork associated with the informed consent process can be confusing and burdensome. As discussed later, informed consent forms are developed to meet legal requirements and can contribute to the confusion patients feel regarding the trial and what it entails. In addition, there is sometimes a mistrust of industry-sponsored trials among the public. These feelings of mistrust can further complicate the already difficult decision about whether to join a trial.

GLOBALIZATION OF CLINICAL TRIALS

The increasing trend toward conducting clinical trials outside the United States is an important consideration in discussing ways to improve the efficiency of trials. The number of patients enrolled in clinical trials

is decreasing in the United States and increasing abroad. According to Woodcock, when development programs are conducted entirely outside the United States, the FDA questions the extent to which the results can be translated to U.S. clinical practice. The applicability of foreign trials results depends on the disease being studied and the state of current clinical practice in that area.

Califf suggested that the difficulties inherent in conducting clinical trials in the United States have contributed to the relative decline in U.S. clinical trials described in Chapter 2. Citing a recent paper that he coauthored, he noted that one-third of phase III trials for the 20 largest U.S. pharmaceutical companies are being conducted solely outside the United States (Glickman et al., 2009). For these same firms and studies, a majority of study sites (13,521 of 24,206) are abroad (Glickman et al., 2009). Califf stated that the situation is the same across study sponsors—NIH, industry, and academia all look to conduct trials internationally.

Califf suggested that globalization is a positive trend overall, one in which he and his home organization, the Duke Clinical Research Institute (DCRI), are engaged. However, the current situation in which clinical research is being sent abroad just to get trials completed is unsustainable. One reason for this situation is that clinical trials in a number of other countries cost less than they currently do in the United States (Table 3-1) (see also the discussion of costs below). If a large outcome trial requires enrolling tens of thousands of patients, for example, selecting trial sites in Russia or India instead of the United States can result in hundreds of millions of dollars in savings. The overall cost associated with gathering the necessary resources to conduct a clinical trial is an important factor in the choice of a trial site. For instance, physician salaries in a number of countries are lower than in

TABLE 3-1 Global Research Costs: Relative Cost Indexes of Payments to Clinical Trial Sites

Country	Cost of Clinical Trials Relative to the United States
United States	1.00
Australia	0.67
Argentina	0.65
Germany	0.50
Brazil	0.50
China	0.50
Russia	0.41
Poland	0.39
India	0.36

SOURCE: Califf, 2009.

the United States. In these countries, the charges to clinical trial sponsors for conducting a clinical trial with physician involvement are lower than they would be in the United States. Some also argue that clinical trials conducted outside of the United States are of higher quality because of better adherence to trial protocols and better patient follow-up.

THE COST OF CLINICAL TRIALS

Clinical trial costs can vary widely depending on the number of patients being sought, the number and location of research sites, the complexity of the trial protocol, and the reimbursement provided to investigators. The total cost can reach $300–$600 million to implement, conduct, and monitor a large, multicenter trial to completion. Table 3-2 outlines the various costs of an exemplar large, global clinical trial, which in this case add up to about $300 million.

Christopher Cannon, senior investigator in the Thrombolysis in Myocardial Infarction (TIMI) Study Group, stated that two clinical trials on which he is working cost a total of $600 million. To put this cost in perspective, it represents approximately half of the $1.1 billion allocated for comparative effectiveness research in the American Recovery and Reinvestment Act of 2009. According to Cannon, the exorbitant cost of clinical trials today points to the need to move toward simpler large trials that would study a broader population, include less data, and cost less overall.

The federal government funds a large portion of clinical research in the United States, primarily through NIH. In some cases, it has been estimated that NIH institutes pay research sites 20–40 percent less than the actual cost of conducting trials. Michael Lauer, Director of the Division of Cardiovascular Diseases, National Heart, Lung, and Blood Institute (NHLBI),

TABLE 3-2 Breakdown of the Costs for a Large, Global Clinical Trial (14,000 patients, 300 sites)

Expense	Cost (in millions of $)
Site payments	150.0
Monitoring	90.0
Data management and statistics	12.0
Project and clinical leadership	12.0
Interactive voice response systems (IVRS) and drug distribution	10.8
Publications	.1
Total	~300

SOURCE: Califf, 2009.

National Institutes of Health, responded that to remedy the issue of appropriate NIH payments to research sites, the solution will likely involve a combination of increasing the amount of money paid by NIH to sites and decreasing the charges associated with conducting the research. Lauer further explained that because NIH's funding is relatively flat, if research site payments are increased, an equivalent decrease in funding in other areas will be necessary. Given this zero-sum calculation, it will be politically difficult to increase payments for research sites. Lauer believes that simplifying trials could be most effective in reducing their cost. He suggested that good science comes from high-quality observations that are followed by focused experiments to test these observations. The trials that have had the greatest impact on clinical decision making and patient care have been simple (e.g., uncomplicated study protocols, short case report forms). Thus, if the research community could keep trials simple and large enough to answer the study question(s), costs could decrease, while the impact and relevance of the results would increase.

Workshop participants also discussed the inequality of NIH payments to research sites across the various NIH institutes. This variation has created a scenario in which some institutes that pay research sites more are seen as the "haves," while those that pay less are seen as the "have-nots." Judith Fradkin, Director of the Division of Diabetes, Endocrinology, and Metabolic Diseases in the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) at the National Institutes of Health, noted that inconsistency across Clinical and Translational Science Awards (CTSA) institutions in the level of clinical trial support they provide makes it difficult for NIH to determine how its payments to research sites should be adjusted to take CTSA support into account.

NARROW INCENTIVES FOR PHYSICIAN PARTICIPATION IN CLINICAL RESEARCH

As discussed earlier, the current clinical research enterprise in the United States is largely separate from traditional clinical practice. In part because the United States does not have a nationalized health care system in which services are provided to all citizens through government-funded providers, clinical research takes place in various types of sites, frequently outside of the community-based, primary practice setting where most patients receive care. Moreover, as noted above, private practice physicians have disincentives to refer their patients to clinical trials. The fewer physicians are involved in developing and implementing clinical trials, the less scientific the practice of medicine will be. A number of workshop attendees suggested that a mechanism to adequately compensate physicians for referring patients to clinical trials could improve recruitment rates of U.S. patients.

Making it easier for community-based physicians to participate actively in clinical trials could also have a positive effect on patient recruitment; enhance the engagement of the community in important research; and increase the chances that physicians will change their practice behavior based on research results they were involved in generating, thereby strengthening the trend toward evidence-based medicine in the United States. Workshop participants also suggested that, to encourage physician participation in clinical trials, the study questions and protocol should be designed in the context of clinical practice—that is, the procedures required by a trial protocol should be easily incorporated into practice.

It is also important to consider that the research questions clinical trials seek to answer reflect the incentives and interests of those developing the questions. In this respect, the capability of the health care system to act on trial results is part of the clinical research decision making process. For instance, Amir Kalali, Vice President, Medical and Scientific Services, and Global Therapeutic Team Leader CNS (central nervous system), at Quintiles Inc., explained that his company ran the two largest clinical trials testing the combination of psychotherapy and medication to treat depression. Despite scientific evidence for the benefits of psychotherapy, it has seen limited uptake. According to Kalali, this is because patients have limited access to psychotherapy as a medical treatment in the United States. Thus, the capability of the health care system to implement or act on research findings can be an important consideration in conducting clinical trials to test alternative treatments for a condition.

SHRINKING CLINICAL RESEARCH WORKFORCE

Research involving human subjects has become an increasingly complex environment in which to work and be successful. Thus, it is not surprising that, as noted in Chapter 1, the clinical investigator workforce is plagued by high turnover. Clifford Lane, Clinical Director, National Institute of Allergy and Infectious Diseases (NIAID), shared data from NIAID revealing the trend that fewer professionals are entering the research field than in the past. As Figure 3-1 indicates, the number of tenure-track principal investigators conducting research within the NIAID/NIH intramural program decreased from 74 in 2003 to 42 in 2008. While there was a slight increase to 53 tenure-track investigators in 2009, this number is still well below that in 2003.

The majority of phase III clinical trials are conducted by extramural researchers. However, trends in intramural NIH programs add to our general understanding of the issues and challenges facing investigators today. Lane commented that the overall decrease in intramural investigators is due in part to the fact that more researchers are turning to laboratory work be-

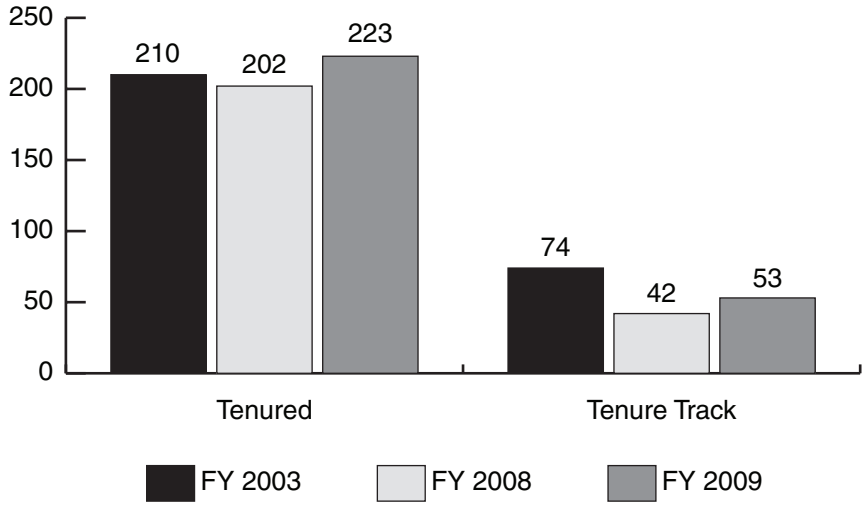


FIGURE 3-1 While the number of senior NIAID/NIH tenured investigators is relatively stable, the number of NIAID/NIH tenure-track principal investigators is decreasing.
SOURCE: Lane, 2009. Courtesy of John Gallin, 2009 (unpublished).

cause publishing results from this work is easier, and the difficulties of getting a clinical trial protocol approved can be avoided. Accordingly, NIAID has created a protocol development program to decrease the burden of regulatory and administrative requirements and optimize the use of existing clinical research tools. The program's goal is to allow investigators to focus on their work as clinical scientists rather than having to serve as operations managers of a complex regulatory process. When investigators provide a robust scientific idea with a strong hypothesis, appropriate endpoints, and a sound study design, NIAID's Office of the Clinical Director helps them navigate such regulatory issues as ethics review, technology transfer, safety concerns, and interactions with Institutional Review Boards (IRBs) and the FDA. This support can help investigators implement a trial successfully. In addition to principal investigators, multidisciplinary support staffs are necessary to complete a clinical trial successfully. Biostatisticians, epidemiologists, laboratory technicians, and administrative support personnel are just a few of the types of staff needed.

The importance of involving knowledgeable staff throughout a study was highlighted in a discussion of cardiovascular and depression clinical trials. Califf referred to the crucial role of a well-trained, intelligent data monitoring committee tasked with evaluating interim trial results. Data fluctuations revealed by interim trial monitoring require analysis but do not always

indicate that a trial should be discontinued. For instance, when death is the primary outcome of a trial, data fluctuations may indicate an adverse effect on mortality of the treatment being studied or a regular clinical occurrence unrelated to the study drug. Califf noted that if it were not for a particularly well-informed data monitoring committee, the ISIS-2 (Second International Study of Infarct Survival) trial would have been most recently discontinued at 5,000 patients, with aspirin showing an adverse effect on mortality. William Potter, most recently Vice President of Translational Neuroscience, Merck Research Labs, Merck & Co., Inc., indicated that in the depression studies in which he has been involved, interim data that indicate a possible adverse effect usually result in a trial's being discontinued.

Because clinical trials are conducted in an ad hoc fashion, and study personnel of varying professional quality are recruited and trained anew at each site, inconsistencies in trial execution across sites are not unusual. Woodcock explained that the failure to execute a clinical trial successfully is often attributable in part to the fact that ensuring proper execution of a single trial is no one's full-time job. The core activities of a clinical trial are largely supplemental responsibilities assigned to a variety of staff in addition to their full-time work.

Califf noted that clinical investigators often are unsupported by their academic institutions and are left largely to their own devices to design a trial and gather the necessary resources. The major reason for this lack of support, he suggested, is that clinical research is not widely respected among academics as a truly intellectual endeavor. Califf explained that, while investigators who are leading large, multisite trials predicted to have a major impact on clinical practice enjoy such respect, this is not the case for those conducting less visible work or just starting out in their research careers. A number of workshop participants expressed their support for rewarding academic researchers who conduct clinical trials. Early career development at the graduate and postgraduate levels could create incentives for more experts to enter the field of clinical research.

NEED TO NAVIGATE ADMINISTRATIVE AND REGULATORY REQUIREMENTS

The internal requirements of an academic institution, federal agency, or pharmaceutical company for reviewing multiple aspects of a clinical trial can significantly delay its initiation. In the case of an academic institution conducting a clinical trial for a pharmaceutical company, the internal review processes of both organizations are involved. In addition to such internal requirements, myriad federal and state regulatory requirements affect the conduct of clinical trials. Adhering to these many requirements is a significant challenge for investigators. Moreover, the delays incurred

increase the time cost of a trial and decrease its overall efficiency. U.S. academic institutions typically take longer to navigate the approval process (i.e., from budget/contract to IRB approval) compared to private or academic institutions abroad. The protracted timeline to approve a clinical trial through U.S. institutions is one reason industry sponsors look outside the United States to initiate studies.

Institutional Review Board Approval

Gaining IRB approval is a requirement of the clinical trial process.[3] Lane's survey of intramural NIH investigators revealed that the top four barriers to clinical research are:

- Ethical/IRB approval,
- scientific review/protocol approval,
- interaction with industry and issues with technology transfer, and
- adequacy of resources.

Lane noted that there is often a lack of clarity among investigators regarding the roles and responsibilities of different oversight bodies. In focus groups with the investigators polled, it became clear that IRB missions can be difficult to interpret. Institutions have used IRBs for risk management above and beyond what is required for human subjects research, and included in their purview travel policies, conflicts of interest, and other management issues. Investigators often do not know or understand what the IRB expects of them, and the IRB decision-making process can be lacking in timeliness and accountability. Investigators reported that if the IRB process results in a request for changes to a trial, they often lack the resources to fulfill the request.

Paul Hébert, Editor-in-Chief of the *Canadian Medical Association Journal* (CMAJ) and critical care physician at the Ottawa Hospital, commented on the difficulties associated with IRB ethics review. A key concern is that IRBs are accountable only to their own institution and not to the greater public good. Hébert suggested that, to improve the regulatory system, IRBs should be held accountable to the community for the decisions they make. Moreover, decreasing the regulatory burden surrounding clinical trials does not need to be a zero-sum game. For example, decreasing the number of ethics reviews for a trial from 50 to 10 would be a substantial improvement over the current situation.

[3]An IRB is tasked with reviewing a clinical trial protocol to ensure that the study is conducted ethically and study participants are not likely to be harmed. An IRB can decide whether a clinical trial should continue as planned or changes should be made.

Carla Greenbaum, Director of the Benaroya Research Institute Diabetes Program and Clinical Research Center, shared her experiences and insights into the IRB process from the perspective of diabetes research. She noted that regulations vary by geographic location. Depending on location, for example, IRBs have different answers to the question of when research in children is appropriate, and they differ as well in how clinical research terms and phrases such as "minimal risk," "slightly greater than minimal risk," and "benefit" are defined. Geographic variation is also seen in IRB definitions of reportable adverse events, definitions of equipoise[4] and whether a proposed study satisfies this requirement, and rules regarding whether permission can be granted for clinical trial samples to be retained indefinitely by the pharmaceutical sponsor versus NIDDK. Because multiple IRB approvals are required for most large, multisite clinical trials, these inconsistencies in IRB determinations and standards across the country complicate and delay the process of conducting a clinical trial and can inhibit the ability of investigators to implement the same trial protocol across all study sites—a critical factor for developing valid trial results.

Informed Consent

Informed consent refers to the process and documents associated with educating individuals on the details of a clinical trial and potentially gaining their consent to participate in the study.[5] Obtaining informed consent from each subject in a clinical trial requires a significant amount of time. The informed consent process includes developing appropriately worded consent documents, discussing the documents and the clinical trial process with individual patients, obtaining the required patient signatures on the documents, and keeping track of the paperwork generated throughout the enrollment process.

As an example of the time and effort necessary to satisfy informed consent requirements, Greenbaum described a hypothetical scenario from her experience in diabetes research. A family consisting of two parents and four children, one with diabetes, decides to be screened for participation in a diabetes prevention study. The consent process for this family requires a total of 8 separate consent forms, each 6 pages long and requiring 16 signatures, plus 5 Health Information Portability and Accountability Act

[4]Equipoise is the point at which a rational, informed person has no preference between two (or more) available treatments (Lilford and Jackson, 1995). In clinical research, the ethical concept of equipoise is satisfied when genuine uncertainty exists as to the comparative therapeutic benefits of the therapies in each arm of a clinical trial.

[5]The documents and conversations involved in the consent process explain the details of the clinical trial, including its purpose, the treatment procedures and schedule, potential risks and benefits, alternatives to participation, and the rights of participants (NCI, 2010).

(HIPAA) forms. This paperwork is in addition to the extensive monitoring and compliance that accompany the consent process.

Greenbaum stressed the irrationality of the current situation in which an individual's ability to participate in clinical research is dictated by geographic location. As a result of the level of local control exerted over clinical research, patients who frequent a hospital or medical center in one area of town may have access to certain clinical trials, whereas those at a hospital across town do not. For instance, some clinical trials organized through TrialNet are not approved at one institution in Greenbaum's area because it is their policy that studies should not be conducted in children until the therapeutic approach has first been demonstrated to work in adults.

Protracted Time from Protocol Approval to Trial Activation

Administrative burdens are not always imposed on investigators by external laws and regulations. As Lane noted, many bottlenecks arise internally and are imposed by institutions that are home to the research workforce. In the government-sponsored Occluded Artery Trial (OAT), for instance, it took 3 years from the first NIH steering committee meeting to the start of the trial. Because clinical research relies on substantial human effort that incurs large labor costs, the timeline for a clinical trial affects overall cost. DiMasi and colleagues estimated that in 2000, the average cost to develop a new drug was $802 million, and time costs associated with the length of research and development accounted for half of this cost (DiMasi et al., 2003).

For the pharmaceutical industry, protracted timelines increase cost and reduce revenue as medications typically have a finite life before losing patent protection and creating an opportunity for generic competitors. Moreover, when a trial addresses a question important for medical practice, increasing the time it takes to obtain an answer can reduce the impact of the results. Musa Mayer, breast cancer survivor, advocate, and author (AdvancedBC.org), commented that if clinical trials are subject to significant delays, the standard of care can move on in the absence of phase III data. Thus, obstacles and delays in clinical trials move health care further away from evidence-based practice. Moreover, if the time lag is significant, the results of a lengthy, expensive trial may already have been rendered irrelevant by changes in clinical practice when they finally become available.

The one-off nature of trial organization, mentioned by a number of workshop participants as a major barrier to the efficient conduct of trials, is one factor leading to prolonged trial startup times. Years can elapse from the time researchers begin talking about a study idea to the point at

which they assemble the appropriate investigators, develop collaborations, establish study sites, and initiate the trial.

Renzo Canetta, Vice President of Oncology Global Clinical Research, Bristol-Myers Squibb, provided an example of the internal administrative burdens faced by industry. Historically, Bristol-Myers Squibb has required 8 months, or 34 internal review cycles, to produce and activate a new study protocol. Recent efforts to improve the review cycle have been aimed at reducing this internal process to 150 days (5 months). Some individual institutions have exhibited greater flexibility and have been able to further streamline the protocol approval process. The University of Arkansas has a 70-day timeline for activating a new trial, while M.D. Anderson Cancer Center has a project under way (Project Zero Delay) to turn protocols around in 46 days, according to Canetta.

Case Report Forms

Collecting data for each participant in a clinical trial efficiently and accurately and according to the study objectives is essential for regulatory compliance, as well as the success of the research effort. The case report form (CRF) is the tool used by investigators to collect patient information throughout a clinical trial. Data Safety Monitoring Boards (DSMBs) are tasked with ongoing monitoring of the data collected in CRFs. A portion of the monitoring costs for a trial is directly linked to the complexity of the CRF developed for that trial. Complex CRFs with many data points are more expensive to monitor than simpler CRFs. A number of workshop participants noted that efforts to simplify CRFs so they include only the necessary, biologically relevant details of the trial could decrease trial costs.

Beyond the cost issue, the lack of standardized CRFs and trial procedures can create chaos in some study sites. Woodcock reflected on a recent meeting with the FDA and contract research organizations (CROs) in which the CROs openly discussed the monitoring of study sites. Among the problems they reported, many sites were not conducting critical study procedures correctly or entering all of the data required by the study protocol. According to Woodcock, poor understanding of the study protocol is a common problem in clinical trials and can lead to sloppy data collection and poor data quality. Califf suggested that expending resources and enrolling patients in a clinical trial that does not yield useful information could be considered unethical.

Clinical investigators may be trained to use multiple CRFs depending on the number of trials in which they participate. To reduce costs, Canetta suggested developing a standardized, electronic CRF for use across the research enterprise. Doing so would benefit all stakeholders—government and industry included—because it would help clinical investigators do their

job more efficiently. Cooperative groups supported by the National Cancer Institute (NCI) are currently using standardized CRFs, and the Cancer Biomedical Informatics Grid (caBIG) online network is developing a library of standardized CRFs to be used throughout oncology trials.

RECRUITMENT AND RETENTION OF PATIENTS

A core function of a successful clinical trial is finding patients who fit the predetermined eligibility criteria and getting them to participate. Each disease area addressed during the workshop (cardiovascular disease, depression, cancer, and diabetes) has a unique patient base for clinical trials, and the issues that affect patient enrollment in trials can vary according to features of the disease. In addition, workshop participants identified challenges to patient recruitment that transcend disease status.

Patient Education

Mayer presented the results of a Harris Interactive Survey of 6,000 cancer patients that found that 85 percent were unaware that participation in clinical trials was even an option. Of the patients surveyed, 75 percent said that if participation in a clinical trial had been offered, they would have been receptive to the idea. Of those aware of clinical trials and offered the possibility of participation, 71 percent chose not to participate. However, almost all who participated were satisfied with the experience. Thus, according to these survey results, patients' preconceived notions about trial participation could pose a barrier to clinical trial enrollment.

Greenbaum noted that the socioeconomic status of patients plays a role in whether they decide to enroll in clinical trials. In addition to income and education, patients' access to health care services and the network of social support patients have to help them cope with their disease can affect their connection to the medical system and their interest in clinical research. As Mayer noted in her presentation, the online patient network she has developed for metastatic (advanced) breast cancer is composed primarily of younger, better educated, less diverse, and more affluent individuals as compared with the general population. Thus, higher socioeconomic status is associated with having the resources, knowledge, and motivation to seek information about a disease, including access to clinical trials.

Patient Recruitment

According to Woodcock, sites for clinical trials are frequently selected on the basis of where the investigators are located, as opposed to where the patients are, creating difficulties in patient recruitment. When patient

recruitment is impeded, the trial is delayed, sometimes by years, until the number of patients required by the study protocol can be enrolled. Once a trial protocol has been activated, the recruitment of patients requires a significant amount of time and money. Canetta reported that the ability to recruit patients into a trial successfully is similar for the pharmaceutical industry and NCI. Regardless of the trial sponsor, recruitment of patients who meet the requirements of the protocol is difficult: in one study of 14 cancer centers approximately 50 percent of study sites failed to recruit a single patient (Durivage et al., 2009). Thus, patient enrollment can directly affect the number of trials that are completed.

4

Clinical Trials in Cardiovascular Disease

To inform the workshop discussion of ways to improve the overall clinical research enterprise in the Unites States, speakers offered insight into their research efforts in the four disease-specific areas noted in Chapter 1. Gaining an appreciation of the differences in clinical trials by disease helped participants identify aspects of the clinical research enterprise that are working well and those that are not. According to clinicaltrials.gov, cardiovascular trials currently account for 10 percent of all clinical trial participants. The acute nature of many of the health-related events associated with cardiovascular disease and the large number of individuals with the disease make this area of medical research unique in important ways. Presentations summarized in this chapter described a number of different approaches to conducting clinical research in the area of cardiovascular disease and illuminated the overall evolution of clinical trials in this area as compared with other disease areas. This first of four chapters on clinical trials in disease-specific areas begins with a discussion of clinical research models for coronary syndromes. Next, the Thrombolysis in Myocardial Infarction (TIMI) Study Group is discussed as an academic research organization model—a type of clinical research network. The National Institutes of Health (NIH)—sponsored Occluded Artery Trial (OAT) is then presented as an example of the unique strengths and weaknesses of government-sponsored trials. Finally, the chapter summarizes a discussion of the usefulness of large, simple clinical trials in cardiovascular disease.

CLINICAL RESEARCH MODELS FOR CORONARY SYNDROMES

Acute coronary syndromes (ACS) is a broad term referring to a group of conditions ranging from unstable angina, to myocardial infarction (heart

attack), to sudden cardiac death. The condition depends on the degree to which the coronary artery has been obstructed and the health effects the obstruction has caused. A diagnosis of ACS is made by evaluating the results of an electrocardiogram (ECG) and the presence or absence of certain enzymes in the body.

Clinical research efforts in ACS provide a useful model for examining large, multicenter effectiveness trials in an acute, life-threatening disease. Robert Califf, Vice Chancellor for Clinical Research and Director of the Duke Translational Medicine Institute, reflected on the notable successes of the ACS field in translating basic science into early clinical trials, and then into definitive trials that evaluate outcomes related to key clinical questions. Once effective treatments have been identified and disseminated, the final step is measuring their uptake in hospitals and making the results publicly available, which improves adherence to the treatments. A 2004 study examining hospital compliance with quality guidelines (those of the American College of Cardiology/American Heart Association) and in-hospital mortality rates revealed that a 10 percent increase in guideline adherence corresponded to an 11 percent reduction in mortality rates (Peterson et al., 2004). Califf also cited papers based on data from a national registry of myocardial infarction showing that U.S. hospitals show close to 100 percent uptake of evidence-based therapies for ST elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (non-STEMI) at both hospital admission and discharge. The result has been an approximately 30 percent reduction in the risk of death if a patient presents at a hospital with chest pain. Califf stressed that, to establish evidence-based therapies that individuals and institutions can be held accountable for using, clinical trials should be focused on answering the critical questions in that disease area; conversely, trials that are poorly designed and seek to answer peripheral or irrelevant questions should be avoided.

Califf reflected on the evolution of clinical trials in ACS. Califf was part of a small group of people who formed the TAMI Group to address the area of STEMI trials. The group received a small amount of money ($100,000) from Genentech to conduct a randomized controlled trial (RCT) with 340 participants. The trial protocol, or study plan, included three cardiac catheterizations per subject, and the trial results were published in the *New England Journal of Medicine*. Califf highlighted this example of an early ACS trial because he believes the same trial could not be conducted today given the extremely high cost of conducting trials and the large number of patients now required for cardiovascular outcome trials.

The International Study of Infarct Survival (ISIS) group at Oxford had a similar early trial experience that Califf likewise claimed could not be replicated in today's clinical trial environment. The minimum sample size

required to answer the study question of interest to the ISIS group was 10,000 patients. Using unpaid clinical investigators and a one-page case report form the ISIS group randomized the 10,000 patients necessary to answer the relevant clinical question. The ISIS trial changed the study of ACS in that future trials sought larger sample sizes to appropriately answer the main outcome questions of interest in cardiovascular disease. However, the fact that the ISIS trial did not pay investigators makes its duplication in any country today impossible, according to Califf. Another critical change in the conduct of STEMI trials came when the U.S. Food and Drug Administration (FDA) moved toward requiring outcome trials to evaluate critical clinical endpoints related to the safety and effectiveness of a drug. Califf explained that the new FDA standard for STEMI trials changed this field of research and improved the clinical relevance of trials conducted by industry and academia.

Recognizing a practical, clinical inception time for the spectrum of ACS improved the ability of practitioners to identify a study population. The primary medical action in ACS occurs in the first 24 hours of a patient's hospital stay. In the past, diagnosing a type of ACS often required a patient to be admitted, receive an ECG, and have a physician evaluate enzyme levels 24 hours later to determine whether the patient had experienced a heart attack, and then for the physician to refer to the ECG results to determine whether it was STEMI or non-STEMI. Elliott Antman, Senior Investigator in the TIMI Study Group, developed a system for classifying patients at the time of the ECG (Figure 4-1). Califf explained that creating an easily identifiable marker by which to classify patients in the emergency room made it less expensive and time-consuming for busy practitioners to become involved in locating patients for a clinical trial. This practitioner-oriented classification system is especially helpful in facilitating enrollment in cardiovascular disease trials, which typically seek to recruit a large number of patients per trial. Box 4-1 presents a case study illustrating the importance of developing a practical disease inception point.

THE THROMBOLYSIS IN MYOCARDIAL INFARCTION STUDY GROUP

As an example of a disease-focused research network, Marc Sabatine, investigator in the TIMI Study Group, discussed the group's research work and structure. Headquartered at Brigham and Women's Hospital and Harvard Medical School, TIMI is an academic research organization (ARO) conducting clinical trials to improve health outcomes in patients with cardiovascular disease. Conducting studies from phase I to IV, TIMI has completed 45 clinical trials to date, and has 6 ongoing trials and 7 in the planning stages. Trial sizes range from 30 to 25,000 subjects. Sabatine

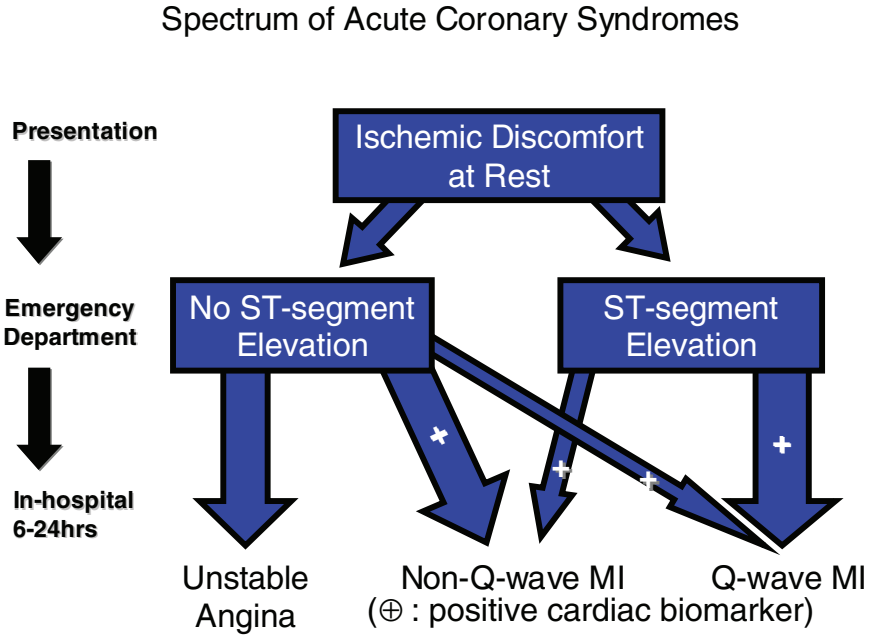


FIGURE 4-1 Classification system for the spectrum of acute coronary syndromes that helps practitioners identify a study population more easily.
NOTE: MI = myocardial infarction.
SOURCE: Califf, 2009. (Adapted from 2007 American Heart Association/American College of Cardiology Guidelines.) Reprinted with permission from Robert Califf 2010.

BOX 4-1
Case Study: Acute Decompensated Heart Failure and Acute Myocardial Infarction

The importance of developing a practical inception point for a disease is highlighted by comparing two diseases—acute decompensated heart failure and acute myocardial infarction (MI). The two diseases affect the same number of people and have roughly the same mortality and readmission risks. As illustrated in the table below, in 2006 acute decompensated heart failure lacked evidence-based guidelines, whereas acute MI had a robust base of scientific evidence based on large randomized trials.

	Acute Decompensated Heart Failure	Acute MI
Hospitalizations/Year	1,000,000	1,000,000
Inpatient Mortality	5–15%	5–10%
30-day Readmission	10–20%	10–20%
Guidelines for Risk Stratification	No	Yes
Guidelines for Therapy	Yes (European Society of Cardiology), No (American Heart Association/American College of Cardiology)	Yes
Largest Randomized Trial	N = 1,412	N = 41,021
Medline Citations (1965–2006)	472	33,908

According to Califf, differences between the two diseases, and particularly the ability to develop an inception point for acute MI, paved the way for large, robust clinical trials and the development of effective therapies in this disease area. Califf reported that the FDA was also critical in requiring that acute MI trials be oriented toward the outcomes that mattered most. In contrast, heart failure lacks a clear inception point, and the surrounding ambiguity can lead to challenges and delays in diagnosis.

Califf highlighted a recent positive development—the development of a large clinical trial to answer the question of whether a marketed drug, nesiritide, is effective against heart failure. Nesiritide originally gained market approval based on the results of a number of small clinical trials, but a subsequent meta-analysis of patient data called the drug's performance into question and suggested an increased mortality risk. The current large trial testing nesiritide has been exceeding expectations in terms of patient enrollment. Califf suggested two reasons why this trial has been successful in recruiting patients: (1) it addresses an interesting and important research question that people are eager to answer, and (2) payments to study sites adequately compensate the investigators for the expense and extra effort associated with implementing the study protocol.

SOURCE: Califf, 2009.

noted that the academic leadership at the core of TIMI's work participates in each stage of the clinical trial process, including:

- **Reviewing the compound**—reviewing the pharmacokinetic (PK), pharmacodynamic (PD), animal model, and phase I data for a compound being considered for further study.
- **Refining the scientific question**—asking whether a new compound addresses an unmet clinical need in cardiovascular medicine, as well as what utility the compound has and how it relates to current and evolving concomitant treatments.
- **Initiating the study**—helping to plan and initiate both investigator- and industry-initiated studies.
- **Developing study design**—helping to determine the study population, the timing of the intervention, the appropriate control arm and background therapy, the endpoints and timing of ascertainments, and the statistical analysis plan.
- **Developing key trial documents**—collaborating on the development of the trial protocol, case report form, Clinical Events Committee (CEC) charter, and Data Safety Monitoring Board (DSMB) charter.
- **Study startup**—considering the country and site for a trial, the applicability of trial results in the United States, the acceptability of the trial to other countries, and the cost of conducting the trial.
- **Monitoring study progress**—monitoring patient enrollment, any changes in the medical landscape, aggregate event rates (efficacy and safety), and the retention of patients.
- **Leading study analysis**—conducting data analysis on a database separate from that received by trial sponsors and moving rapidly to present the data at scientific meetings, as well as drafting primary manuscript of the trial results and engaging in subsequent data analyses.

When Eugene Braunwald founded the group in 1984, TIMI trials were funded by the National Heart, Lung, and Blood Institute (NHLBI). Today the trials are funded by industry, with some NIH grant support for ancillary studies. In response to a question from Califf, Sabatine described TIMI's studies as being relatively complex, having case report forms that are more than one or two pages, and seeking to answer a variety of questions. Strong academic support for the trial activities listed above is important to the group as a whole and would be very difficult to maintain through government funding alone.

Sabatine stated that one of the strengths of the TIMI group is the relative leanness of the organization. The physician staff includes the study chairman, 12 staff cardiologists, three senior cardiology fellows, and a

rotating staff of research residents from Brigham and Women's Hospital. Operational staff includes a director, eight project directors and managers, and research assistants. Core biostatistics staffs, including a director and multiple programmers, round out the TIMI group. Sabatine described an intense working relationship between physician staff and operational staff as important to ensuring that the trials are conducted in the best possible way. For a typical TIMI trial, two physicians and multiple operational staff work closely on planning and execution. Physician and operational staff offices are located next to one another, which facilitates daily conversations to guide a trial from inception to completion.

Investigator- and Industry-Initiated TIMI Studies

TIMI trials generally fall into two broad categories: (1) investigator-initiated studies, in which an academic investigator who is interested in the field of cardiovascular medicine is the driving force behind the study, and (2) industry-initiated studies, in which the TIMI group is approached by a company to address a particular question. Both Sabatine and Christopher Cannon, senior investigator, TIMI Study Group, noted that TIMI involves practicing cardiologists and researchers in the development of scientific questions to be addressed and encourages them to consider where they see the field moving in terms of current and evolving therapy for cardiovascular disease.

Sabatine presented case examples of both investigator- and industry-initiated studies. In each example, the flexibility of the TIMI group is highlighted, as well as its trademark of core academic leadership.

Investigator-Initiated TIMI Study

At the suggestion of TIMI investigator Cannon, the study group approached the makers of an antiplatelet drug, clopidogrel, which had been approved for patients with less severe types of heart attacks. Cannon wanted to test whether clopidogrel would also benefit patients with more severe STEMI. As a result, the phase III CLARITY TIMI 28 trial involving nearly 3,500 patients was launched. The trial showed that administering clopidogrel to patients receiving a thrombolytic therapy for their heart attack decreased the odds of their having a blocked artery and translated to a decreased rate of clinical events. Simultaneous to the CLARITY TIMI 28 study, a very large, simple trial of the drug in China in which patients received a non-Western form of care (e.g., without the use of angiography) yielded similar results. Taken together, the results of CLARITY TIMI 28 and the Chinese trial provided a compelling case for including clopidogrel

in the care of STEMI patients. As a result, in 2007 guidelines adopted this change and made STEMI a Class I indication for the drug.

The TIMI work with clopidogrel continued when data were released indicating that there was some variability in response to the drug. Certain individuals were found to be "clopidogrel-resistant," meaning the drug did not result in substantial platelet inhibition. Observational studies linked the clopidogrel resistance to worse clinical outcomes. Eli Lilly subsequently approached TIMI with a new drug, prasugrel, which is in the same class as clopidogrel. The academic leadership at TIMI examined data for prasugrel and clopidogrel and determined that the potential increased platelet inhibition of prasugrel made it a promising compound to study. TIMI conducted a phase II efficacy trial, which found that prasugrel showed promise compared with clopidogrel for decreasing the risk of heart attack. These phase II results led to a very large international, multicenter phase III double-blind RCT of prasugrel and clopidogrel involving more than 13,000 patients. The TRITON TIMI 38 trial showed a benefit of prasugrel over clopidogrel with respect to cardiovascular death, nonfatal heart attack, and nonfatal stroke. However, the increased platelet inhibition that brought these heart benefits also translated into an increased risk of bleeding in patients taking prasugrel. The end result of this series of trials was FDA approval of Eli Lilly's prasugrel in July 2009. In this case, the investigator-initiated small phase II trial led to a more robust clinical trial that ultimately resulted in a new FDA-approved drug to treat cardiovascular disease.

Industry-Initiated TIMI Study

TIMI is frequently contacted by companies with new compounds for study and potential further development. Sabatine shared an example of an industry-initiated study run by TIMI that yielded a positive result for the sponsoring company's competitor drug. PROVE-IT TIMI 22 was sponsored by Bristol-Myers Squibb to compare its drug, pravastatin, with a new drug, atorvastatin, which had been shown in earlier trials to be effective in lowering LDL cholesterol. According to Sabatine, the company was confident of the positive results of a number of RCTs comparing pravastatin with placebo and believed pravastatin offered patients additional benefits that atorvastatin lacked. However, PROVE-IT TIMI 22 showed that atorvastatin outperformed pravastatin in helping patients achieve lower LDL. The results of this trial and others led to an update in clinical practice guidelines for targeting LDL.

U.S. Enrollment in TIMI Trials

Sabatine discussed the competing factors that influence the decision of TIMI leaders to study a drug in the United States or internationally. He noted the importance of conducting trials in the United States so as to understand the drug's applicability to the U.S. patient population. But, he noted, there are also reasons to ensure that clinical trials have a global presence. For example, in a global market, regulatory bodies in other countries will insist that a trial be conducted in their countries as well. When TIMI conducts phase II trials, involvement in multiple countries is desirable in anticipation of an international phase III trial. The lower cost associated with international trial sites is also a consideration in determining trial locations (see Chapter 3). TIMI created a Steering Committee of National Lead Investigators comprising key opinion leaders from various countries. This infrastructure allows TIMI to maintain an international presence throughout the clinical trial process, from site selection to patient follow-up and retention.

As Michael Lauer, Director of the Division of Cardiovascular Diseases, NHLBI, indicated in his presentation (see below), medical practice in the United States recently shifted from thrombolytic, or clot-busting, medications to primary angioplasty. As the manual opening of arteries became more prevalent in the United States, it became more difficult to find centers that were using medications, or lytic therapy, to break up clots. Worldwide, thrombolytic medications are still the most common form of reperfusion therapy, according to Sabatine. Thus, for trials that involve testing lytic therapy, international sites can provide patients more readily than U.S. sites.

Sabatine noted that not having adequate U.S. representation in clinical trials can be dangerous: when the proportion of U.S. patients decreases, the risk of spurious subgroup findings increases. In the recent PLATO trial comparing clopidogrel and ticagrelor (platelet inhibitors), the subgroup of patients in North America showed no benefit of ticagrelor, despite a finding that the 29 other patient subgroups experienced lower rates of clinical events due to the drug. This lack of effect in the U.S. population is likely a spurious finding, according to Sabatine, considering that subgroups in Europe, where practice patterns are similar to those in the United States, saw a large benefit from the drug.

THE OCCLUDED ARTERY TRIAL

Lauer discussed OAT as a case study that highlights a number of common obstacles encountered in conducting a large clinical trial with significant ramifications for clinical practice.

Acute MI (heart attack) is caused by the occlusion of coronary arteries

that supply blood to the heart. A cardiologist treating such a case can perform a percutaneous intervention (PCI), or cardiac catheterization, in which a stent is inserted to open the affected arteries. In the 1990s, observational studies showed a marked improvement in mortality rates for those patients with open arteries. As a result, there was a widespread increase in the use of cardiac catheterization to open the arteries of heart attack patients, and, despite the lack of robust scientific evidence supporting PCI, it became conventional medical wisdom to use this procedure for patients with chronically occluded arteries after a heart attack. OAT, an NHLBI-supported experimental trial, eventually revealed that health outcomes were worse among those subjects randomized to receive stents, dispelling the belief that opening arteries through PCI is always desirable. OAT illustrates the importance of basing medical decision making on well-controlled clinical experiments as opposed to observational correlations. According to Lauer, the trial is also an example of how the federal government can provide real value in clinical research, particularly when focusing on existing clinical practices for which evidence is lacking.

Lauer also explained that a number of logistical and administrative obstacles were encountered in running OAT. Each obstacle highlights the extent to which the incentives and interests of stakeholders, as well as regulatory burdens, can hinder a trial. As indicated in Figure 4-2, OAT included 2,166 patients and took 10 years to complete. Along the way, investigators encountered delays in grant review. Investigators also faced an unexpected requirement to conduct a pilot study, for which they received no funding, to improve their chances of ultimately receiving NIH funding. After final grant approval, of the 926 sites approached to participate in the study, only one-third agreed to do so. The investigators believe this unwillingness to participate was due partly to a pro-PCI bias on the part of physicians. Under this theory, because some physicians believed PCI was clearly the appropriate course of treatment, they saw no value in participating in a clinical trial to test this assumption. Some physicians claimed it would be unethical to assign patients to a control group that would receive the best medicine for the condition but not PCI. Califf suggested that the lack of physician interest in participating in this trial was also associated with the fact that PCI is a profitable procedure for physicians, and participation in the trial would randomize only a portion of their patients to receive the procedure, thus eliminating the opportunity to administer it to every patient.

Recruiting patients to participate in the trial also created delays. Of those sites that did participate, only two-thirds enrolled at least one patient. One-third of the sites filled out all required paperwork and received Institutional Review Board (IRB) approval, but never enrolled a patient. The overall enrollment rate was 0.25 patients per site per month. Ultimately, only 488 of the 2,166 patients were enrolled from 85 U.S. sites; the vast majority of subjects had to be enrolled abroad.

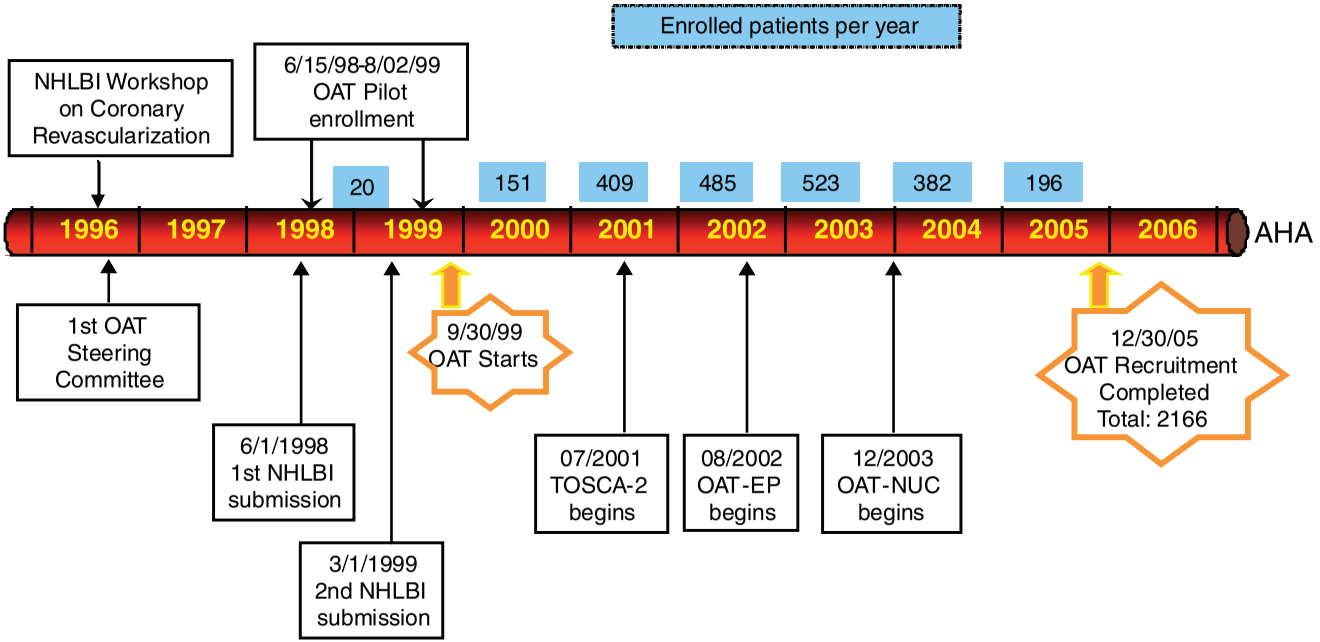


FIGURE 4-2 Timeline for the NIH-sponsored Occluded Artery Trial (OAT).
NOTE: NHLBI = National Heart, Lung, and Blood Institute; OAT = Occluded Artery Trial; OAT-NUC = Occluded Artery Trial Nuclear Study; TOSCA-2 = Total Occlusion Study of Canada-2.
SOURCE: Lauer, 2009. Reprinted with permission from Michael Lauer and Judith Hochman 2009.

According to Lauer, the OAT experience highlights a number of important points:

- **Relying on the gold standard**—RCTs remain the gold standard for proving the effectiveness of a drug or therapy. Observational data and unproven associations are susceptible to confounding and can be misinterpreted.
- **Federally sponsored research**—The federal government plays an important role in funding and conducting large clinical trials to test the effectiveness of clinical practices that are in widespread use but do not have an evidence base.
- **Biases**—Physicians and patients often have strong preferences for and biases toward certain procedures or levels of care they believe to be appropriate, regardless of the evidence supporting them.
- **Misaligned financial incentives**—Financial incentives for physicians are focused on performing a high volume of procedures, which creates a disincentive for them to refer patients to a clinical trial outside of their practice.
- **Lengthy timeline to conduct a large, multicenter trial**—Navigating regulatory barriers and overcoming difficulties in recruiting the right group of patients to participate in a study can lead to substantial delays in conducting a trial (see Chapter 3). In the case of OAT, the timeline was 10 years.

5

Clinical Trials in Depression

Depression is a chronic disease characterized by recurrent episodes that interfere with daily life and normal functioning, exacting large costs for both individuals and society. James McNulty, Vice President of Peer Support at the Depression and Bipolar Support Alliance, presented data from the World Health Organization (WHO) revealing that depression is the primary cause of disability in the United States and Canada for individuals aged 15–44 (WHO, 2002). Indeed, depression and other mental illnesses result in a greater loss of healthy life years to disability and death than cardiovascular disease, cancer, or diabetes (WHO, 2004). The onset of mental illness occurs primarily at a young age—by age 24 in 75 percent of cases (Kessler et al., 2005)—but can strike at any age. Regardless of age at onset, a study by the Council of Medical Directors of the National Association of State Mental Health Program Directors showed that individuals who receive treatment for a serious mental illness still die 25 years earlier than the normal population (NASMHPD, 2006). Disconcertingly, similar statistics are not available for those who do not receive care for a mental illness.

The neuroscience knowledge base underlying the study of depression has been growing since the emergence of biochemical pharmacology and molecular technologies in the 1970s and 1980s. Over this same period of time, pharmaceutical companies, the National Institutes of Health's (NIH's) National Institute of Mental Health (NIMH), and patient advocacy groups have aggressively pursued new treatments for the disease. The success of selective serotonin reuptake inhibitors (SSRIs) and the many structurally similar drugs that followed improved the lives of many patients. However, William Potter, most recently **Vice President of Translational Neuroscience**

at Merck Research Labs, Merck & Co., Inc., explained that a truly novel antidepressant has not been introduced in the last 40 years. According to Potter, the period of SSRI development established a level of comfort in the mental health community that may have temporarily hindered the development of new and better antidepressants. Today, significant effort is focused on understanding the challenges to developing novel antidepressant therapies and designing the informative clinical trials necessary to test the effectiveness of new discoveries.

This chapter begins with a patient's perspective on clinical trials in depression. Next, the commercial contract research organization (CRO) model for conducting clinical trials in depression is described. A discussion of the unique issues in conducting clinical trials in depression is then presented. Finally, the chapter summarizes workshop participants' discussion of specific ways to develop informative clinical trials to accelerate depression research.

CLINICAL TRIALS IN DEPRESSION: A PATIENT PERSPECTIVE

As a patient advocate living with the psychiatric diagnosis of bipolar disorder, McNulty shared his perspective on mental health research and the role of patients in clinical trials. Having participated as a subject in both industry- and NIH-sponsored studies, he received SSRIs in the clinical trial setting and experienced life-changing improvements in his condition due to these breakthrough drugs. McNulty described depression as a protean disease—extremely variable and readily assuming different shapes and forms. In his own life, depression had devastating effects, including the loss of his family and business, as well as a period of homelessness. Noting that there is a significant human dimension to the disease, he explained that his success in battling depression has been due only partially to medications. This is an important point to note because, in McNulty's experience, scientists can become excessively focused on data and lose sight of the real-life manifestation of depression and its effects on individuals and families.

At the age of 20, McNulty experienced his first major depressive episode. In 1985, he received his first diagnosis of mental illness. At one point, he lied about which medication he had previously used so as to become eligible for a clinical trial. Then, after being diagnosed with bipolar disorder type II, he began a period of years during which he searched for stability with medications. His involvement in an NIH-sponsored trial and eventually an Institutional Review Board (IRB) led him to a career focused on national mental health policy and clinical research as the vehicle for answering questions of great importance to the field of mental health.

Referencing the policy debate that surrounds funding for mental health services and the allocation of scarce resources, McNulty noted that it is very expensive *not* to treat mental illness. Although the true cost of mental

illness involves societal and personal costs that are not easily captured in financial terms, the sum of the societal and personal costs of failing to provide care to those who suffer from mental illness is probably greater than the cost of providing the care.

According to McNulty, patient advocates should be involved in developing and conducting clinical trials. Bringing this expertise into the clinical trial process at an early stage could help avoid some of the pitfalls that hinder trials today. An example is the informed consent process. McNulty serves on the board of directors of the Association for Accreditation of Human Research Protection Programs—an organization that resulted from recommendations in the IOM study *Preserving Public Trust: Accreditation and Human Research Participant Protection Programs* (IOM, 2001b). As a member of the IOM study committee for that report, McNulty joined in recommending that the informed consent process for clinical trial participants be simplified and streamlined. According to McNulty, however, the consent process has been hijacked by lawyers who have rendered consent documents unintelligible to both patients and researchers. The need to simplify the informed consent process was echoed by a number of participants throughout the workshop.

Aligning industry efforts more closely with the real-world needs of patients is another area that could benefit from more patient input. McNulty described his experience in which a pharmaceutical company asked a patient group what the ideal antidepressant would be like. He said that for most patients, the ideal antidepressant would be one that restored their life to a presickness state. When doctors were given the opportunity to answer the same question, some responded that sexual functioning was not important to their patients taking antidepressants. McNulty and the patient group clarified that, of course, sexual functioning recedes in importance when other major symptoms are considered, but it is not unimportant. Such divergences of opinion need to be illuminated early in the process of drug development.

THE CONTRACT RESEARCH ORGANIZATION MODEL

As an executive with the largest global contract research organization (CRO) in the world, Amir Kalali shared his perspective on the role of CROs today. Drawing on his experience in randomizing thousands of patients into global clinical trials, he discussed why, in his view, trials are increasingly conducted outside the United States (see also the discussion of this issue in Chapters 3 and 4).

Clinical trials conducted according to the CRO model are not specifically designed to produce results that can be translated into useful information for clinical practice. Rather, most CRO-run preapproval clinical trials

are conducted with the goal of regulatory approval, and complex protocols that involve a number of study questions are often a recipe for failure.

In the area of psychiatry, Kalali stressed the importance of conducting scientifically robust and efficient clinical trials, a theme repeated frequently throughout the workshop. More than any other area, psychiatry has been scrutinized with respect to the drug development process and the role of pharmaceutical companies in the marketing of drugs. High-profile attention has surrounded a number of issues, including antidepressants and suicide, the safety of newly marketed drugs, the dissemination of negative clinical trial data, the lack of evidence-based drug development in psychiatry, and the globalization of clinical trials in this area. These issues have contributed to a decline in the public's trust of the pharmaceutical industry and the clinical research enterprise. Kalali cited the high-profile withdrawal of pharmaceutical products from the market, as well as scientific misconduct, primarily at academic institutions. For these reasons, clinical research, especially in psychiatry, is under increasing scrutiny.

In addressing the issue of globalization, Kalali spoke to the concern about the applicability of global trial results to the U.S. population by noting that for decades medicines were tested only in America and Western Europe yet used around the world. He highlighted the benefits he perceives in conducting global clinical trials:

- wider, early patient and physician access to novel therapies;
- shortened drug development times due to more rapid patient recruitment;
- reduced drug development costs (i.e., the ability to develop more drugs);
- the generation of data to address ethnic diversity;
- study personnel with higher qualifications;
- accelerated local product approval;
- the availability of drug-naïve patients;
- improved patient retention rates;
- better medication compliance rates; and
- stability of the patient population, facilitating long-term follow-up.

According to Kalali, the quality of clinical trials conducted globally is very high. The average level of education and expertise of study personnel abroad is higher than that in the United States, and this greater expertise also comes at a lower cost in the global market. Kalali also pointed to notable differences between U.S. and global study populations. For example, given the large number of chemically similar antipsychotics on the market today, most individuals with schizophrenia in the United States have tried a number of medications to treat the disease. If the seventh in a string of

antipsychotics with a similar mechanism of action is developed, there is little reason to believe it will be effective for individuals with schizophrenia who have not responded to previous drugs. In contrast, a patient population of individuals with schizophrenia in Ukraine has likely been exposed to various drugs with different mechanisms of action (e.g., haldol, chlorpromazine). As a result, the Ukrainian population might be responsive to the new antipsychotic drug.

Kalali explained that there is no inherent interest in conducting research outside the United States. The United States is the largest pharmaceutical market in the world, and companies are unlikely to abandon U.S.-based clinical trials. The U.S. Food and Drug Administration (FDA) requires that, to gain access to the U.S. market, global clinical trials include a separate U.S. population. This requirement is aimed at the development of U.S.-based data on the safety and efficacy of a drug for the population in which it will be marketed. In selecting the best clinical trial sites, however, it no longer makes sense to choose 50 U.S. sites, 20 of which could be inadequate and fail to enroll patients, when there are significant advantages to choosing sites globally.

Califf responded by questioning whether it is appropriate to market a new drug in the United States that has been tested on a very different patient population, for example, in Ukraine. In addition, he suggested that the solution to improving clinical research in the United States is not to move clinical trials abroad. Rather, U.S.-based global companies, such as Quintiles and many other CROs, should help fix problems with the current U.S.-based clinical trial system.

ISSUES IN CONDUCTING CLINICAL TRIALS IN DEPRESSION

According to Madhukar Trivedi, Professor and Chief of the Division of Mood Disorders in the Department of Psychiatry at the University of Texas Southwestern Medical Center at Dallas, two of the greatest challenges in depression research are (1) the lack of a definitive marker for diagnosing depression—a pathophysiologic "smoking gun," as he described it; and (2) the fact that a significant number of trials in depression are not focused on answering the most important clinical questions—that is, there are many uninformative trials in the field.

As was discussed in Chapter 4, the successful classification of acute coronary syndromes allows clinical investigators to identify the appropriate patient population for a study quickly and easily. Similar to the difficulties seen with the diagnosis of heart failure, depression currently lacks a robust mechanism for diagnosis. The current standard for measuring depression in clinical trials is the Hamilton Depression Rating Scale (HAM-D), a rating system based on the subjective determination of the diagnosing physician or

other qualified personnel. The result, according to a number of workshop participants, is the identification of patient populations inadequate for distinguishing treatments for depression.

Trivedi further explained that there is very little scientific evidence regarding which patients will respond to which of 25 to 30 treatments for depression. Treatments are similar but may be different in important ways. The result is substantial variation in clinical practice patterns for depression. It is unclear in many cases which antidepressant a clinician should choose for a patient, as well as how long to treat the patient with a given drug.

Identifying a Study Population for a Heterogeneous Disease

Presenters discussed the issues involved in identifying the correct study population for a successful clinical trial in a heterogeneous disease such as depression. First, as suggested above, the diagnosis of depression is less technical and more subjective than that of other diseases. Moreover, changes in the way depression has been diagnosed over time call into question the use of large, historical databases. There is significant uncertainty as to whether a population diagnosed with depression in 1990 would be comparable to a population diagnosed with depression in 2000. Potter further explained how two patients diagnosed with depression at the same time might have very little in common. The criteria for diagnosing depression require that the patient have a depressed mood or a markedly diminished interest in pleasure (anhedonia). Hypothetically, one depressed patient could have a depressed mood as well as weight gain, hypersomnia, and recurrent thoughts of death, while another could have anhedonia, weight loss, and insomnia. Both of these patients would be diagnosed with depression and yet have no symptoms in common, and both could be enrolled in a clinical trial for depression. This treatment of a heterogeneous disease as if it were homogeneous is one reason clinical research in depression struggles to distinguish among antidepressants.

Potter described the difficulty of using entry criteria for clinical trial participants based on the severity of their disease. The standard minimum criterion for enrolling an individual in a clinical trial for depression is a total HAM-D score greater than 18. Conventional wisdom in the psychiatry field is that increasing the severity criterion creates a study population with more severe cases of depression, which in turn reduces the placebo response rate. Potter described his research to better understand the effects of the severity-based entry criterion on trial outcomes. He and his colleagues studied the relationship between patients' and physicians' ratings according to the HAM-D over the course of a 6-week trial. Potter said it was not surprising to find in the first week of the trial that physicians rating patients for admittance to

the trial gave them at least the minimum score to get them into the study. When patients were asked to rate themselves (via telephone) during the first week of the trial, the HAM-D scores ranged from high to low and were of a normal distribution. As the trial continued, the patient and physician ratings increasingly converged. Kalali explained that after their high initial ratings designed to get patients into the trial, physicians began rating the condition of patients accurately. The result was a large drop in the HAM-D scores, which made the placebo appear effective.

Potter's research highlights the difficulties inherent in setting a severity criterion for entry into a clinical trial in which the measure of disease is subjective and easily manipulated. The result can be to introduce bias into a study and create significant statistical problems due to the skewed distribution of the patient population. Kalali added that HAM-D is an incomplete measure in that it does not include anhedonia, cognition, or the painful physical symptoms that are important in depression. Potter noted that while research is being conducted to understand the issues surrounding the use of severity criteria for trials in depression, solutions to the problem have yet to be developed.

Trivedi estimated that in the last 3 to 5 years, more than 300 randomized controlled trials (RCTs) for antidepressants have been conducted. He described the patient populations studied in these trials as "symptomatic" volunteers. His example of a symptomatic volunteer is an individual who responds to an advertisement for a clinical trial in depression and who would otherwise not seek treatment for depression outside the trial setting—that is, the clinical trial is the patient's only interaction with the treatment setting. This unique, symptomatic patient population in which antidepressants are tested is different from the depressed population that will eventually be treated with the drug in the real-world clinical setting. Patients in clinical trials for depression often are not chronically ill and rarely have comorbidities, whereas it is well known in psychiatry that patients with major depressive disorder frequently have a number of comorbidities. In addition, there is overwhelming evidence that a patient with depression is at increased risk for cardiovascular disease, diabetes, and a number of other conditions. Thus, excluding patients with comorbidities from depression trials, as is most often the case, diminishes the applicability of the trial results to the real-world population.

Kalali also addressed the existence of "professional patients" in psychiatry. These patients seek to enroll themselves in multiple trials or study sites at once as a source of money and medicines. Kalali said active efforts to screen out these professional patients have been necessary. In one trial involving 300 patients, for example, 30 were found to be randomized to the same study by separate study sites.

Clinical Trial Methodologies and Placebo Response

The effect of placebo response rates in clinical trials for depression has added a layer of complexity and difficulty to the process of designing trials and interpreting the trial results. Placebo response refers to a patient's clinical improvement in response to an inactive substance (e.g., sugar pill). Most clinical trials in depression are placebo-controlled. The ethical issue of whether placebo-controlled trials should be conducted when effective therapies are available remains contentious. McNulty noted that while placebo-controlled studies are not required by the FDA, it is difficult to design a trial the FDA will accept without including a placebo study arm.

Placebo response rates in clinical trials for depression have been increasing, but variable, over time. The paper cited by Potter (Walsh et al., 2002) reports that the response to placebo across trials varied significantly—from approximately 10 percent to more than 50 percent—and was frequently substantial: in approximately half of the studies, 30 percent or more of patients assigned to placebo exhibited a clinically significant improvement. In addition, over the course of 2 decades (1980–2000), the proportion of patients responding to placebo increased at the rate of approximately 7 percent per decade (Walsh et al., 2002). The proportion of patients responding to active medication over this time period showed a similar increase. It should be noted that placebo response is a significant issue in the design of trials in many different disease areas.

According to Potter, the variability in placebo response rates over time has made it difficult to plan large clinical trials in depression. In designing clinical trials, it is customary for researchers to look to prior experiences with similar trials in the medical literature to determine how to power the study statistically and develop a target sample size. When there is such dramatic variability in placebo response rates across studies, researchers are left with little information with which to construct an informative, adequately powered study.

DEVELOPING INFORMATIVE CLINICAL TRIALS FOR DEPRESSION

A number of workshop participants noted that the current state of research in depression is marked by an inability to effectively distinguish one antidepressant treatment from another and identify the patient populations best served by a particular drug. In discussing how best to advance clinical research in depression, presenters and audience members raised a number of issues and possibilities.

Combination Therapy: Antidepressants and Psychotherapy

Deborah Zarin, Director of clinicaltrials.gov, National Library of Medicine, highlighted nonpharmacologic interventions for depression (e.g., psychotherapy) and studies that have shown such interventions to be at least as effective or sometimes more so than pharmacologic treatments. She suggested that future depression research further explore such interventions or combinations either alone or in combination with pharmacologic interventions to develop the best treatments. Potter questioned whether it would be better to focus new research efforts on identifying a meaningful distinction between two antidepressants before trying to develop the optimal combination of psychotherapy and antidepressant. Kalali referred to Quintiles' efforts in conducting two of the largest trials testing the combination of psychotherapy and medication but cited the limited availability of psychotherapy in the United States as a major barrier to its widespread use. In addition, he pointed out that psychotherapy has been shown to be successful in treating mild to moderate depression, but that many individuals with more severe forms of depression would not be candidates for psychotherapy.

Trivedi suggested that depression-focused psychotherapy should be included in research efforts to understand treatment effectiveness. However, many of the same issues affecting medication research also plague psychotherapy research. In response, Zarin suggested that studies of antidepressants could be improved by successfully characterizing the intensity of the patient visits that occur in a clinical trial; that is, there is an impact from the half-hour visits that take place during a clinical trial that goes beyond the effects of the drug being studied. This type of clinical management should be characterized further and could explain some of the variability in clinical trial outcomes for antidepressants, according to Zarin. Potter agreed that more sophisticated tools for measuring what happens in patient visits are necessary. He also mentioned Eli Lilly's effort to design tools for measuring the impact of clinical trial visits on depression treatments. In the end, the measurement tools varied significantly based on individual trial site characteristics and were determined to be too imperfect for practical use.

Accelerating Depression Research

Potter suggested that, despite the importance of creating new therapies for depression, investment in this area is no longer a top priority for some in the pharmaceutical industry because no path forward exists for obtaining clear, interpretable answers to essential research questions. The challenges facing depression research go beyond simply improving the efficiency of clinical trials and include gaining a deeper understanding of what consti-

tutes useful clinical trial information, as well as how signal detection can be improved. Potter explained that moving beyond a single rating instrument (HAM-D) for depression will probably be necessary.

Also reflecting on current challenges, Trivedi suggested that the field of neuroscience has made a number of breakthroughs in recent years, but the area of depression research has yet to combine these breakthroughs in a meaningful way. Thus large investments will be required to combine clinical moderators with genetic, serological, and other biomarkers to map depression and develop more comprehensive markers for disease severity. Further research into various markers for depression could help distinguish which treatments work for which patients. In addition, Trivedi explained that the vast majority of clinical trials in depression are short term and focus on the first 8 to 10 weeks of treatment. Studying the long-term effects of treating depression, a chronic disease, could help accelerate the development of new therapies.

Trivedi also mentioned the importance of developing new animal models for studying depression subtypes. For instance, no animal model for treatment-resistant depression exists. Thus, if a new therapy for treatment-resistant depression were developed today, it would be studied with the same animal models used for other conditions.

In addition to developing new animal models to advance drug development in psychiatry, Kalali noted that it is important to increase collaboration among industry, academia, and government to advance the interests of patients and move the field of psychiatry forward at a time when the high rate of failure in drug development is driving investment away from psychiatry and toward easier targets and diseases. Kalali suggested that more pharmaceutical companies should share their data regarding the rate at which the placebo response diverges from the response to active medication (i.e., placebo separation data) in clinical trials. These data could improve overall understanding of placebo response in depression trials and help in developing new, more effective trial methodologies. As an example of a large collaborative effort, Kalali highlighted his work as Chair of the Evidence Based Methodology Initiative (EMI) of the International Society for CNS (central nervous system) Drug Development. The EMI is currently conducting a Cochrane-like review of the literature (published and unpublished) in clinical trial methodologies in CNS and assigning a level of evidence to each example.[1] The goal is to create a better understanding of the gaps that exist in current methodologies and the areas that require

[1]Cochrane reviews explore the evidence for and against the effectiveness and appropriateness of treatments in specific circumstances to facilitate the choices of doctors, patients, policy makers, and others in health care (http://www.cochrane.org/reviews/clibintro.htm).

more evidence. The EMI hopes to create a pathway for improving CNS clinical trial methodologies.

To accelerate the development of new drugs to better serve patients, McNulty believes there should be greater integration of clinical and basic science. For example, if neurologists discover interesting differences in the brain potentially linked to placebo response rates, they should have some way to work with a basic scientist to research the meaning of these differences and explore them for the benefit of patients. Drawing on a wide range of scientific expertise could be useful in accelerating drug development for depression. Even in the promising area of genomic research, answers have been limited, according to McNulty. For instance, the gene for Huntington's disease has been known for a number of years, yet no new therapies to treat or cure the disease have been developed. Huntington's is a single-gene disorder, whereas depression is likely a polygenic disease in which environmental factors and genes interact in a way that is even more complex than in Huntington's. Thus, significant challenges exist in the application of advances in genomics to depression research.

The appropriate study size for depression research was debated during the workshop discussions. Potter mentioned that placebo-controlled inpatient trials of early antidepressant medications were small studies—approximately 50 patients per study arm. According to Potter, these small trials were predictive of the benefit many patients receive from the medications. Potter suggested that large trials are not necessary for signal detection as long as the trial includes the right patient population. Paul Hébert expressed surprise that sample sizes for depression trials are so small, considering depression is a disease affecting a large portion of society. He suggested that depression researchers embrace the idea of larger trials to distinguish among different treatment effects. Califf also expressed surprise at the extent to which the field focuses on designing smaller, more precise trials. He suggested that if the same data were examined in his field of research, the conclusion would be to conduct trials 10–20 times larger than they are today.

In addition to study size, workshop participants considered the appropriate length of a clinical trial in depression. Trivedi noted that in a chronic, long-term illness such as depression or diabetes, clinical trials that follow patients for a significant length of time are important. Long-term studies for chronic diseases require successful patient retention strategies to be effective since significant dropout rates over time can jeopardize the validity of trial results. To illustrate the power of large, multicenter, long-term clinical trials for evaluating depression therapies, Trivedi described the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial (see Box 5-1).

BOX 5-1
Case Study: STAR*D

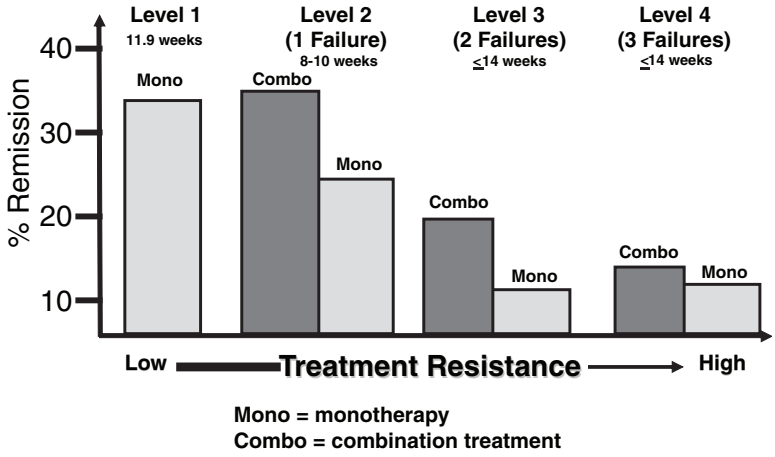
The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study was a large, federally funded clinical trial that tested the effectiveness of antidepressants in a population diagnosed with major depressive disorder. The trial enrolled more than 4,000 patients and included 7 years of patient follow-up. To generate results applicable to the traditional clinical care setting, the diverse study population included individuals seeking treatment from a physician in a specialty or primary care setting, as well as patients with other psychiatric or medical comorbidities. STAR*D was by far the largest and longest trial to date comparing treatments for depression; the next largest trial in this area included approximately 700 participants.

STAR*D used a sequential treatment method to treat depression and did not include a placebo arm. After the first treatment step (monotherapy with an SSRI), one-third of patients achieved remission (i.e., were symptom-free). Those patients who did not achieve remission in the first treatment step proceeded to the second, third, and fourth steps depending on their response at each step. As patients progressed from the first step, the number who achieved remission declined (see the figure below).

The decline in remission following initial treatment failures is similar to that seen with other chronic diseases. However, Trivedi noted his concern that after the first two treatment failures for depression, the number of treatments currently available becomes limited. With each new treatment level, relapse rates increase for patients, and remission becomes more difficult.

Because STAR*D was a large, long-term trial and not placebo-controlled, comparing its results with those of the more typical, placebo-controlled depression trials has been useful. For instance, in a placebo-controlled study, patients with a wide range of disorders would be accepted into the trial (e.g., both anxious and nonanxious depression patients) and randomized to receive the active treatment or placebo. In contrast, patients in the STAR*D study chose a treatment acceptable to them, and randomization was limited to their acceptable treatment range;

thus all patients received an active treatment as opposed to placebo. Looking at subgroup results, the STAR*D study revealed a difference in outcomes for those with anxious and nonanxious depression. At the first antidepressant treatment level, those with anxious depression had poorer outcomes than those with nonanxious depression. In contrast, when anxious and nonanxious depression populations are combined in a randomized, placebo-controlled trial, this difference in outcome disappears. Thus, STAR*D provided more information on differential outcomes than some traditional placebo-controlled studies.



STAR*D clinical trial results: remission rates by treatment level (monotherapy or combination treatment).
SOURCE: Trivedi, 2009. (Adapted from: Trivedi et al. Am J Psychiatry 2006, Trivedi et al. N Engl J Med 2006a, Rush et al. N Engl J Med 2006b, Nierenberg et al. Am J Psychiatry 2006, Fava et al. Am J Psychiatry 2006, McGrath et al. Am J Psychiatry 2006.) Reprinted with permission from Madhukar Trivedi, 2010.

Finally, Potter explained that intention-to-treat analysis is useful and can be especially effective in depression research.[2] According to Potter, this methodology allows outcome measurements to be continued at the end of the study even if the intervention does not continue.

[2]In an intention-to-treat analysis, subjects who started in the trial are included in the final analysis regardless of whether they finished the treatment (i.e., dropouts are treated as if they finished the trial). The approach seeks to evaluate a treatment as it would be administered in the real world.

6

Clinical Trials in Cancer

Cancer rates increase as the population ages. Diagnoses of cancer are increasing worldwide, including in developing countries. Renzo Canetta, Vice President, Oncology Global Clinical Research, Bristol-Myers Squibb Company, noted that for the most part, cancer is an equal opportunity disease—throughout the world there are no dramatic differences in its biology and paths of treatment. Despite significant progress in cancer prevention, early diagnosis, and treatment, there is a large unmet medical need for treatments for major cancers (e.g., lung, prostate, breast, colon).

Canetta cited three main factors that are currently affecting the clinical trial enterprise in oncology: cost, time, and motivation. He contended that the cost of conducting clinical trials in cancer, the length of time required, and the commitment of investigators and patients to participating are interconnected. According to PhRMA, there are currently more than 800 new anticancer drugs in the development pipeline. At the same time, the participation rate in trials among adult cancer patients is extremely low. Questions arise, then, as to who will study all of these drugs, who will prioritize their study, and how enough patients will be identified to study them, especially given limitations in the infrastructure necessary to conduct clinical trials, including investigators and patients, discussed in Chapter 3.

This chapter begins with presenting a patient's perspective on clinical trials in cancer. Next, the National Institutes of Health's (NIH's) National Cancer Institute (NCI) Clinical Trials Cooperative Group Program is dis-

cussed as one of the major sponsors of clinical research in cancer. The chapter ends with a discussion of industry-sponsored clinical trials in cancer.

CLINICAL TRIALS IN CANCER: A PATIENT PERSPECTIVE

According to data presented by Margaret Mooney, Chief, Clinical Investigations Branch, Cancer Therapy Evaluation Program within NCI, and Musa Mayer, breast cancer advocate of AdvancedBC.org, approximately 3 percent of adult cancer patients participate in clinical trials. An analysis of more than 500 NCI Cancer Therapy Evaluation Program (CTEP) trials by Steven Cheng revealed that 40 percent of trials failed to achieve minimum patient enrollment, and more than three of five phase III trials failed to do so. As discussed in Chapter 3, the failure of clinical trials to enroll enough patients moves health care further away from evidence-based practice and represents a tremendous amount of wasted effort.

Patient Perceptions of Clinical Trials

In an analysis of 23 oncology studies and 6,000 patients, some of the barriers to participating in clinical trials cited most frequently by patients were (1) fear of a reduced quality of life, (2) concern about receiving a placebo, (3) potential side effects, and (4) concern that the experimental drug might not be the best option (Mills et al., 2006). In addition, patients also cited barriers such as inconvenience of participation, dislike of randomization, wanting one's own doctor to make decisions, feeling coerced, and loss of control over treatment decisions. The single most influential factor in enrolling patients in clinical trials is physician influence. As discussed in Chapter 3, however, a number of barriers affect a physician's willingness to refer patients to clinical trials.

As a breast cancer advocate and a 20-year cancer survivor, Mayer has focused her work on metastatic breast cancer, the most advanced form of the disease. Over the last 10 years she has participated in an online community (BCMets.org) of women with metastatic breast cancer and their families. Mayer described the 1,100-person community as relatively typical Internet users seeking health care information; they tend to be younger, better educated, less diverse, and more affluent (i.e., of higher socioeconomic status) than the general population. As metastatic breast cancer patients, they are keenly aware that their treatment options are limited and thus are profoundly vested in the search for the next drug to treat their disease. Mayer noted that because of these factors, women with metastatic breast cancer should be good candidates for clinical trials of new drugs.

Mayer conducted an informal, qualitative survey of 49 women from the BCMets.org community to explore the level of physician and patient

involvement in clinical trials, attitudes about participating in trials, eligibility criteria issues, motivation for participation or nonparticipation, and the overall clinical trial experience. The survey results revealed the following barriers to patient participation in clinical trials:

- **Lack of encouragement** (or active discouragement) from treating physicians to participate. More than half of the women surveyed said their oncologists never mentioned clinical trials to them or actively discouraged them from participating. Oncologists who did recommend trials to patients were usually investigators themselves or recommending a trial at their own institution.
- **Inconvenience** of trial participation (travel, cost, missing work and/or time with family).
- Misinformation in that women fear **getting "no treatment"** (placebo), even though providing the best standard of care is the ethical requirement in cancer trials. Equipoise[1] is poorly understood by patients; some believe that the control arm of the trial will offer them no treatment and that the experimental arm is inherently better.
- The misconception that clinical trials are a **last-ditch effort**, and one should participate only after failing to respond to approved, conventional treatments.
- Difficulty with **eligibility criteria**. Some women reported that in trying to enter a clinical trial, they were disqualified because of:
  - — past treatment regimens (i.e., "extensively pretreated" or too much chemotherapy);
  - — stage of disease (i.e., not recently diagnosed) or the presence of brain metastases; or
  - — the presence of advanced disease when many drug trials test first-, second-, or third-line treatments.

Advanced-disease patients and those who have had extensive pretreatment are the most motivated to participate in clinical trials, according to Mayer, but, as indicated by the survey results, are frequently disqualified because of a trial's eligibility criteria. Conversely, recently diagnosed patients who are frequently sought for clinical trials are attempting to cope with the news of their diagnosis and tend to follow the standard treatment protocols prescribed by their doctor rather than participating in clinical trials. On the other hand, as noted in Chapter 3, patients who participate in trials

[1]As noted in Chapter 3, equipoise is the point at which a rational, informed person has no preference between two (or more) available treatments (Lilford and Jackson, 1995). In clinical research, the ethical concept of equipoise is satisfied when genuine uncertainty exists as to the comparative therapeutic benefits of the therapies in each arm of a clinical trial.

generally report having an overwhelmingly positive experience. Access to emerging therapies and a desire to help other women through advances in research were two of the reasons reported by the women in Mayer's survey for participating in a clinical trial.

Public Education on Clinical Trials

Well-designed clinical trials play a key role in medical advances and the development of evidence-based health care. However, Mayer noted that public education on the true value of clinical research and the reality of participating in a clinical trial is seriously lacking. As described above, a large number of myths and misconceptions about the experience of participating in a trial exist. Therefore, public education on the link between improvements in health care and clinical research—specifically, clinical trials—is needed. Mayer suggested that involving trained patient advocates at each step of the clinical research process, even in preclinical phases, could provide significant benefit in helping to design informative trials, as well as recruit patients to participate.

Melvyn Greberman, President of Public Health Resources, LLC, referred to the collaboration of the Cancer Biomedical Informatics Grid (caBIG), the Dr. Susan Love Research Foundation, and the Avon Foundation for Women in creating the Army of Women—an initiative designed to enhance consumer participation in clinical research. According to Greberman, the Army of Women has reached 400,000 of the 1 million women it has committed to signing up as potential participants in cancer research studies. The Army of Women collaboration is interested in working with industry and provides a good format for addressing patient and public education issues.

THE NATIONAL CANCER INSTITUTE'S CLINICAL TRIALS COOPERATIVE GROUP PROGRAM

The federal government plays a large and important role in funding and organizing clinical research in oncology. NCI funds approximately half of all cancer trials in the United States. Mooney described the unique structure of NCI's Clinical Trials Cooperative Group Program.

NCI coordinates a large number of clinical research networks through the Clinical Trials Cooperative Group Program. The program includes nine groups focused on cancers that affect adults and one that focuses on pediatric cancers. Some of the adult groups look at multiple diseases, while some, such as the Gynecologic Oncology Group, specialize by focusing on one area of cancer. Since the 1960s, the NCI cooperative groups have grown from primarily regional sites to large, nationwide networks that encompass a range of different sites and participants. The successes of the program

have resulted in improved care and outcomes for cancer patients. Mooney explained that the program's accomplishments over the past 50 years have been a result of the direct involvement of clinical investigators, patients, and their families in designing, conducting, and monitoring clinical trials. The early and ongoing involvement of patient advocacy communities in designing and conducting clinical trials has resulted in some of the most robust improvements in cancer treatment to date.

Because the NCI cooperative groups are not oriented to gaining regulatory approval for a new drug, as is the case in industry, they can take a broader, public focus and examine multiple types of research questions in one trial. This breadth of focus is significant with respect to the amount of useful research data that has been generated by going beyond the traditional primary endpoint of a trial. Mooney explained that the large amount of data collected in response to multiple research questions in NCI-sponsored trials can be extremely helpful in learning more about cancer and how to manage it effectively, but also makes some of the trials less pristine in terms of efficiency.

As the field of oncology has progressed over the last 50 years, the true diversity of the set of cancer diseases has been uncovered. Mooney explained that the new understanding of the molecular classification of cancer diseases has allowed a greater focus on particular treatments and patient populations. Thus, new sets of challenges in cancer clinical research have been created. Screening patients for particular molecular characteristics using tissue samples has introduced a new level of scientific and logistic complexity to clinical trials. Mooney explained that the search for rare patient subsets is one reason why clinical trials have become increasingly global—enough patients cannot be found in the United States.

Streamlining NCI's Clinical Trials Process

Despite differences in research focus, the NCI system shares with industry and all medical disciplines the growing pressure to reduce research costs in the face of declining budgets. In response to this challenge, the NCI Clinical Trials Working Group was launched in 2004. This group is charged with developing recommendations and an implementation plan to optimize the NCI clinical trials system in five critical areas (Box 6-1).

INDUSTRY-SPONSORED CANCER CLINICAL TRIALS

Many issues and obstacles encountered in the clinical trial process are common across organizations that sponsor the research, whether government or industry. In terms of cost, Canetta noted six major drivers for industry-sponsored clinical trials in cancer:

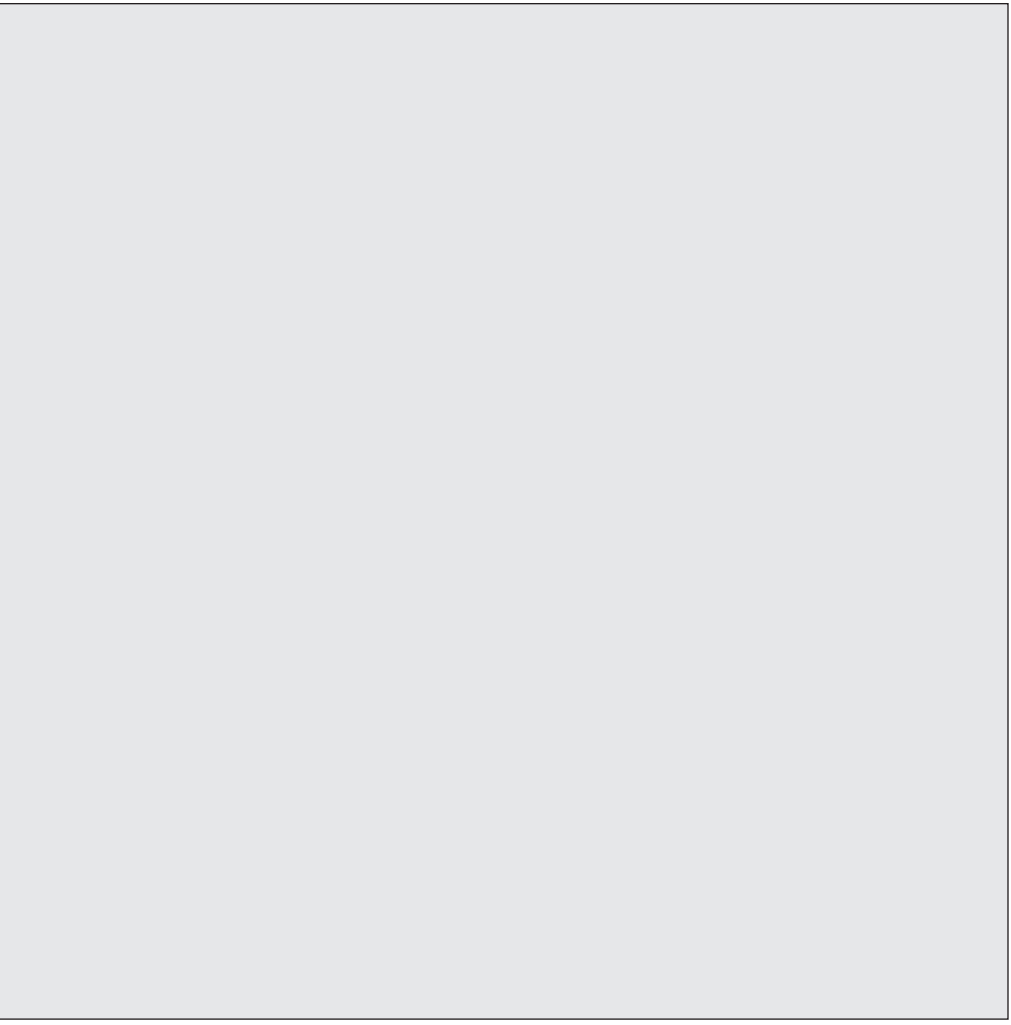
BOX 6-1
Current Initiatives of NCI's Clinical Trials Working Group to Optimize the Clinical Trials System

Coordination through information sharing and collaboration. In addition to increasing collaboration within cooperative groups, NCI is working to enhance coordination with other NIH institutes (e.g., the National Heart, Lung, and Blood Institute [NHLBI] through the Bone Marrow Transplant Clinical Trials Network) and international networks (both industry-sponsored and those sponsored by the country of origin). A successful international collaboration is the ongoing trial in osteosarcoma, a rare tumor in children, between the U.S. Children's Oncology Group and several pediatric oncology clinical research networks in Europe. Each country adheres to its own regulatory and human subjects protection requirements, but the trial has a single, central coordinating center and one data safety monitoring database.

Prioritization of clinical trials for funding. Scientific Steering Committees have been created to oversee particular disease areas within oncology (gastrointestinal, gynecologic, head and neck, genitourinary, breast and lung, and hematologic malignancies, as well as symptom management and health-related quality of life). The committees include broad representation from practicing physicians with clinical trial experience, translational scientists, biostatisticians, community oncologists, and patient advocates. All phase III treatment trials sponsored by NCI's Clinical Trials Cooperative Group Program are evaluated, prioritized, and approved by those committees.

Standardization and promotion of common tools. Through CaBIG at NCI, a number of technological tools will be standardized. The most recent of these is the Oncology Patient Enrollment Network (OPEN), a Web-based portal that provides a centralized enrollment system for registration of patients in NCI-sponsored cooperative group clinical trials and patient randomization across the cooperative group system. OPEN

- **clinical research personnel**—investigational staff and the infrastructure to support the clinical trial;
- **clinical supplies made by industry**—procuring of comparators (drugs used in the control arm of a clinical trial), which often involves relabeling and approval to use the comparator as an experimental agent;
- **processing of trial-related specimens**—acquiring and banking tumors and biological fluids;
- **negotiating of research grants**;



- **adjudication committees' fees**—more of an issue outside of the United States (adjudication committees are necessary when endpoints of time-to-event are used, such as progression-free survival in cancer); and
- **fees associated with IRBs and Data Monitoring Committees (DMCs).**

At each phase of clinical research (phases I, II, and III), the cost increases. Canetta explained that the later the stage of development in which a compound fails, the higher the cost of that failure will be. In cancer, the

rate of success for bringing a compound through the drug development process to patients is less than stellar. Thus, there is significant interest in reducing the cost of clinical research and thereby the cost of drug development failures.

Canetta mentioned three aspects of clinical research that have the potential for cost reduction:

- **Data collection**—Standardized case report forms (CRFs) would help investigators conduct a trial more efficiently. Also, reducing the number of data points that require monitoring for each patient in a clinical trial (i.e., selective monitoring) could make it possible to reduce cost while maintaining quality.
- **Comparator and experimental drug charging**—Acquiring and relabeling expensive comparator drugs for a clinical trial is a significant cost driver. Canetta suggested that comparator drugs being used in a clinical trial for an approved indication could be paid for by the insurance industry as a way to induce more patients to enroll.
- **Time cost**—As discussed throughout the workshop, activating clinical trials has become a lengthy process. Canetta identified four aspects of the clinical trial initiation process that could benefit from increased efficiency: (1) internal review by the sponsor, (2) contract negotiations with institutions and investigators, (3) local regulations (IRBs), and (4) special protocol assessments (from the FDA in the United States) or scientific advice (outside the United States).

Canetta reported that historically the internal review process at Bristol-Myers Squibb involves 34 review cycles for each individual trial protocol, totaling 8 months for the company to produce/activate a trial protocol. Efforts are currently under way to bring the company's timeline for internal review down to 5 months by aligning review cycles with various internal functions.

The time to activate a clinical trial protocol varies across institutions and clinical trial sponsors. In the United States, for example, the Eastern Cooperative Oncology Group (ECOG) requires a median of 808 days to complete the steps necessary to activate a clinical trial protocol (Dilts et al., 2008). Canetta presented data from individual institutions revealing shorter times to activation. At the University of Arkansas, for example, the median is 70 days. Canetta suggested that this shorter time is due to the fact that the university is a small operation and thus can streamline internal processes more easily. Outside the United States, the time required for approval of clinical trial protocols are very similar to those in the United States—that is, lengthy.

7

Clinical Trials in Diabetes

An estimated 7.8 percent of the U.S. population has diabetes, a chronic disorder affecting the body's metabolism. The most common form is type 2 diabetes, affecting approximately 90–95 percent of those with the disease. Type 2 diabetes is most often associated with older age, obesity, a family history of diabetes, physical inactivity, and certain ethnicities (NDIC, 2008). In addition, new research has also improved our understanding of the genetic underpinnings of type 2 diabetes. The diagnosis of type 2 diabetes includes the identification of insulin resistance, or the body's inability to process insulin, which ultimately results in a build up of glucose in the body. In contrast to type 1 diabetes, the symptoms of type 2 diabetes develop slowly over time. Recent research focuses on preventing or delaying type 2 diabetes in at-risk populations and has revealed that lifestyle interventions and some medications can reduce the development of diabetes.

The origin and progression of type 1 diabetes is notably different from that of type 2. Jay Skyler, Chairman of the Type 1 Diabetes TrialNet, explained that individuals are born with a genetic predisposition to type 1. Autoimmune, genetic, and environmental factors are believed to play a role in the immune system's attack on insulin-producing beta cells and the development of this form of the disease (NDIC, 2008). At some point during early life, perhaps even in utero, an environmental trigger initiates such an attack.

Prior to the clinical appearance of type 1 diabetes through an oral glucose test, a number of stages in the development of the disease are amenable to intervention. Intervention studies can be conducted in an attempt to develop methods or therapies that can interrupt the process of developing

the disease. Because type 1 diabetes affects such a small proportion of the diabetic population, however, there has been less investment in the development of new therapies for the disease relative to the more prevalent type 2.

This chapter begins with a discussion of government-sponsored diabetes clinical trials. Next, a clinical research network—TrialNet—is described, along with the ways in which it conducts trials in diabetes. A case study that illuminates some of the strengths and weaknesses of government versus industry-sponsored clinical trials in diabetes is then presented. Finally, the chapter turns to innovative ways in which regulatory challenges to conducting clinical trials can be overcome.

GOVERNMENT-SPONSORED TRIALS IN DIABETES

Judith Fradkin, Director of the Division of Diabetes, Endocrinology, and Metabolic Diseases in the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) at the National Institutes of Health, discussed NIDDK's research efforts and the process of conducting government-sponsored clinical trials in diabetes. She explained that NIDDK seeks to conduct diabetes trials that are typically not pursued by drug companies. Because NIDDK's focus has been on conducting clinical trials evaluating various approaches to diabetes therapy as opposed to analyzing particular drugs, large-scale trials with a fairly long timeline are necessary.

The NIDDK Clinical Trial Development Process

Fradkin discussed the advantages and disadvantages of NIDDK's process for developing and implementing clinical trials. Advisory groups first identify an important research question. Once the agency has determined that funding exists to support a new research initiative, a competitive Request for Applications (RFA) is issued. After reviewing applications submitted by investigators, NIDDK makes awards to a data coordinating center and clinical sites to design and implement the trial. At this point, the process can move quite slowly as a diverse group of diabetes and clinical trial experts have many different ideas about how the trial should be designed and conducted. In addition, a significant amount of money is flowing during the trial design process, and contracts and negotiations surrounding these financial transfers can affect general progress on trial development.

Fradkin explained that the RFA process for identifying diabetes trial investigators has advantages that include the diverse expertise that is brought to bear in the trial design phase and the rigorous, iterative process of site selection, which has resulted in highly robust multicenter clinical trials that have transformed diabetes therapy. When NIDDK issues an RFA for a new study, considerable uncertainty exists regarding such issues as the primary

outcome of the trial, the sample size, the effect size, and the retention rate of trial participants. Because of these factors, the duration of the trial and its total budget are unknown throughout the RFA process. Thus, disadvantages of the RFA process are its length, uncertainty regarding the feasibility of the trial design, and the undetermined budget.

NIDDK recently tried a new approach to conducting diabetes clinical trials—the investigator-initiated planning grant. In this process, a principal investigator (PI) assembles a team of investigators and receives a planning grant to develop a trial protocol and a manual of procedures. Compared with the RFA process, the planning grant has the potential to be more efficient (shorter process, cost savings in the trial design phase, and a budget that is largely determined prior to initiation). On the other hand, because investigators are chosen by the PI, diverse viewpoints may be minimized in the planning grant process.

Developing Informative Clinical Trials for a Chronic, Heterogeneous Disease

Since NIDDK-sponsored clinical trials seek to examine approaches to diabetes therapy rather than particular drugs, subjects are often followed after the trial has ended or after its primary outcome measures have been assessed. Because diabetes is a chronic disease with complications that develop over a long period of time, lengthy follow-up increases understanding of the disease. Fradkin stressed that critical scientific findings have resulted from this follow-up after the completion of a trial. For example, the Diabetes Control and Complications Trial studied more than 1,000 type 1 diabetes patients, comparing intensive glucose control with standard glucose control over a 6.5-year study period. The trial revealed that intensive glucose control dramatically reduced the rate of development of complications associated with type 1 diabetes. By continuing to follow these patients for an additional 10 years, however, it was discovered that the benefits of the finite period of intensive glucose control were prolonged well into the future; a "metabolic memory" was created, even once the glycemic control of the two groups was similar. Trials in type 2 diabetes revealed similar findings. Fradkin noted that these findings from extended patient follow-up provided information on the importance of good glucose control early in the course of diabetes, before complications develop. In addition, significant pathophysiologic information gained from the prolonged follow-up provided a greater understanding of the etiology of the disease and how complications develop over time. At the same time, the resources expended on follow-up can limit the ability of NIDDK to initiate new studies, a consideration that becomes increasingly important as financial resources are limited and NIH funding remains flat.

A prolonged study time to evaluate the progression of diabetes also yields benefits for payers in the health care system. For instance, some outcomes in a randomized controlled trial (RCT) may be insufficient for payers. In the case of evaluating the effects of a lifestyle intervention to delay or prevent the onset of diabetes, payers seek information on the effects in preventing diabetes and on how durable those effects are. A study that evaluates the extent to which patients cross over the diabetes continuum (i.e., from pre-diabetes to diabetes) is generally less informative than one that evaluates the extent to which preventing diabetes stalls the complications of the disease. To provide more informative trial results on the long-term effects of diabetes prevention, NIDDK has invested significant resources in a follow-up study to the Diabetes Prevention Program (DPP).

Studying type 2 diabetes also introduces some challenges to the design of informative trials. For instance, the pathophysiologic heterogeneity of type 2 diabetes (i.e., the wide-ranging combinations of symptoms exhibited by patients) can make it difficult to identify which subsets of patients actually respond better to a certain drug or approach to therapy. For example, different type 2 diabetes patients have different combinations of insulin resistance and decreased beta cell function. When these heterogeneous manifestations of the disease are combined into a single group based on a given glycemic level for the purposes of a clinical trial, the opportunity to identify patients who benefit from a particular therapeutic approach can be lost. Fradkin mentioned that the heterogeneity of type 2 diabetes has assumed a larger role as the number of different classes of drugs to treat the disease has increased over the years, making it especially important to identify the subset of patients who respond better to a certain drug.

Fradkin also highlighted the success of NIH/NIDDK multicenter trials in recruiting racially and ethnically heterogeneous populations, suggesting that NIH studies have the advantage over industry-funded trials in this regard. For example, the government-sponsored DPP included 45 percent minority populations. The study looked at diabetes incidence rates for three study arms—lifestyle intervention, metformin, and placebo. The benefits of lifestyle interventions and metformin in reducing the incidence of type 2 diabetes appeared to be manifest across all of the ethnic and racial groups studied (see the further discussion of these results below). That is, the progression rate of type 2 diabetes in the placebo group did not differ by race/ethnicity. This is an especially critical finding given that type 2 diabetes affects minority populations disproportionately.

In addition to the inclusion of ethnically diverse populations, government-sponsored trials have excelled in characterizing patients with diabetes by phenotype. Careful phenotyping in the Diabetes Control and Complications Trial included measures of C-peptide, an indicator of how much insulin beta cells are producing, and resulted in the striking finding that patients

with some residual C-peptide did better in terms of glycemic control and decreased hypoglycemia. As a result of this finding, the FDA has agreed to allow C-peptide to serve as a clinical endpoint for type 1 diabetes new-onset trials. This unanticipated finding resulting from phenotyping in the Diabetes Control and Complications Trial has had important effects on the development of type 1 diabetes trials. In the DPP, phenotyping by means of pharmacogenomics analyses revealed that even for those individuals at increased genetic risk for type 2 diabetes, lifestyle interventions were effective in decreasing their risk for the disease. Fradkin noted that this was a powerful result—genetics is not destiny in terms of developing type 2 diabetes.

NIDDK: A Model for Clinical Trial Collaborations

NIDDK's research is highly collaborative—most of its studies involve working with other NIH institutes, according to Fradkin. These collaborations have resulted in unanticipated yet important findings. For example, in the collaboration with the National Institute on Aging (NIA) on the DPP, it was a prerequisite that at least 20 percent of the clinical trial participants be older patients. Initially, investigators were concerned that older patients would be unwilling to participate in the lifestyle intervention aspect of the study. NIA countered that the highest prevalence of diabetes is in older populations, so they should be included in the study. As it turned out, the study revealed that older patients were more sensitive than other age groups to the lifestyle change.

Given the prevalence of diabetes in older adults, the protracted time course of the disease, and the fact that diabetes is a major driver of Medicare costs, Fradkin believes diabetes is a good candidate for collaboration between NIH and the Centers for Medicare and Medicaid Services (CMS). Very few of the practices Medicare pays for have been rigorously examined in RCTs. Given NIDDK's track record in conducting paradigm-shifting diabetes trials in diverse populations, conducting clinical trials in the Medicare population could offer an opportunity for cost savings. NIH would pay the research costs, CMS would pay the costs of providing clinical care, and the trial results would have the benefit of being conducted in a real-life health care setting. Tracking clinical trial results via Medicare beneficiary claims would generate meaningful, long-term outcomes with potentially compelling economic cases.

TRIALNET: A NETWORK APPROACH TO TYPE 1 DIABETES TRIALS

Funded jointly by NIH, the Juvenile Diabetes Research Foundation International (JDRF), and the American Diabetes Association (ADA), as

well as a special appropriation from Congress, TrialNet is an international network of researchers exploring ways to prevent, delay, and reverse the progression of type 1 diabetes.[1] TrialNet researchers are drawn from 18 clinical centers in Australia, Canada, Finland, Germany, Italy, New Zealand, the United Kingdom, and the United States. More than 150 medical centers and physician offices participate in the TrialNet network.

Skyler described the TrialNet protocol development process and the network's efforts to end type 1 diabetes. TrialNet receives protocols from investigators within the network, external academic investigators, and industry. The network conducts trials in a range of type 1 diabetes areas, including natural history, prevention (including vaccines), treatment for early onset, and mechanisms of action. Four TrialNet committees initially review protocols:

- The Scientific Review Committee examines the scientific validity of the study's approach.
- The Clinical Feasibility Committee examines whether the study protocol can reasonably be implemented.
- The Ethics Review Committee weighs ethical considerations of the study design and its practical implementation.
- The Infectious Disease Safety Review Committee ensures that immunomodulatory agents are being used properly.

Based on the recommendation of an Institute of Medicine (IOM) report that the scientific review, ethical review, and subject safety functions be carried out separately, these four independent committees review the proposed study protocol before sending their results to the Intervention Strategies and Prioritization Committee. That committee includes members from both TrialNet and outside organizations, such as JDRF and the Immune Tolerance Network, as well as international experts. Once the protocol has been approved, the Protocol Development Team uses its standardized tools (e.g., case report forms) to translate protocol procedures into practice. Simultaneously, the Protocol Committee, consisting of the person who originally proposed the study and others with expertise in the study area, collaborates to further develop the study protocol and finalize its use. To complete the process, the TrialNet Chairman's Office, the Coordinating Center, center directors, and trial coordinators implement the protocol and carry out the study.

According to Skyler, his experience in conducting clinical trials in type 1 diabetes suggests, first, that clinical decisions should be based not on

[1]Additional information on TrialNet can be found at http://www.diabetestrialnet.org/index.htm.

small pilot studies but on adequately powered RCTs. Second, clinical trial designs should not be changed in the middle of the trial. If a design change is necessary, the analysis of trial data should account for the impact of that change. And third, study subjects in type 1 diabetes trials should be within the age range of 9–15 as this is the age of peak onset of the disease.

CASE STUDY: GOVERNMENT- VS. INDUSTRY-SPONSORED TRIALS IN TYPE 2 DIABETES

Steven Kahn, Professor of Medicine in the Division of Metabolism, Endocrinology, and Nutrition at the University of Washington and VA Puget Sound Health Care System in Seattle, compared two RCTs in the area of type 2 diabetes. One was a government (NIH)-sponsored prevention trial and the other an industry-sponsored intervention trial.

The primary aim of the NIH-sponsored trial, DPP, was to examine whether type 2 diabetes can be prevented in people with impaired glucose intolerance. The three intervention arms of the trial were (1) metformin, the commonly used first-line therapy for type 2 diabetes; (2) lifestyle changes aimed at weight loss and increased exercise duration; and (3) placebo. After 4 years, it was found that metformin reduced the risk of developing diabetes by 31 percent in study subjects. Lifestyle changes had an even greater impact—a 58 percent reduction in the risk of developing diabetes compared with placebo (no treatment). The benefits of metformin and lifestyle changes were so dramatic that the data safety monitoring board (DSMB) stopped the study early because continuing the placebo study arm was considered unethical.

The second trial, A Diabetes Outcome Progression Trial (ADOPT), sponsored by GlaxoSmithKline, was a head-to-head comparison of three different marketed drugs (rosiglitazone, metformin, and glyburide) for people recently diagnosed with type 2 diabetes. ADOPT was a large, multicenter, international clinical trial. After 4 years of follow-up, it was found that glyburide was the least effective of the three drugs in maintaining glucose control, rosiglitazone was the most effective, and metformin was intermediate. ADOPT was a landmark clinical trial that changed first-line treatment decisions in favor of drugs that maintain glucose control to a greater degree. It was also unique for the pharmaceutical industry to engage in a comparative effectiveness study that explored issues beyond whether a drug can lower glucose. Through the ADOPT results, broader areas of diabetes management were explored, including durability, beta cell function, and a number of issues related to the link between diabetes and cardiovascular disease.

Kahn highlighted the differences in recruitment and retention of subjects for the DPP and ADOPT studies. After screening 30,996 individuals by

means of oral glucose tolerance testing, the DPP study randomized 3,234 to the three study arms. The remarkable feature of the DPP recruitment efforts was that 97.4 percent of the 3,234 participants completed the study. Even after 12 years in the DPP study, the retention rate was 88 percent. Kahn argued that this success was due in large part to the structure and design of the DPP study and the use of designated staff and budgeted resources for specific recruitment and retention efforts (see Figure 7-1). The investigators and staff at each of the 27 centers implementing the protocol felt invested in the study, according to Kahn, and the presence of a formal Recruitment and Retention Committee kept study monitors in constant contact with the centers. Any problems could be dealt with quickly through the network of committees overseeing the trial. Managing a relatively complex organizational structure by means of a 25-member Steering Committee and the Protocol Oversight Program, NIDDK was able to maintain tight control over the conduct of the trial and ensure compliance with the trial protocol.

In contrast to the DPP, the ADOPT trial employed a relatively simple study management design. Of 6,676 individuals screened for the ADOPT trial 4,360 were randomized to the three study arms. Of the 4,360 who were recruited, only 60.3 percent completed the trial. The simple management structure (Figure 7-1) included the sponsor (GlaxoSmithKline), which worked with the DSMB; a nine-person Steering Committee; and an independent Adjudication Committee. Kahn suggested that, with no committees to oversee clinical operations, the investigators involved in the study may have been slightly less committed to the study than those involved in the DPP study. Moreover, the fact that ADOPT had 488 centers across 17 countries made it impossible to bring the 488 principal investigators and study coordinators together on a regular basis to discuss study progress.

The number of subjects per research site also differed significantly between the DPP trial and ADOPT. The largest ADOPT center had 48 subjects enrolled in the trial, whereas the largest DPP site had 200 individuals enrolled (see Table 7-1).

The reimbursement process for clinical trial staff is another key distinction between government- and industry-sponsored trials that can affect the quality of the research. The NIH approach to reimbursement provides financial support to full-time equivalent (FTE) trial staff. Kahn commented that this approach has contributed to the success of government-sponsored trials because it allows for the retention of trial staff and the appropriate number of study participant visits, even in long-term trials with two to three patient visits per year.

The large dropout rate in ADOPT (40 percent) introduced potential bias into the study and could cast doubt on the significance of the differences among the three treatments. A rigorous sensitivity analysis by study staff, as well as statisticians independent of the study, determined that the

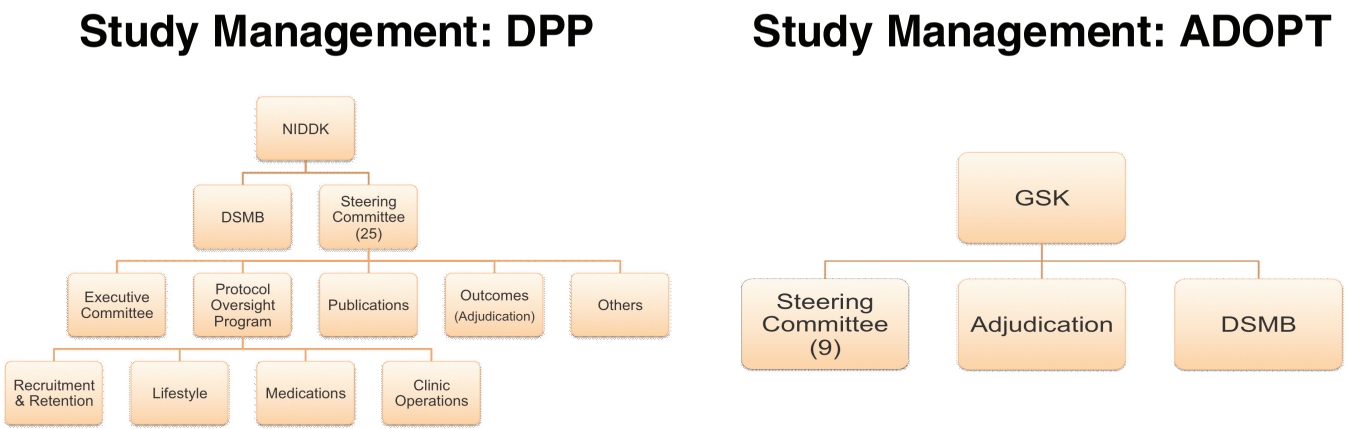


FIGURE 7-1 Study management structure for a government-sponsored randomized controlled trial (Diabetes Prevention Program [DPP]) and an industry-sponsored randomized controlled trial (A Diabetes Progression Outcomes Trial [ADOPT]).
SOURCE: Kahn, 2009. Reprinted with permission from Steven Kahn 2009.

TABLE 7-1 Structure of Study Centers for a Government-Sponsored Randomized Controlled Trial (Diabetes Prevention Program [DPP]) and an Industry-Sponsored Randomized Controlled Trial (A Diabetes Progression Outcomes Trial [ADOPT])

	DPP	ADOPT
No. of Countries	1 (USA)	17 (USA, Canada, Europe)
No. of Centers	27	488
No. of Subjects	3,819	4,360
Subjects per Center	62–193 (Nat. American: 20–80)	1–48
Caucasian	55%	88%
Reimbursement	FTE based	Visit based

NOTE: FTE = full-time equivalent.
SOURCE: Kahn, 2009.

difference between the best drug (rosiglitazone) and the worst drug (glyburide) in the study was not attributable to bias and therefore still reliable. However, bias could not be ruled out as the cause of the observed difference between the best (rosiglitazone) and intermediate (metformin) drugs. In the DPP trial, the designation of specific staff and budgeting of resources for retaining participants were successful in achieving a 97 percent retention rate, thus avoiding bias in the study results.

The DPP was likely more expensive than ADOPT in terms of cost per patient, according to Kahn. However, the 97 percent patient retention rate in the DPP was perhaps worth the additional cost given that large dropout rates can call into question the legitimacy of the results of any trial. The DPP could have been completed and found the same reduction in the risk of developing type 2 diabetes with a less intensive, less costly level of lifestyle intervention. In general, however, the results of NIH-sponsored, long-term studies such as the DPP, which have high rates of participant follow up, are often more valuable than those of industry-sponsored studies conducted over a short period of time and with dropout rates in the range of 20–25 percent.

OVERCOMING REGULATORY CHALLENGES

In addition to the challenges discussed in Chapter 3, Carla Greenbaum, Director of the Benaroya Research Institute Diabetes Program and Clinical Research Center, reflected on her experience conducting clinical trials

in type 1 diabetes. She addressed key issues and strategies for overcoming challenges in recruiting and retaining clinical trial subjects, designing trial protocols for Institutional Review Board (IRB) approval, and navigating requirements of the informed consent process.

Patient Recruitment and Retention

Greenbaum described the process of identifying, screening, and recruiting patients to participate in a type 1 diabetes natural history/prevention trial. To achieve enrollment of the 300–400 patients necessary for a prevention trial, 200,000 relatives of people with type 1 diabetes will need to be screened, a number representing approximately 2–3 percent of the total potential pool of such individuals. About 4 percent, or 8,000, of these 200,000 individuals will be antibody positive—the necessary trait for participating in the trial. After 5 years of patient recruitment efforts, approximately 70,000 relatives have been screened; progress has been steady but remains a challenge. Greenbaum noted that the magnitude of the screening effort necessary to find the relatives at risk for type 1 diabetes and eligible for the prevention study is sustainable only with the broad support of a clinical research network, in this case TrialNet.

Limited information is available regarding how people approach the decision of whether or not to participate in a diabetes clinical trial. Greenbaum speculated whether people with diabetes know that their families are at 15 times greater risk for the disease than the general population, and whether they know that they can be tested or know but prefer not to be tested. In the absence of any systematic, rigorous study in this area, Greenbaum offered a few anecdotal thoughts about why people participate in diabetes trials. In her experience in the northwestern United States, rural participation in diabetes clinical trials is much greater than urban or suburban participation. Greenbaum hypothesized that in urban and suburban areas, families may already be so overwhelmed by such demands as having to take children to various school events and team practices that joining a clinical trial would be an additional, and unwanted, burden.

Greenbaum also described the age distribution of the relatives screened for the type 1 diabetes prevention study. Young adults (ages 19–32) are participating in research at a much lower rate than other age groups. In Greenbaum's experience, the young adult population is difficult to recruit for clinical research because it is generally characterized by a level of self-absorption that does not lend itself to voluntary participation in a clinical trial that may or may not lead to any personal benefit.

In contrast to prevention studies, clinical trials on the new onset of type 1 diabetes have had greater success in identifying and recruiting participants. Figure 7-2 shows the recruitment rates for four such trials. Greenbaum

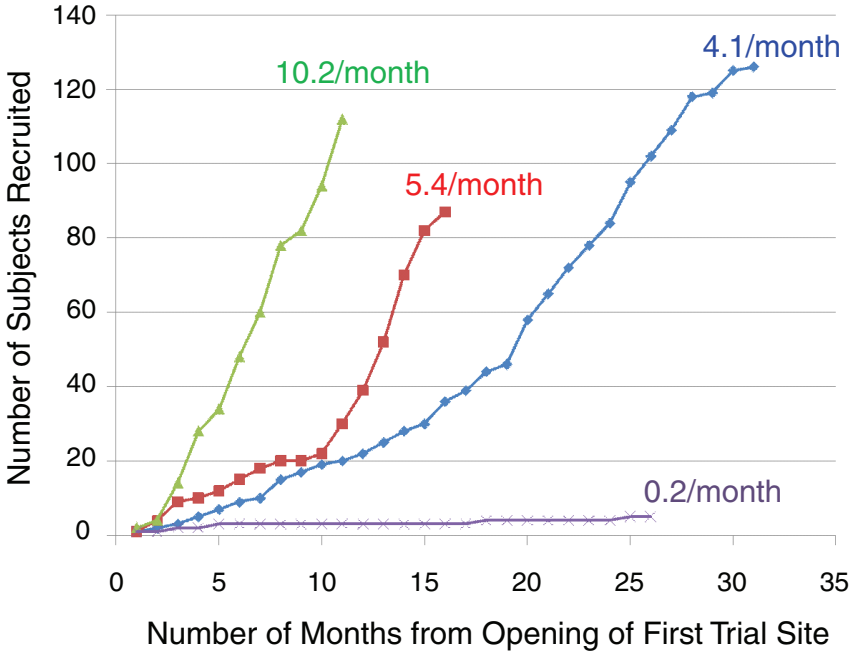


FIGURE 7-2 Patient recruitment rates for four type 1 diabetes trials.
SOURCE: Greenbaum, 2009. Reprinted with permission from Carla Greenbaum 2009.

discussed some of the factors associated with each study that she believes affected their ability to attract patients in an efficient manner.

For each trial depicted in Figure 7-2, the sites were large diabetes centers that are highly committed to recruiting patients. Thus, differences in recruitment rates should not be attributable to variation in the commitment level of trial sites. The trial that recruited 4.1 subjects per month required daily, chronic medication therapy. In the trial that recruited 5.4 patients per month, the drug treatment was two doses (not a chronic therapy), and some follow-up visits were required. The study with the most successful patient recruitment rate is surprising because it involved younger subjects, who, as noted, are typically difficult to recruit, for an intravenous (IV) infusion over 24 visits, one visit per month. In contrast, the study with the lowest recruitment rate has yet to recruit the 10 subjects it requires. Greenbaum explained that this is a phase I study, started at only one site and including only individuals aged 18 and older. In addition, subjects have to have been diagnosed with type 1 diabetes at least 4 years previously, but still have significant insulin secretion to qualify for enrollment in the study.

In light of these differences in recruitment rates, Greenbaum discussed factors that, in her view, can impact patient enrollment and retention:

- **Enthusiastic health care providers**—Greenbaum and Kahn both referred to the importance of having research teams that are supported by full-time equivalent (FTE) employees. With time dedicated to clinical research, staffs have a greater sense of responsibility for enrolling and retaining patients in a trial. Greenbaum indicated that within her home institution, the successful recruitment and retention of study participants is due to the connections research staffs have with patients and families. The relationship between staff and patients engenders a strong sense of loyalty to the study, as well as to each other.
- **Patient vulnerability**—There is a level of vulnerability associated with patients who are newly diagnosed with a disease. In Greenbaum's experience, individuals entering clinical trials are looking to cure their diabetes, regardless of the information presented to them on consent forms. Perhaps people who are further from diagnosis are not enrolling in clinical trials at the same high rate as those who are newly diagnosed because they have adapted to the lifestyle of their condition and are more attuned to the risks and benefits of a particular study. Greenbaum also noted the high level of clinical trial participation among children and speculated that it may be associated with parents' sense of guilt and fear and their desire to do anything they can to help their children, including enrolling them in clinical trials.
- **Socioeconomic status**—Greenbaum noted, as did Musa Mayer (Chapter 6), that variations in socioeconomic status (income, education, occupation) affect an individual's level of engagement with the health care system and exposure to clinical trials. An individual with higher socioeconomic status may be more likely to be aware of the clinical research opportunities available and better equipped to weigh the risks and benefits of participating as a research subject.
- **Physician support**—The critical importance of physician support in recruiting and retaining patients in clinical trials was noted by Greenbaum, as well as a number of workshop participants. Most clinical trial subjects cite their physician's encouragement as the reason why they decided to participate in a clinical trial.

Reflecting on her work with TrialNet, Greenbaum also highlighted a number of effective tools this network brings to the clinical trial process and to the recruitment and retention of patients. TrialNet uses FTE-supported

clinical centers with dedicated time to conduct its trials. In addition, TrialNet draws on a large affiliate network that includes several hundred physician practices across the country. It also uses a professional media group to draw attention to its research efforts. Most recently, the Jonas Brothers and Miss America have served as spokespersons for TrialNet studies. Also, an important attraction of TrialNet studies is the fact that the travel costs of clinical trial participants are paid for by the network. In addition, TrialNet is able to build on its connection with JDRF and ADA. JDRF's website continues to be an important tool for referring patients to clinical trials.

Navigating the IRB Process

The reality of conducting clinical research today is that multicenter trials, with multiple local IRBs, are required to implement a trial capable of providing robust, informative answers. Greenbaum explained that TrialNet has put a great deal of effort into adapting to this situation. For one thing, it has adopted a proactive approach of providing explicit instructions to IRBs to help guide their decision-making process. For example, TrialNet protocols are drafted with specific language stating that it is permissible to study children in a particular trial and citing the guidelines and rules that apply. Greenbaum said IRBs appreciate the inclusion of this specific language in the protocol because it relieves them of the responsibility for making the decision as to which guidelines or rules apply in the case of a particular research study.

TrialNet also has a protocol template that includes a number of sections designed to facilitate the regulatory approval process. The sections range from substantial additions citing federal regulations regarding research in children to minor variations in the language of informed consent forms for patients. Greenbaum noted that in her experience, the key to creating a successful trial protocol (i.e., reducing the need for protocol amendments and deviations) is the inclusion of open wording. For example, a trial protocol might state that "no more" than a particular amount of serum or plasma will be drawn from each research subject in the trial. Because the amount of serum or plasma needed at a particular time in the study is likely to change, this wording allows for the necessary variation and eliminates the need to submit additional paperwork (i.e., a protocol deviation or resubmittal for a protocol revision). Preparing such carefully written protocols that include deliberate yet open wording has therefore helped TrialNet conduct more efficient clinical trials in terms of the recruitment and retention of patient subjects.

Informed Consent

Although efforts have been made to streamline and improve the informed consent process, it remains a challenge for both investigators and patients. Greenbaum stated that the overlap between the confidentiality language of informed consent forms and federal requirements under the Health Insurance Portability and Accountability Act of 1996 (HIPAA) makes drafting clear, readable consent documents somewhat difficult. Despite the growing tendency in the field to emphasize obtaining the final patient signature on an informed consent document, TrialNet has tried to make informing and educating patients a priority instead of merely obtaining their signature. TrialNet has developed patient participant handbooks and quizzes separate from the consent process to ensure that patients really understand what the trial involves. In addition, TrialNet requires that physicians be actively involved in the informed consent process for patients, a feature not commonly found in other study settings, according to Greenbaum.

During the workshop discussion, Perry Cohen, a Parkinson's patient advocate, noted that his organization, Parkinson Pipeline Project, has developed a research participant bill of rights and responsibilities. The document lays out the features of clinical research that patients desire if they are to participate in a trial. The declaration includes patient requests and responsibilities related to informed consent issues, as well as rights to post study data (e.g., trial results and options for care after the trial ends).[2]

[2]More information on the Parkinson Pipeline Project and the Declaration of Clinical Research Rights and Responsibilities for People with Parkinson's can be found at http://www.pdpipeline.org/advocacy/rights.htm.

8

Building a Robust Clinical Trials Infrastructure

The first day of the workshop focused on the organization of clinical trials and considered various approaches based on different types of diagnosis, study sponsor, and research entity, as well as other factors. The case studies and discussions highlighted a wide range of concerns about how clinical trials are currently conducted and the potential decline in the nation's capacity to conduct trials at a time when demand for them is increasing. The absolute number of meaningful inquiries that can be made into new products, services, and ways of delivering health care is limited by cost and the availability of qualified investigators and patients willing to participate. Thus, while the number of research questions is rapidly expanding, there are serious questions about the capacity of the U.S. clinical research enterprise to answer more than a fraction of them.

Drawing on the insights and discussions from the first day of the workshop, day two provided an opportunity for participants to consider current strategies and new approaches for conducting clinical trials in the United States. The need to develop a learning health care system that bridges the gap between clinical research and clinical practice was a key theme throughout the meeting. The goals of comparative effectiveness research (CER) are closely aligned with those of a learning health care system—in CER, clinical research is conducted in settings that are as similar as possible to those in which the intervention will be applied in practice (IOM, 2009d). Various forms of clinical research can support a learning health care system. Randomized controlled trials (RCTs) that take place in an academic setting remain the gold standard for clinical inquiry and will continue to be an important tool for future research. But new approaches, skills, and

capacity will be needed to carry out the range of research necessary to meet the needs of a learning health care system.

This chapter begins with an overview of some current efforts to improve clinical trials in the United States, as well as some international examples. The chapter then turns to the suggestions for improving clinical trials that resulted from the four disease-specific breakout session discussions. Finally, Janet Woodcock's vision for a stable, continuously funded clinical research network in the United States is described.

CURRENT EFFORTS TO IMPROVE CLINICAL TRIALS

Any effort to effect large-scale improvements in the clinical research enterprise must be informed by an examination of smaller-scale efforts already under way. While a number of individual institutions, companies, and nonprofit organizations are engaged in streamlining the clinical trials process, the workshop focused on the efforts of the Clinical and Translational Science Awards (CTSA) program, particularly in the creation of templates for agreements used in the clinical trials process; the Clinical Trials Transformation Initiative (CTTI); the National Institutes of Health's (NIH's) Roadmap for Medical Research; and an overview of international efforts.

Efforts of the Clinical and Translational Science Awards (CTSA) Program

Barbara Alving, Director, National Center for Research Resources (NCRR) within NIH, described the CTSA program and its role in improving clinical trials in the United States. Launched in 2006 and directed by NCRR, the program makes grants to institutions that provide an academic home for clinical and translational science throughout the United States, working to accelerate the translation of laboratory discoveries into new treatments for patients. The five strategic goals of the CTSA consortium of institutions are:

1. to build national clinical and translational research capacity;
2. to provide training and career development for clinical and translational scientists;
3. to enhance consortium-wide collaborations;
4. to improve the health of communities and the nation; and
5. to advance T1 translational research to move basic laboratory discoveries and knowledge into clinical testing.[1]

[1]T1 refers to the first stage of translational research, in which basic scientific discoveries are developed into new therapies, diagnostics, or preventive tools to be tested in humans. In the second stage of translational research (T2), clinical trial results are used to inform everyday clinical practice and health care decision making.

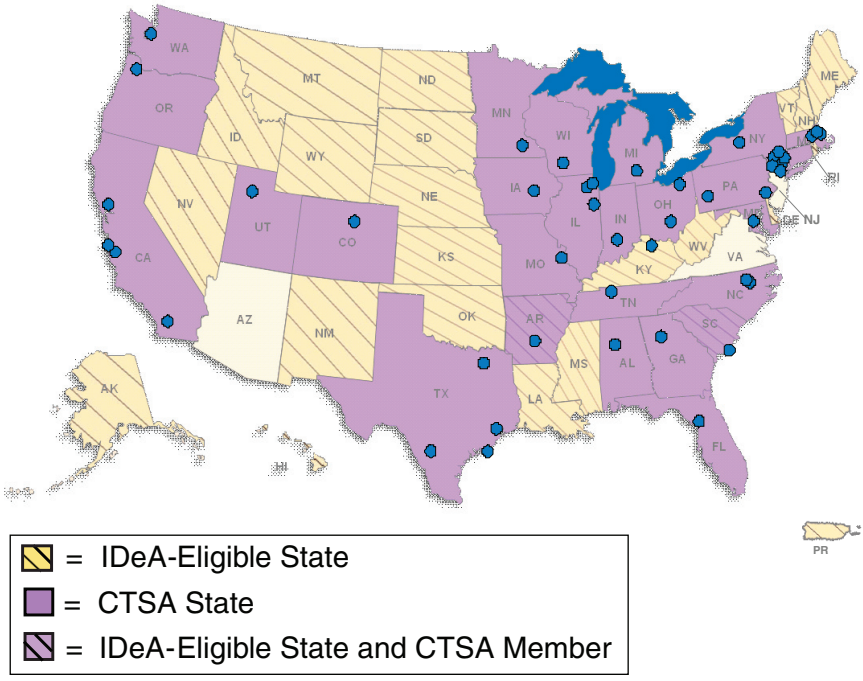


FIGURE 8-1 CTSAs include 46 institutions in 26 states. When the program is fully implemented in 2011, it will include approximately 60 institutions.
NOTE: IDeA = Institutional Development Award.
SOURCE: Alving, 2009. Reprinted from the National Center for Research Resources, NIH.

Currently, 46 academic institutions make up the CTSA consortium, covering 26 states (Figure 8-1). Alving noted that CTSAs are deployed so that their reach is effectively nationwide. In the western United States, the University of Washington works with a number of sites in Idaho, Montana, and Wyoming that do not have medical schools. The IDeA-eligible[2] states are funded to create Centers of Biomedical Research Excellence.

CTSA institutions are also engaged in public–private partnerships. For instance, the University of Rochester has created an Intellectual Property

[2]Institutional Development Awards (IDeAs) are funded by NCRR/NIH to foster health-related research and enhance the competitiveness of investigators at institutions located in states in which the aggregate success rate for applications to NIH has historically been low. Additional information on the IDeA program can be found at http://www.ncrr.nih.gov/research_infrastructure/institutional_development_award/.

Portal[3] to aggregate and market technologies from CTSA institutions and NIH. Fifteen CTSA institutions are currently contributing information on their technologies to the site. Alving mentioned another Web-based tool, the CTSA Pharmaceutical Assets Portal,[4] which links those with an interest in pharmaceutical products to investigators nationwide, as well as at NIH, who want to study the products.

Alving listed the six areas in which the CTSA program is focusing significant effort to facilitate improvements in the clinical trial process:

- developing data-driven approaches to process improvement;
- reviewing steps involved in the initiation of clinical trials;
- naming "Champions of Change" at academic health centers—individuals with the authority to effect changes;
- educating academic health centers about uniform templates for clinical trial agreements (CTAs) (see below);
- developing tools for enrollment of clinical trial participants; and
- developing Web-based tools for management of clinical trial data.

Alving noted that currently, the performance of CTSA institutions with respect to the length of time it takes for clinical trial contracts to be initiated is similar to that of non-CTSA academic institutions: both experience significant delays from the point at which a clinical trial protocol reaches an Institutional Review Board (IRB) office to the point at which initial ethical review is complete. While CTSA institutions vary greatly in terms of the time frames involved, Alving hopes that as a consortium, they can develop best practices to effect widespread improvement in these time frames across both CTSA and non-CTSA institutions.

As a broad-based network of academic institutions dedicated to clinical and translational research, the CTSA consortium represents a number of key academic stakeholders engaged in clinical trials. Alving pointed out that while CTSA institutions enjoy the benefits of close collaboration with each other, some CTSA initiatives are available to all institutions, CTSA and non-CTSA alike.

Alving stated that it takes anywhere from 4 to 7 months to negotiate a CTA between an academic institution and industry. She noted that, regardless of the disease of focus in a clinical trial, a contracts office is responsible for negotiating the contract, and providing templates (disease-specific as well as general) for that office to choose from can facilitate the negotiation pro-

[3]Additional information on the Intellectual Property Portal can be found at http://www.rochesterctsa.org/ip/.

[4]Additional information on the CTSA Pharmaceutical Assets Portal can be found at http://www.CTSApharmaportal.org/.

cess. To streamline the lengthy negotiation process, the IOM Drug Forum commissioned the development of templates for both CTAs and material transfer agreements (MTAs).[5] The templates, which are intended for widespread use, incorporate language considered acceptable to key stakeholders. Where companies and universities tend to have significant differences, the templates annotated the standard language to highlight and provide context for those differing positions. Alving described CTSA program efforts to disseminate the CTA and MTA templates to the CTSA consortium and to educate academic health centers on how they can be used effectively. The National Cancer Institute (NCI) also has created template agreements to facilitate contract negotiations. The NCI templates—Standard Terms of Agreement for Research Trial (START) Clauses—are based on the results of a survey of all NCI cancer centers.

Alving also described the following programs supporting CTSA institutions and other clinical research programs:

- **Research Electronic Data Capture (RedCap)**[6] gives research teams an easy way to collect, disseminate, and protect the privacy of study data. It comprises two secure Web-based applications and provides software and support to partners (CTSA institutions, General Clinical Research Centers, Research Centers in Minority Institutions, and other institutions) at no charge in exchange for participation in the consortium. Alving reported that 3,000 researchers currently use RedCap across 56 institutions and 22 countries.
- **CTSApedia**[7] will be a comprehensive online resource for those seeking courses in clinical and translational research. This resource will be available to both CTSA and non-CTSA institutions.
- **Researchmatch.org**, launched in October 2009, is a Web-based patient recruitment registry connecting willing clinical trial volunteers with researchers. It currently supports the CTSA consortium of institutions.[8]

[5]The CTA and MTA templates can be found at http://iom.edu/~/media/Files/Activity%20Files/Research/DrugForum/April27-28/TemplateCTA%2042209.ashx and http://iom.edu/~/media/Files/Activity%20Files/Research/DrugForum/April27-28/TemplateMTA%2042209.ashx.

[6]Additional information on RedCap can be found at http://www.project-redcap.org/.

[7]Additional information on CTSApedia can be found at http://www.ctspedia.org/do/view/CTSpedia/WebHome.

[8]Additional information on the Research Match Network can be found at https://www.researchmatch.org/partners/.

Clinical Trials Transformation Initiative (CTTI)

CTTI is a public–private partnership founded by FDA's Office of Critical Path Programs and Duke University. The initiative, which includes stakeholders from government, industry, academia, patient advocacy groups, professional societies, and other organizations, has the goal of identifying practices whose broad adoption will increase the quality and efficiency of clinical trials.[9] In clinical trials, most of the costs are associated with human time and effort, so unnecessary complexity can be both burdensome and expensive. In the United States, where labor costs are higher than in other parts of the world, unnecessarily complex clinical trial processes can put the United States at a disadvantage.

NIH Roadmap for Medical Research

The NIH Roadmap for Medical Research, issued in 2003, set forth a vision for what the clinical research enterprise in the United States should look like. The Roadmap envisioned that in 10 years there would be a national clinical research system, based on electronic health records, in which all Americans would participate. Data in this system would be open and transparent. Robert Califf said that, although this vision has not yet been fully realized, many of the necessary components are being put in place. He suggested that avoiding additional layers of bureaucracy and focusing only on the core goals of clinical research would help create the system envisioned in the Roadmap. In contrast to the current model of a single coordinating center and a number of research sites conducting a clinical trial (Figure 8-2), existing networks would be linked using electronic health records and patient registries to create a more interconnected exchange of clinical research information (Figure 8-3).

International Examples

The United Kingdom, Canada, Germany, and Australia are engaging in a similar dialogue on strategies to improve their clinical research infrastructure. According to Paul Hébert, the dialogue on the type of infrastructure needed to carry out clinical trials varies depending on the trial designs one wishes to use and the outcomes one seeks. In the United Kingdom, for example, large, pragmatic trials that have broad eligibility criteria and include a sizable number of patients are frequently used to test the effectiveness of drugs or medical interventions. Data collection in such trials is usually

[9]Additional information on the Clinical Trials Transformation Initiative (CTTI) can be found at https://www.trialstransformation.org/.

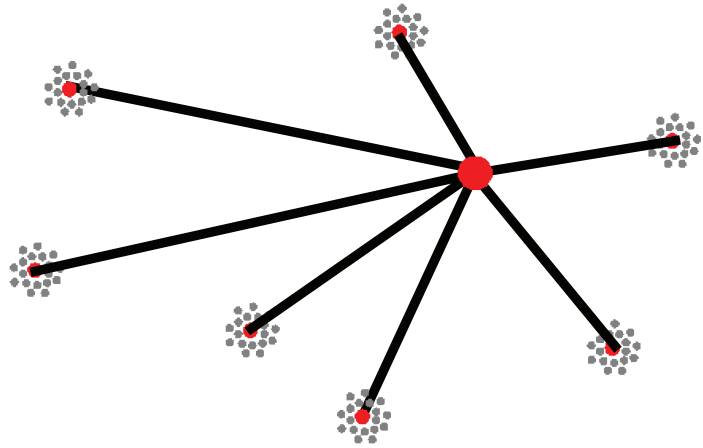


FIGURE 8-2 Typical NIH clinical trial network with academic health center sites surrounding the hub of a data coordinating center.
SOURCE: Califf, 2009. Reprinted with permission from Robert Califf 2010.

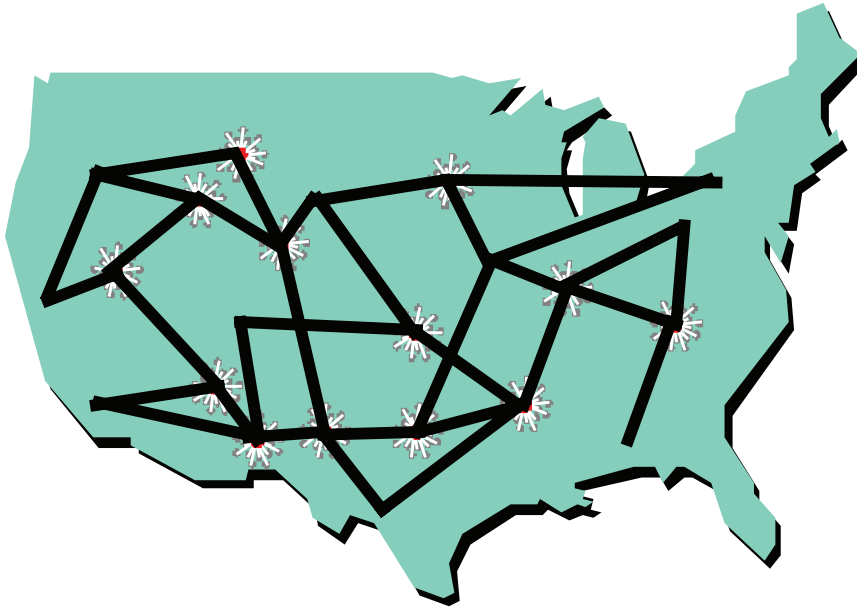


FIGURE 8-3 A vision of an integrated clinical research system linking existing networks (patients, physicians, and scientists) to form communities of research and conduct clinical trials more effectively.
SOURCE: Califf, 2009. Reprinted with permission from Robert Califf 2010.

minimal (two to three pages), compared with other trial designs that involve the collection of multiple binders of data.

Hébert explained that in the United Kingdom, national clinical research networks exist on six major themes, and each includes 7 to 10 local clinical investigator networks. The local networks serve primarily as recruiting centers for large, national trials. To support this system, the British government initiated a realignment of research funding so that it is coordinated centrally and provided nationally.

In a discussion of patient registries, Christopher Cannon echoed the sentiment that the goal of clinical research—the outcomes sought—should shape the way a research infrastructure is built. Although the confounding that characterizes registries (why an individual received one therapy versus another) makes it impossible to use these data to compare different therapies, Cannon suggested that patient registries could provide the data collection infrastructure for a system of large, pragmatic trials. For instance, as health information technology advances, the passive collection of data becomes easier. A simple randomization of therapies in a broad population (e.g., the Medicare population), with data being collected inexpensively, could provide the infrastructure necessary to conduct more large, simple trials in the United States, similar to those popular in the United Kingdom.

International agencies and governments are also grappling with ways to overcome the barriers to clinical research. Hébert shared the results of a survey of U.S. and European companies indicating that the process of negotiating contracts for clinical research is a major burden in terms of both time and cost. While collaborations can be useful for generating new research, the contract and negotiation process across multiple entities can be extremely difficult. For instance, the development of contracts for a large, multisite, international trial that requires funding from a number of different collaborators requires a significant amount of time and money—Hébert estimated the process can take 2 years.

Hébert also cited current efforts to improve clinical research in Canada. These efforts include investing in the workforce (e.g., biostatisticians, health economists, and epidemiologists), using the flexibility and support functions of 89 large national networks already in existence, and integrating research into clinical practice through the development of 20 to 30 support units across the country.

The health care system largely drives the way in which clinical research is conducted, according to Hébert. The United Kingdom and Canada, for instance, have single-payer systems that facilitate centralized control of the clinical research enterprise. Hébert suggested that the United States can learn from the experiences of other countries but that ultimately, the solution to improving its clinical research enterprise will need to be tailored to the U.S. context and take into account the unique driving forces (i.e., the

health care system, political perception and motivation of decision makers) behind any systemic change.

LARGE, SIMPLE CLINICAL TRIALS

The NCI and the National Heart, Lung, and Blood Institute (NHLBI) are cofunding a large, simple trial on the effects of vitamin D. Called the VITAL trial, it will enroll 10,000 men over age 60 and 10,000 women over age 65, who will receive daily high doses of oral vitamin D and omega-3 fatty acids.[10] The goal of the trial is to determine whether vitamin D and omega-3 fatty acids lower the risk for cardiovascular disease and cancer. The trial will cost $150 per participant and take place over 5 years.

Because the VITAL trial involves a low-risk, preventive intervention in a primarily healthy population, it offers the opportunity to implement a unique and efficient trial methodology that bypasses the physician and works directly with the study participants. In the VITAL trial, study forms and pills are mailed directly to patients, and no clinic visits are necessary. Michael Lauer described the VITAL trial design as similar to that of the Physicians' Health Study, in which investigators rather than practicing physicians communicate with study participants. This design can facilitate recruitment of study subjects—an important consideration for a trial that seeks to enroll thousands of patients for a low overall cost. The Internet has been an especially useful tool for trials that require such direct communication with patients. Recruiting patients, communicating study details, and collecting data via the Internet will likely become increasingly useful for conducting clinical trials, according to Lauer.

Amir Kalali referred to iguard.org, a Web-based tool that can aid in the recruitment of patients for trials. Created in 2007 and funded by Quintiles, this website allows patients, providers, and caregivers to monitor the safety of medications. Individuals can enter the medications they are taking and receive any alerts from the FDA on those medications. In addition, if an individual takes multiple prescriptions, the service will provide an alert as to any medication interactions. Kalali explained that he believes iguard.org has attracted millions of subscribers because it offers information not provided by doctors. In addition to answering questions about medications, iguard.org asks patients whether they are interested in participating in clinical research. Kalali noted that this Web-based method of finding patients for trials has been particularly useful for conducting the type of large, simple trial that bypasses interaction with physicians and relies on direct communication with patients.

[10]Additional information on the VITAL trial can be found at www.vitalstudy.org.

SUGGESTIONS FROM THE BREAKOUT SESSIONS

On the second day of the workshop, small groups were formed around each of the four disease areas (cardiovascular disease, depression, cancer, and diabetes). Each group was asked to:

- describe a concise vision of clinical research within its disease area that would better support the goal of a learning health care system;
- identify the gap between this vision and current practices;
- identify best practices (from any disease area) or untested but potentially powerful approaches to organizing clinical trials that could address this gap; and
- identify the key impediments to implementing such approaches that would have to be addressed for the vision to be realized, such as infrastructure, public–private investment, workforce, legal and institutional constraints, academic culture, and traditions.

Following the discussions, the breakout chairs reported the groups' findings to the larger workshop audience.

Cardiovascular Disease Breakout Session

Discussion in this breakout session focused largely on strategies and policies that could lead to the creation of a national clinical research network positioned to accelerate research efforts in all disease areas. The group suggested that a national network could be based in the primary care setting but should go beyond physicians to include the full spectrum of the primary care workforce. The group discussed components of such a network that might already be in place today. An example is the 46, soon to be 60, CTSA institutions that encompass much of academic medicine in the United States. In addition, 52 Practice-Based Research Networks (PBRNs) comprise groups of primary care practices throughout the country. Historically, PBRNs have been underfunded, but the fact that physicians have joined these networks without the promise of core funding indicates that there is significant interest among practicing community-based clinicians in developing clinical questions and producing research results that can effectively improve everyday clinical practice.

Patient advocacy and voluntary health organizations would have an important role in driving the effort to build a national research network. Groups with experience in using social networking and other outreach mechanisms could be highly effective in engaging the public and building broad interest in clinical research.

NIH and industry, as the key sponsors of clinical research in the United States, also have an interest in building a national research network that would improve the efficiency of clinical trials, with the overarching goal of answering more of the most important research questions.

Several key barriers to creating a more efficient clinical research enterprise were discussed in the breakout session:

- **ethics review**—delays and difficulties encountered in obtaining approval for a clinical trial protocol;
- **contract negotiations**—contentiousness and delays surrounding the contract negotiation process between NIH and clinical trial sites; and
- **intellectual property**—agreements that include requirements that human subjects research results be kept confidential for 5 years. (It was suggested by discussants that they believed that beyond phase II research, intellectual property should not be a contentious issue in the academic arena.)

Depression Breakout Session

This breakout session formulated a broad vision for future research efforts in depression that included successfully treating the disease in all forms and settings, with a goal of achieving remission for 60 percent of patients. The development of sensitive research tools and measures of depression that would accurately convey the state of the disease could improve the development of informative clinical trials. Similar to a point made in the diabetes session, a 100-year goal for depression could be preventing the onset of the disease.

Creating unified standards for every human measure and the data systems to manage them would help in ensuring that the significant investment each human subject confers in agreeing to participate in a clinical trial results in the highest possible value to the clinical trial enterprise. Involving patients and patient advocates throughout the trial design and implementation process would also help improve clinical trials and the validity of the results they generate. Expanding clinical trial design toolkits and increasing the number of depression studies that examine long-term outcomes would also be useful.

The group also discussed the idea of including research in the routine delivery of care so as to remove the current divide between the clinical research enterprise and clinical practice. Integrating these two worlds would require new models to better align research and health care delivery as well as culture change at all levels (e.g., patients, providers, educators, and legislators). To facilitate culture change, large outcome studies that answer

important questions could be used to engage stakeholders and gain public trust and involvement.

Cancer Breakout Session

Meeting patients' expectations of the clinical research enterprise was the focus of this group's discussion. Patients should expect that their treatment is evidence-based and that their treatment experience will form the basis for an increase in knowledge, which in turn will lead to improvement in their care. In such a learning health care system, physicians, nurses, data managers, payers, patients, and regulators would all contribute to the process by which health care outcomes would inform clinical practice.

Numerous gaps exist between the current health care system and the ultimate goal of a learning health care system. The group discussed, for instance, the need to correct public misconceptions about clinical trials and the overall value of clinical research. For practitioners, the progression through the core curriculum of medical school and eventually continuing medical education includes limited instruction in conducting clinical research. In addition, misaligned incentives exist in a reimbursement system based on the volume of patient visits or procedures completed. Another important gap is the lack of coordination and prioritization of clinical trial research questions. These and other barriers discussed in Chapter 3 characterize the inadequate research infrastructure that exists at every level of the health care system. The group also highlighted significant gaps in the instruments used to analyze issues surrounding end of life and quality of life.

While the above gaps are substantial, the group discussed four areas of oncology that have exhibited best practices in clinical research:

- **Pediatric oncology**—Based on a relatively small network of practicing pediatric oncologists, this area of medicine has created a culture shift in which oncologists in training have mentors and role models in the field to further the circulation of clinical information. The majority of practitioners are salaried, which removes the traditional focus on performing a high volume of procedures. In addition, the field of pediatric clinical oncology includes significant patient and family involvement, enhancing the flow of information throughout the network and overall public investment into this area of clinical research and practice. Many children with cancer have been enrolled in clinical trials, which have resulted in significant advances in cancer treatment and patient health.
- **Gastrointestinal stromal tumor (GIST) and chronic myeloid leukemia (CML)**—In these two areas, patients have largely instigated the

sharing of information on clinical research and the use of effective treatments for these conditions.

- **Multiple myeloma and prostate cancer**—The advocacy community has assumed significant responsibilities for financing research and clinical trials in these two areas, thus creating an alternative and more flexible structure than the NIH funding system.
- **Breast cancer**—Advocacy collaborations between patients and researchers have influenced federal legislation and the allocation of additional funding to clinical research.

The group also discussed how payers would benefit from supporting and financing clinical trials in that they could be the first to demand the most effective, evidence-based treatments. In the case of solid tumor transplantation, for example, payers are already demanding fast screening, whereas the FDA has yet to improve the test for this type of screening. Putting payers on the cutting edge of clinical research could be a powerful approach to advancing clinical practice.

During the discussion, it was noted that, to accelerate clinical research and improve the infrastructure underlying clinical trials, leadership and coordination from the highest levels of government would be necessary. A caution was expressed, however, that the bureaucratization of clinical research should be avoided—care should be taken when considering the creation of new structures and the accompanying regulatory and legal constraints.

Finally, discussion focused on the need to build a sufficient clinical research workforce. An important step in this direction would be to improve the academic culture such that clinical investigation is widely viewed as a legitimate academic pursuit.

Diabetes Breakout Session

This group's discussion focused primarily on how the clinical research system can meet the needs and expectations of patients. Patients should be empowered and provided access to the clinical research enterprise. Voluntary health organizations such as the American Heart Association (AHA) and the American Diabetes Association (ADA) could be instrumental not only in improving patient awareness of clinical trial opportunities, but perhaps more importantly, in helping individuals understand the role of clinical research in improving health care.

In addition, the clinical research enterprise should be founded on the enthusiasm of providers. To create such a system, clinical investigators and academic leaders should be rewarded, not just financially, for their efforts in clinical research. In addition, trust in the clinical research system needs to

be restored and skepticism regarding associations with the pharmaceutical industry needs to be reduced.

The discussion identified the prioritization of clinical research needs as the main challenge to any new clinical research system. A key question is who will decide which areas of disease research will receive resources.

Finally, the group acknowledged that information technology holds great promise for long-term improvement in the way clinical research is conducted. However, revamping the regulatory and ethical foundations of clinical research is essential in the short term.

TRANSFORMING CLINICAL RESEARCH

In light of the presentations and discussions regarding the significant challenges facing clinical research in the United States today, Janet Woodcock shared her vision for a transformed clinical research enterprise. While many individual aspects of the clinical trial process could be enhanced, she focused on the need for a transformational change in the way clinical research is conducted. She described a vision of a clinical research infrastructure in the United States akin to the national highway system or the national energy grid—in other words, a large public works project designed to ensure that patients, clinicians, and academic researchers all have access to a system that links research and community practice, and facilitates universal participation in the generation of new clinical evidence and its subsequent adoption by physicians.

In Woodcock's vision, a permanent network of resources (e.g., research sites, investigators, and support staff) would be available to anyone conducting scientific inquiries in health care. As opposed to the ad hoc manner in which clinical trials are conducted today, this network of resources would be continuously funded and permanent. The investigators that are part of this network would be organized regionally or nationally around disease or practice areas, or "nodes." This structure would allow the network to address questions ranging from health care delivery (e.g., psychiatrists vs. clinical psychologists in various care settings) to the appropriate medical intervention (e.g., antidepressants vs. talk therapy). The required features of the research network would include community trust and involvement (patients and practitioners), high quality and sufficient quantity of research conducted, and demonstrated efficiency in conducting clinical research (rapid trial implementation and patient enrollment).

Supporting and uniting the investigators would be core clinical trial and disease experts with dedicated time to support, run, and organize the clinical research infrastructure. These experts would likely be academics because of their engagement in the scholarly study of disease and clinical trial methodology. Core research personnel would also form the backbone

of this cadre of experts. Regulatory experts to guide a study through the IRB process, data managers, biostatisticians, and administrative personnel would be available so that investigators would not need to reinvent the wheel for each study. The network of resources could be utilized by single investigators, academic groups, foundations, or industry for a fee and based on mutual agreement between the network and the research sponsor.

The clinical research infrastructure would be supported through continuous federal funding for the research network and the cadre of experts around the country. The basic funding mechanism would be contracts, not grants, because, according to Woodcock, the episodic nature of grant proposals is not ideal for building infrastructure. Woodcock elaborated on this key feature of her vision by hypothesizing that if grants had been used to build the highway system or energy grid in the United States, we would not have the successful infrastructures we have today.

Workshop participants discussed the many potential benefits of implementing such a vision and the transformational change it would introduce to the clinical research enterprise in the United States. Currently, industry-sponsored clinical trials entail the recruitment of individual investigators and the ad hoc creation of a trial infrastructure around the selected investigators. Under Woodcock's vision, a core set of trial experts would engage in a collective decision-making process regarding whether to accept a research proposal. Thus, Woodcock suggested, her vision could create a structural distance between industry-sponsored trials and investigators. This separation could have a positive effect on the general public's trust in clinical research. Peter Honig, Head of Global Regulatory Affairs, AstraZeneca, referenced a Harris poll finding that 68 percent of the American public recognizes that clinical research has substantial value, while 42 percent of Americans distrust pharmaceutical companies. In light of these data, reducing the intensity and directness of relationships between industry and investigators could improve public trust in clinical research and redress the mismatch between the public's perception of the value of clinical research and its distrust in how the research is conducted.

In discussing the strengths and weaknesses of Woodcock's proposal, Steven Kahn stressed the importance of having a strong, universal health care system as the backbone for such a vision—something the United States lacks. Workshop participants echoed the sentiment that adding a layer of infrastructure for clinical research to the fragmented health care system in the United States would be difficult and potentially ineffective. Participants also raised the question of who would pay for a permanently funded clinical research infrastructure. Califf suggested that the flow of research jobs abroad could provide significant motivation for a broad coalition of federal agencies to support this domestic initiative. Woodcock added that current approaches to studying health care will not deliver the amount or quality of

information needed. The U.S. Congress and federal agencies administering health programs throughout the country constantly ask which health care products and procedures to pay for (i.e., what is reasonable and necessary) or how to structure benefits and services. However, the clinical trials needed to answer these questions cost millions of dollars each and require years of development and implementation. While the United States currently lacks the capacity to examine the large number of research questions that must be answered to form the foundation of a learning health care system, Woodcock's vision for a permanent, continuously funded clinical research infrastructure is one possible strategy for improving clinical research capacity in the United States.

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Appendix A

Agenda

The goals of this workshop are to examine the state of clinical trials in the United States, identify areas of strength and weakness in our current clinical trial enterprise, and consider transformative strategies for enhancing the way clinical research is organized and conducted. Through a series of case studies and stakeholder perspectives, participants will examine clinical research networks in four disease areas—cardiovascular disease, depression, cancer, and diabetes. The goal is to understand the approaches that these networks have utilized in addressing the special issues and problems they face, successfully or not, and thereby derive lessons that can be applied throughout the clinical research enterprise.

Day One
Wednesday, October 7, 2009
8:30 a.m.–5:15 p.m.

8:30–8:35 **Welcome and Opening Remarks**

Jeffrey Drazen, Workshop Chair
Drug Forum Co-Chair
New England Journal of Medicine

8:35–10:00 **Session 1: State of the Clinical Research Enterprise**

This session will provide a broad overview of the current state of clinical research in the United States, its strengths and weaknesses, its recent evolution and future trajectory, and the types of problems that are commonly

encountered in conducting clinical trials. In order to establish a baseline of data and an assessment of the current situation, a paper commissioned by the Institute of Medicine will be presented. A distinguished panel of experts will then discuss the paper's conclusions and reflect on the state of clinical research from their own perspectives.

	Jeffrey Drazen, Moderator Drug Forum Co-Chair *New England Journal of Medicine*
8:35–9:00	Ronald Krall GlaxoSmithKline (retired)
9:00–9:15	Clifford Lane National Institute of Allergy & Infectious Diseases, NIH
9:15–9:30	Christopher Cannon Harvard Medical School and Thrombolysis in Myocardial Infarction (TIMI) Study Group
9:30–9:45	Paul Hébert *Canadian Medical Association Journal* and Canadian Critical Care Trials Group
9:45–10:00	Discussion/Q&A
10:00–10:15	**Break**

Models of Clinical Research

Sessions 2 through 5 will examine approaches to organizing and conducting networks involved in large, multisite phase III clinical trials. In order to examine a cross section of contexts, the sessions will consider examples of research networks for the following types of conditions: acute/life threatening; chronic/not acutely life threatening; and chronic/life threatening. Speakers will draw upon their experiences in clinical research to distill lessons learned and make suggestions as to how we can improve the likelihood that a clinical trial will be successful (i.e., effective in translating trial results into actionable and useful information for clinical practice). Topics to be considered include

- Strategies for organizing clinical research networks—e.g., academic-industry relationships, centralized versus decentralized models,

network size and scope, and established versus single-purpose networks;
- Differences between investigator-initiated, industry-driven, and patient group sponsored research efforts;
- Infrastructure to support researchers—e.g., information technology, training, enrollment, patient management systems, and overall funding per patient;
- Management of clinical research networks—e.g., standardization and quality control, incentives, use of performance metrics, informed consent issues, and payment issues; and
- Metrics for assessing the effectiveness of alternative approaches.

JEFFREY DRAZEN, Workshop Chair
Drug Forum Co-Chair
New England Journal of Medicine

10:15–11:30 **Session 2: Models of Clinical Research: Acute Myocardial Infarction & Heart Failure—Acute and Chronic Life-Threatening Conditions**

ROBERT CALIFF, Moderator
Duke University Medical Center

10:15–10:30 MICHAEL LAUER
National Heart, Lung, and Blood Institute, NIH

10:30–10:45 MARC SABATINE
Harvard Medical School, Thrombolysis in Myocardial Infarction (TIMI) Study Group

10:45–11:00 ROBERT CALIFF
Duke University Medical Center

11:00–11:30 Discussion/Q&A

11:30–12:45 The Role of Clinical and Translational Science Awards (CTSA) in the Clinical Trial Process

11:30–12:00 *Working lunch*

12:00–12:45 JEFFREY DRAZEN, Moderator
Drug Forum Co-Chair
New England Journal of Medicine

Luncheon Keynote
BARBARA ALVING
National Center for Research Resources, NIH

Discussion/Q&A

12:45–2:15 **Session 3: Models of Clinical Research: Depression—Chronic/Not Acutely Life-Threatening Condition**

WILLIAM POTTER, Moderator
Merck Research Labs

12:45–1:00 MADHUKAR TRIVEDI
University of Texas Southwestern Medical Center

1:00–1:15 WILLIAM POTTER
Merck Research Labs

1:15–1:30 AMIR KALALI
Quintiles, Inc.

1:30–1:45 JIM MCNULTY
Depression and Bipolar Support Alliance

1:45–2:15 Discussion/Q&A

2:15–3:30 **Session 4: Models of Clinical Research: Cancer—Chronic/Life-Threatening Condition**

RENZO CANETTA, Moderator
Bristol-Myers Squibb

2:15–2:30 MARGARET MOONEY
National Cancer Institute, NIH

2:30–2:45 RENZO CANETTA
Bristol-Myers Squibb

2:45–3:00 MUSA MAYER
AdvancedBC.org

3:00–3:30 Discussion/Q&A

3:30–3:45 **Break**

3:45–5:15 **Session 5: Models of Clinical Research: Diabetes—Chronic/Not Acutely Life-Threatening Condition**

JAY SKYLER, Moderator
University of Miami, Miller School of Medicine

3:45–4:00 JUDITH FRADKIN
National Institute of Diabetes and Digestive and Kidney Diseases, NIH

4:00–4:15 STEVEN KAHN
VA Puget Sound Health Care System and University of Washington

4:15–4:30 JAY SKYLER
University of Miami, Miller School of Medicine

4:30–4:45 CARLA GREENBAUM
Benaroya Research Institute

4:45–5:15 Discussion/Q&A

JEFFREY DRAZEN, Workshop Chair
Drug Forum Co-Chair
New England Journal of Medicine

5:15 **Adjourn**

Day Two
Thursday, October 8, 2009
8:00 a.m.–12:30 p.m.

8:00–9:15 **Envisioning a Transformed U.S. Clinical Research Enterprise**

JEFFREY DRAZEN, Moderator
Drug Forum Co-Chair
New England Journal of Medicine

8:00–8:30 JANET WOODCOCK
Food and Drug Administration

8:30–9:15 Reaction & Discussion

ROBERT CALIFF
Duke University Medical Center

MIKHAIL GISHIZKY
Strategic Opportunity Ventures

PETER HONIG[1]
Merck Research Labs

STEVEN KAHN
VA Puget Sound Health Care System and University of Washington

9:15–11:00 Session 6: Breakout Sessions

During breakout sessions, participants will synthesize evidence presented in earlier sessions, and consider a range of strategies for transforming clinical research, with a focus on Phase III clinical trials, in order to advance toward a learning health care system. Promising models from existing research networks and collaborations will be considered along with innovative approaches that are as yet untried. A representative from each session will prepare a summary of the session's conclusions and recommendations, and present them in plenary session, where they will be discussed by all attendees. These findings, in turn, will inform the subsequent workshops that will probe specific strategies and their public policy implications in depth.

The breakout groups will develop a concise set of findings and report back to the full session on the following:

1. Describe a concise vision of clinical research (within this disease area) that more fully supports the goal of a learning health care system.
2. Identify the gap between current practices and the vision described in 1.
3. Identify best practices (from any disease area), or untested but potentially powerful approaches to organizing clinical trials, that could address this gap.
4. Identify the key impediments to implementing such approaches that must be addressed—e.g., infrastructure, public/private investment,

[1] Since the workshop, Dr. Honig joined AstraZeneca as Head of Global Regulatory Affairs.

workforce, legal and institutional constraints, academic culture and traditions.

Charge to the Breakout Groups
JEFFREY DRAZEN, Workshop Chair
Drug Forum Co-Chair
New England Journal of Medicine

Breakout A: Acute Myocardial Infarction & Heart Failure—Acute and Chronic Life-Threatening Conditions
Keck Room 100
Chair: Robert Califf, Duke University Medical Center

Breakout B: Depression—Chronic/Not Acutely Life-Threatening Condition
Keck Room 206
Chair: William Potter, Merck Research Labs
Facilitator: Linda Brady, National Institute of Mental Health, NIH

Breakout C: Cancer—Chronic/Life-Threatening Condition
Keck Room 109
Chair: Renzo Canetta, Bristol-Myers Squibb
Facilitator: Musa Mayer, AdvancedBC.org

Breakout D: Diabetes—Chronic/Not Acutely Life-Threatening Condition
Keck Room 208
Chair: Carla Greenbaum, Benaroya Research Institute
Facilitator: Scott Campbell,[2] American Diabetes Association

11:00–12:15 Session 7: Breakout Reports

JEFFREY DRAZEN, Moderator
Drug Forum Co-Chair
New England Journal of Medicine

11:00–11:15 Breakout A Report and Discussion
Robert Califf, Duke University Medical Center

[2] Since the workshop, Dr. Campbell joined the Foundation for the National Institutes of Health (FNIH) as Executive Director and CEO.

11:15–11:30 **Breakout B Report and Discussion**
William Potter, Merck Research Labs

11:30–11:45 **Breakout C Report and Discussion**
Renzo Canetta, Bristol-Myers Squibb

11:45–12:00 **Breakout D Report and Discussion**
Carla Greenbaum, Benaroya Research Institute

12:00–12:15 Discussion/Next Steps

12:15–12:30 **Closing Remarks and Adjournment**

GAIL CASSELL
Drug Forum Co-Chair
Eli Lilly and Company

Appendix B

Participant Biographies

Barbara Alving, M.D., MACP, is the Director of the National Center for Research Resources (NCRR), which funds the development of new technologies for basic and clinical research, supports training for researchers in the biomedical sciences, develops preclinical models, and provides health and biomedical education for the public. The NCRR is responsible for developing the new Clinical and Translational Science Award (CTSA) program that has evolved from the NIH Roadmap initiative to re-engineer clinical research. Dr. Alving received her M.D. cum laude from Georgetown University School of Medicine in Washington, DC. After an internship in internal medicine at Georgetown University Hospital, she completed a residency in internal medicine and a fellowship in hematology at the Johns Hopkins University Hospital in Baltimore, MD. Dr. Alving then became a research investigator in the Division of Blood and Blood Products at the Food and Drug Administration on the NIH campus. In 1980, she joined the Department of Hematology and Vascular Biology at the Walter Reed Army Institute of Research and became Chief of the Department in 1992. She left the Army at the rank of Colonel in 1996 to become the Director of the Medical Oncology/Hematology Section at the Washington Hospital Center in Washington, DC. In 1999, she joined the National Heart, Lung, and Blood Institute (NHLBI), serving as the Director of the extramural Division of Blood Diseases and Resources until becoming the Deputy Director of the Institute in September 2001. From September 2003 until February 1, 2005, she served as the Acting Director of the NHLBI. From October 2002 until January 2006, she served as the Director of the Women's Health Initiative, which is funded through the NHLBI. In March 2005, she became

the Acting Director of NCRR and was named Director in April 2007. Dr. Alving is a Professor of Medicine at the Uniformed Services University of the Health Sciences in Bethesda, a Master in the American College of Physicians, a former member of the subcommittee on Hematology of the American Board of Internal Medicine, and a previous member of the FDA Blood Products Advisory Committee. She is a co-inventor on two patents, has edited three books, and has published more than 100 papers in the area of thrombosis and hemostasis.

Linda Brady, Ph.D., serves as the Director of the Division of Neuroscience and Basic Behavioral Science at the National Institute of Mental Health (NIMH). During the past 10 years, she has administered programs in the areas of neuropharmacology, drug discovery, and clinical therapeutics and served as a coordinator for the discovery and preclinical development of novel imaging agents and pharmacologic ligands as research tools for use in pathophysiological studies and in drug development. Dr. Brady has organized consortia focused on ways to accelerate the development and clinical application of low-mass, high-specificity radiotracers in clinical research and drug development. She has spearheaded many programs, including: Development and Application of PET and SPECT Ligands for Brain Imaging Studies, National Cooperative Drug Discovery Groups for the Treatment of Mood Disorders and Nicotine Addiction, and has been actively involved in the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia), and TURNS (Treatment Units for Research on Neurocognition in Schizophrenia) programs. Dr. Brady serves as co-lead for the Molecular Libraries and Imaging Roadmap, a trans-NIH initiative to provide biomedical researchers access to small organic molecules that can be used as chemical probes to study the functions of genes, cells, and biochemical pathways. Dr. Brady has received NIH Director's Awards and NIH Merit Awards, in recognition of her activities in biomarker development, drug development for mental disorders, and the molecular libraries roadmap, as well as an outstanding supervisor award from NIMH.

Robert Califf, M.D., was born in Anderson, South Carolina, in 1951 and attended high school in Columbia, SC, where he was a member of the 1969 AAAA South Carolina Championship basketball team. He graduated from Duke University, summa cum laude and Phi Beta Kappa, in 1973 and from Duke University Medical School in 1978, where he was selected for Alpha Omega Alpha. He performed his internship and residency at the University of California at San Francisco and his fellowship in cardiology at Duke University. He is board-certified in internal medicine (1984) and cardiology (1986) and is a Master of the American College of Cardiology (2006). He

is currently Vice Chancellor for Clinical Research, Director of the Duke Translational Medicine Institute (DTMI), and Professor of Medicine in the Division of Cardiology at the Duke University Medical Center in Durham, North Carolina. For 10 years he was the founding Director of the Duke Clinical Research Institute (DCRI), the premier academic research organization in the world. He is the Editor-in-Chief of Elsevier's *American Heart Journal,* the oldest cardiovascular specialty journal. He has been author or coauthor of more than 800 peer-reviewed journal articles and a contributing editor for theheart.org, an online information resource for academic and practicing cardiologists. He was recently acknowledged as one of the 10 most cited authors in the field of medicine by the Institute for Scientific Information (ISI). Dr. Califf led the DCRI for many of the best-known clinical trials in cardiovascular disease. With an annual budget of over $100 million, the DCRI has more than 1,000 employees and collaborates extensively with government agencies, the medical-products industry, and academic partners around the globe in all therapeutic areas. In cooperation with his colleagues from the Duke Databank for Cardiovascular Disease, Dr. Califf has written extensively about the clinical and economic outcomes of chronic heart disease. He is considered an international leader in the fields of health outcomes, quality of care, and medical economics. Dr. Califf's role as Director of the Duke Translational Medicine Institute, which is funded in part by an NIH Clinical and Translational Science Award (CTSA), includes service as Co-Chairman of the Principal Investigators Steering Committee of the CTSA. Dr. Califf has served on the Cardiorenal Advisory Panel of the U.S. Food and Drug Administration (FDA) and the Pharmaceutical Roundtable of the Institute of Medicine (IOM). He served on the IOM committees that recommended Medicare coverage of clinical trials as well as the removal of ephedra from the market and on the IOM's Committee on Identifying and Preventing Medication Errors. He is currently a member of the IOM Forum in Drug Discovery, Development, and Translation and a subcommittee of the Science Board of the FDA. He was the founding director of the coordinating center for the Centers for Education & Research on Therapeutics™ (CERTs), a public–private partnership among the Agency for Healthcare Research and Quality, the FDA, academia, the medical-products industry, and consumer groups. This partnership focuses on research and education that will advance the best use of medical products. He is now the Co-Chairman of the Clinical Trials Transformation Initiative (CTTI), a public–private partnership focused on improving the clinical trials system. Dr. Califf has been married to Lydia Carpenter since 1974, and they have three children—Sharon Califf Boozer, a graduate of Elon College; Sam, a graduate student at the University of Colorado–Boulder; and Tom, a recent graduate of Duke University—and one grandchild. Dr. Califf enjoys golf, basketball, and listening to music.

Scott Campbell, Ph.D., received his Ph.D. in basic biomedical sciences in 1985. He spent 16 years in academia where his primary area of research interest was hypertension, heart failure, and the renin-angiotensin system. He is the author of 36 peer-reviewed articles, 8 invited reviews, and 14 book chapters. Dr. Campbell joined the American Diabetes Association in 2001 as National Vice President of Research Programs. In addition to overseeing all research-related programs at the ADA, he is also responsible for helping acquire major donations to the ADA Research Foundation. In 2010, Dr. Campbell joined the Foundation for the National Institutes of Health (FNIH) as Executive Director and CEO.

Renzo Canetta, M.D., Vice President, Oncology Global Clinical Research, Bristol-Myers Squibb Company, Research and Development, Wallingford, Connecticut. During his early years at the Istituto Nazionale Tumori in Milan, Italy (1974–1980), Dr. Canetta's focus was on clinical trials in lymphomas and gastrointestinal tumors, among others. Since joining Bristol-Myers Squibb (BMS) in 1980, Dr. Canetta has held numerous roles of increasing responsibility and leadership, including head of clinical cancer research; head of development, life cycle management; and, currently, as vice president, oncology global clinical research. His experience can be summarized with the introduction of 16 new BMS chemical entities and the approval of over 50 regulatory dossiers for additional indications/formulations, including some outside of oncology. Education: Universita' degli Studi, Milan, Italy. Graduate, Medicine and Surgery (M.D.), 1976. Instituto Nazionale Tumori, Milan, Italy, State certification, clinical oncology, 1977. Universita' degli Studi, Milan, Italy. Board Certification, Clinical and Laboratory Hematology, 1979. Area of expertise: cancer patient care, diagnosis and experimental treatment of hematologic malignancies and solid tumors, methodology of clinical trials, and new drug development.

Christopher P. Cannon, M.D., Senior Investigator, TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital, Associate Professor of Medicine, Harvard Medical School, Boston, Massachusetts. Dr. Cannon is a senior investigator in the Thrombolysis in Myocardial Infarction (TIMI) Study Group, leading trials such as TACTICS-TIMI 18, PROVE IT-TIMI 22, and CLARITY-TIMI 28. He earned his M.D. from Columbia University College of Physicians and Surgeons in New York, and after completing his residency in internal medicine at Columbia Presbyterian Medical Center, he was a cardiovascular fellow at Brigham and Women's Hospital. Dr. Cannon has published over 500 original articles, reviews, book chapters, and electronic publications on the topic of acute coronary syndromes, including works in *Circulation*, *Journal of the American College of Cardiology*, *Lancet*, and the *New England Journal of*

Medicine. He has received numerous awards, including the Alfred Steiner Research Award, and the Upjohn Achievement in Research Award, and he serves as Chairman for several ACC and AHA committees. He is Editor-in-Chief of the ACC's website, *Cardiosource* (www.cardiosource.com) as well as the journal *Critical Pathways in Cardiology* and a 40-book series *Contemporary Cardiology*. He has authored or edited seven books, including the *New Heart Disease Handbook* for patients.

Gail H. Cassell, Ph.D., is currently Vice President, Scientific Affairs, and Distinguished Lilly Research Scholar for Infectious Diseases, Eli Lilly and Company, Indianapolis, Indiana. She is former Charles H. McCauley Professor and Chair of the Department of Microbiology, University of Alabama Schools of Medicine and Dentistry at Birmingham, a department that ranked first in research funding from the National Institutes of Health (NIH) during the decade of her leadership. She obtained her B.S. from the University of Alabama in Tuscaloosa and in 1993 was selected as one of the top 31 female graduates of the twentieth century. She obtained her Ph.D. in microbiology from the University of Alabama at Birmingham and was selected as its 2003 Distinguished Alumnus. She is past President of the American Society for Microbiology (the oldest and single largest life sciences organization, with a membership of more than 42,000). She was a member of the NIH Director's Advisory Committee and of the Advisory Council of the National Institute of Allergy and Infectious Diseases. She was named to the original Board of Scientific Councilors of the Center for Infectious Diseases, Centers for Disease Control and Prevention (CDC), and served as chair of the board. She recently served a 3-year term on the advisory board of the director of CDC and as a member of the Secretary of Health and Human Services' Advisory Council of Public Health Preparedness. Currently, she is a member of the Science Board of the U.S. Food and Drug Administration (FDA). Since 1996, she has been a member of the U.S.–Japan Cooperative Medical Science Program, responsible for advising the respective governments (U.S. State Department/Japanese Ministry of Foreign Affairs) on joint research agendas. She has served on several editorial boards of scientific journals and has authored more than 250 articles and book chapters. Dr. Cassell has received national and international awards and an honorary degree for her research in infectious diseases. She is a member of the Institute of Medicine (IOM) and is currently serving a 3-year term on the IOM Council, the institution's governing board. Dr. Cassell has been intimately involved in the formulation of science policy and legislation related to biomedical research and public health. For 9 years she was Chair of the Public and Scientific Affairs Board of the American Society for Microbiology; she has served as an advisor on infectious diseases and indirect costs of research to the White House Office of Science

and Technology Policy, and has been an invited participant in numerous congressional hearings and briefings related to infectious diseases, antimicrobial resistance, and biomedical research. She has served two terms on the Liaison Committee on Medical Education (LCME), the accrediting body for U.S. medical schools, as well as other national committees involved in establishing policies on training in the biomedical sciences. She recently completed a term on the Leadership Council of the School of Public Health of Harvard University. Currently, she is a member of the Executive Committee of the Board of Visitors of Columbia University School of Medicine, the Executive Committee of the Board of Directors of the Burroughs Wellcome Fund, Research!America, and the Advisory Council of the Johns Hopkins School of Nursing.

Jeffrey M. Drazen, M.D., was born in Missouri. He attended Tufts University, with a major in physics, and Harvard Medical School, and served his medical internship at Peter Bent Brigham Hospital in Boston. Thereafter, he joined the Pulmonary Divisions of the Harvard hospitals. He served as Chief of Pulmonary Medicine at the Beth Israel Hospital, Chief of the combined Pulmonary Divisions of the Beth Israel and Brigham and Women's Hospitals, and finally as the Chief of Pulmonary Medicine at Brigham and Women's Hospital. Through his research, he defined the role of novel endogenous chemical agents in asthma. This led to four new licensed pharmaceuticals for asthma with over 5 million people on treatment worldwide. In 2000, he assumed the post of Editor-in-Chief of the *New England Journal of Medicine*. During his tenure, the Journal has published major papers advancing the science of medicine, including the first descriptions of SARS and papers modifying the treatment of cancer, heart disease, and lung disease. The Journal, which has over a million readers every week, has the highest impact factor of any journal publishing original research.

Judith E. Fradkin, M.D., is Director of the Division of Diabetes, Endocrinology, and Metabolic Diseases in the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) at the National Institutes of Health. In her 30-year career at NIDDK, Dr. Fradkin has created or directed a diverse array of high-impact clinical and basic research programs, including multi-centered clinical trials to evaluate new approaches to prevent and treat diabetes and its complications, scientific consortia to define the genetic and environmental triggers of diabetes, and diabetes research centers. She came to NIDDK as a clinical associate in 1979 after an endocrinology fellowship at Yale University. Dr. Fradkin graduated from Harvard College, earned her M.D. from the University of California at San Francisco in 1975, and completed an internship and residency at Harvard's Beth Israel Hospital in Boston. In addition to her oversight of major biomedical research

programs, she serves as an endocrinology consultant at the National Naval Medical Center in Bethesda, MD. Dr. Fradkin is the 2003 recipient of the American Medical Association's Dr. Nathan Davis Award for outstanding public service in the advancement of public health.

Mikhail Gishizky, Ph.D., has more than 25 years experience in research and development within the academic, biotechnology and pharmaceutical industry settings where he led efforts in the development of revolutionary signal transduction inhibitor drugs for the treatment of cancers and other diseases. Dr. Gishizky has been instrumental in establishing two biotechnology companies (SUGEN, Entelos) whose technology is helping bring the promise of personalized medicine to the patient's bedside. Most recently, as the Chief Scientific Officer at Entelos, Dr. Gishizky supervised the development of capabilities and scientific programs that employ computer simulation models to identify patient populations who would benefit most from new medicines and combination therapies. Use of these capabilities result in faster and more cost effective drug development programs by helping drug developers predict patient responses prior to initiation of therapy, thus helping physicians optimize the beneficial outcome and minimize the risk to the patient. Dr. Gishizky has been a member of the Institute of Medicine's Forum on Drug Discovery, Development, and Translation since 2005. Earlier in his career, Dr. Gishizky held positions of increasing management responsibility at SUGEN, Pharmacia, and Pfizer as Vice President and Research Zone Head, developing targeted therapies and signal transduction pathway analysis tools to identify patients most likely to respond to given therapies (i.e., Sutent, a leader in the class of signal transduction inhibitors marketed by Pfizer). Dr. Gishizky received his degree in endocrinology at the University of California, San Francisco where his work focused on defining the molecular mechanisms responsible for the development and progression of diabetes mellitus. Dr. Gishizky's post-doctoral training and academic work focused on cancer biology, hematopoietic cell development. His research led to the development of in vitro systems and an animal model for human chronic myeloid leukemia that was instrumental in the development of Gleevec. Dr. Gishizky has published extensively in the areas of diabetes mellitus and oncology research. During his tenure within the biotech/pharma industry Dr. Gishizky has led research efforts across a broad range of therapeutic areas including oncology, immunology, inflammation, CNS, and metabolic diseases.

Carla J. Greenbaum, M.D., is a Member of the Benaroya Research Institute, where she serves as the Director of the Diabetes Program and the Clinical Research Center and is on the Institutional Review Board. She received her undergraduate (1978) and medical (1981) degrees at Brown University, and

completed her endocrinology fellowship at the University of Washington. Dr. Greenbaum is a leader in clinical investigations and trials to prevent or intervene with the diabetes autoimmune process. She currently serves as Vice-Chair of Type 1 Diabetes TrialNet, an NIH-sponsored international consortium to conduct multiple clinical trials in type 1 diabetes. In this role, she is responsible for protocol development and clinical issues study wide. Dr. Greenbaum serves as Director of the North American Network of the Type 1 Diabetes Genetics Consortium and is principal or collaborating investigator on clinical trials for the NIH-sponsored Immune Tolerance Network, Type 1 Diabetes TrialNet, as well as Phase I/II pharmaceutical trials. She also conducts investigator-initiated clinical research in translational and human immunology with a focus on autoimmunity. Dr. Greenbaum is an Associate Editor of the journal, *Diabetes Care*, and a member of the University of Washington's CTSA leadership group. She serves on various national and international scientific review committees focusing on clinical and translational research. Currently, Dr. Greenbaum is on the board of directors for the Washington State American Diabetes Association and the Benaroya Research Institute.

Paul C. Hébert, M.D., FRCPC, MHSc, is a Critical Care Physician at the Ottawa Hospital and a Senior Scientist in the Clinical Epidemiology Program at the Ottawa Health Research Institute (OHRI). He also holds the rank of Full Professor in the Department of Medicine (Critical Care) at the University of Ottawa, with cross-appointments to the Departments of Anesthesiology and Surgery as well as Epidemiology & Community Medicine. During his 16 years on the faculty at the University of Ottawa, Dr. Hébert established the Clinical Epidemiology Program at the General Campus of the Ottawa Hospital (1998) and the University of Ottawa Centre for Transfusion Research (1999). In his role as Vice-Chair of Research from 2003 to 2007, he was responsible for the overall strategic direction of research for the Department of Medicine at the University of Ottawa. Among other awards, Dr. Hébert was honored with the "Researcher of the Year Award" from the OHRI (2001) and also received a "Premier's Research Excellence Award" from the Ontario Ministry of Health and Long-Term Care (2002). On January 2, 2007, Dr. Hébert was appointed Editor-in-Chief of the *Canadian Medical Association Journal* (CMAJ). Dr. Hébert's research interests center on the examination of transfusion practice (when and what to transfuse), including the use of alternatives to transfusion, blood conservation and resuscitation fluids, as well as on cardiac resuscitation and trauma. He led a groundbreaking trial titled Transfusion Requirements in Critical Care (TRICC), which was published in the *New England Journal of Medicine*. This trial showed that patients treated aggressively with trans-

fused blood had a greater rate of organ failure and a higher rate of death during hospitalization than patients whose doctors waited to order a transfusion. As a result, this trial has impacted how clinicians approach blood transfusions worldwide and has generated a significant research agenda around the world. Based upon this seminal trial, Dr. Hébert has undertaken more than 30 research projects with a focus on transfusion practice and bleeding control. To date, he has published in excess of 200 articles, obtained a large number of peer-reviewed grants (with a combined value in excess of $31 million) and trained and mentored numerous individuals. He continues to participate on national peer-review panels, including Canadian Institutes of Health Research (CIHR), National Sciences and Engineering Research Council of Canada (NSERC), and Canada Foundation for Innovation panels. Dr. Hébert is also leading the National Strategy on Patient-Oriented Research (NSPOR), an initiative to set up a new patient-oriented clinical research program for Canada through CIHR. This is a part-time role in addition to his other roles.

Peter K. Honig, M.D., M.P.H., joined AstraZeneca as Head of Global Regulatory Affairs in 2010. Dr. Honig served as Executive Vice President for Worldwide Regulatory Affairs and Product Safety within Development at Merck Research Laboratories since March of 2002. In this role, he is responsible for Global Regulatory Affairs, Worldwide Product Safety and Quality Assurance, Preclinical Pharmacology/Toxicology as well as Worldwide OTC Development. He is former Director of Office of Drug Safety in the FDA's Center for Drug Evaluation and Research (CDER). He received his baccalaureate, medical, and public health degrees from Columbia University in New York. He has post-graduate training and is board certified in internal medicine and clinical pharmacology and is a Fellow of the American College of Physicians (FACP). Dr. Honig retains faculty appointments at the Uniformed Services University of the Health Sciences and Georgetown University Medical School. He recently served as President-Elect of the American Society of Clinical Pharmacology and Therapeutics (ASCPT) and has previously served as a Vice President and Chair of its section on Pharmacoepidemiology, Drug Safety, and Outcomes Research. He is the PhRMA representative to the International Conference on Harmonization (ICH) Steering Committee. Dr. Honig joined CDER as a medical officer in the Division of Oncology and Pulmonary Drug Products in 1993. He also served as the FDA representative to the CERTs Steering Committee (Centers for Education and Research on Therapeutics), CDER liaison to the Harvard Clinical Investigators fellowship training program and CDER representative to the MedDRA Management Board , Maintenance and Support Services Organization (MSSO) and the ICH E2B Expert Working Group.

Steven E. Kahn, MB, ChB, is a Professor of Medicine in the Division of Metabolism, Endocrinology, and Nutrition at the University of Washington and VA Puget Sound Health Care System in Seattle. Additionally, he is Associate Director of the Diabetes Endocrinology Research Center at the University of Washington. Dr. Kahn's research interests include islet β-cell function in normal subjects and the pathogenesis of hyperglycemia in patients with type 2 diabetes. He has also done extensive work on the role of islet amyloid in the pathogenesis of the islet lesion in type 2 diabetes. He continues to be actively involved in two NIH clinical trials—Diabetes Prevention Program Outcomes Study and Look AHEAD—and in A Diabetes Outcome Progression Trial (ADOPT), which he has co-chaired. Among his awards are the Herman Ostrum Memorial Award, the Dana Foundation Feasibility Award, the Novartis Award in Diabetes, the American Diabetes Association Distinguished Clinical Scientist Award, and the R.H. Williams–Rachmiel Levine Award. He has been elected to membership in the American Society for Clinical Investigation and the American Association of Physicians. He has been a member of the National Council of the American Federation of Medical Research (AFMR) and the board of directors of the American Diabetes Association. He currently serves as Deputy Editor of the *Journal of Clinical Endocrinology and Metabolism*.

Amir Kalali, M.D., is currently Vice President, Medical and Scientific Services, and Global Therapeutic Team Leader CNS, at Quintiles, Inc., focusing on developing novel compounds for the treatment of disorders of the central nervous system (CNS). He is globally responsible for the medical and scientific aspects of development programs in psychiatry and neurology. He is also Professor of Psychiatry at University of California, San Diego. He was the Founding Chairman of the Executive Committee of the International Society for CNS Drug Development (ISCDD), and currently the Executive Secretary. Dr. Kalali is also Chair of the Membership Committee of the International Society for CNS Clinical Trials and Methodology (ISCTM), as well as a member of the Scientific Committee. In these roles he is active in facilitating scientific collaboration between academia, government, and pharmaceutical industry scientists. Dr. Kalali received his M.D. from the University of London, United Kingdom. He completed his psychiatry training at University College and Middlesex School of Medicine, London University. He was then appointed to a clinical research faculty position at the University of California, Irvine, where he also held several positions, including Director of the Mood and Anxiety Disorders Clinical Research Program and the Director of the Consultation-Liaison Psychiatry Program at the Clinical Cancer Research Center. He was also involved as an investigator on several NIH center research programs, including the Center for Neuropathological and Genetic Abnormalities in Depression and the Center

for Neuroscience and Schizophrenia, investigating neurobiological brain abnormalities in schizophrenia. Dr. Kalali has been an academic investigator in over 70 psychopharmacological clinical trials and at Quintiles has had medical and scientific responsibility for more than 200 clinical trials. He is an expert in CNS clinical trial methodology, including clinical rating scales, and has trained investigators from over forty countries. Dr. Kalali is the Editor of the journal *Psychiatry*, and is on the editorial board of several other journals. He has published widely in journals such as the *Archives of General Psychiatry*, the *American Journal of Psychiatry*, and the *British Journal of Psychiatry*. Dr. Kalali regularly presents at national and international scientific meetings, and lectures frequently on psychopharmacological and drug development topics. He is particularly interested in educating clinicians worldwide, and is facilitating this currently by being the Chairman of the Educational Committee of the Collegium Internationale Neuro-Psychopharmacologicum (CINP). Dr. Kalali is an active member of the scientific advisory boards of many pharmaceutical companies and sits on the board of directors of Cypress Bioscience. In 2005, 2006, and 2008 *PharmaVOICE* magazine named Dr. Kalali as one its 100 most inspiring leaders in the life sciences. Dr. Kalali is an active member of many professional societies, including the American Association for the Advancement of Science, the American Association of Pharmaceutical Physicians, the American Society for Clinical Psychopharmacology, the American Psychiatric Association, the Canadian College of NeuroPsychopharmacology, the Collegium Internationale Neuro-Psychopharmacologicum, the Drug Information Association, the International Society for CNS Drug Development, the International Society for CNS Clinical Trials and Methodology, the Royal College of Psychiatrists, United Kingdom, and the Society for Neuroscience.

Ronald L. Krall, M.D., holds a B.A. in mathematics from Swarthmore College and an M.D. from the University of Pittsburgh and completed his training in neurology and a fellowship in clinical pharmacology at the University of Rochester. Over 25 years in the pharmaceutical industry, Dr. Krall worked for four companies (Lorex Pharmaceuticals, Abbott Laboratories, Zeneca/AstraZeneca, and GlaxoSmithKline), holding a variety of positions responsible for drug development and safety of medicines. He concluded his career as Senior Vice President and Chief Medical Officer for GlaxoSmithKline. Over his career he has overseen in some capacity the development of over 20 medicines, including: Ambien; Hytrin for benign prostatic hypertrophy; Depakote for migraine and bipolar disorder; Nolvadex, Arimidex, and Faslodex for breast cancer; Seroquel; Accolate; Diprivan; Iressa; Tykerb; and Entereg. Dr. Krall is a member of the Executive Board of the Observational Medical Outcomes Partnership and of the

Advisory Board of the University of Pennsylvania Center for Bioethics. He also serves as a consultant to Frazier Healthcare Ventures.

Clifford Lane, M.D., Clinical Director, National Institute of Allergy & Infectious Diseases, National Institutes of Health (NIH). H. Clifford Lane, a native of Detroit, Michigan, received his M.D. degree from the University of Michigan in 1976. He then completed an internship and residency at the University of Michigan Hospital, Ann Arbor, MI. In 1979, Dr. Lane came to NIH as a Clinical Associate in the Laboratory of Immunoregulation (LIR) at the National Institute of Allergy & Infectious Diseases (NIAID). In 1985, he was appointed Deputy Clinical Director, NIAID and in 1989, he became the Chief of the Clinical and Molecular Retrovirology Section (CMRS) of the LIR, a position he still holds. In 1991, Dr. Lane became Clinical Director of NIAID and in 2006, Director of the Division of Clinical Research and Deputy Director for Clinical Research and Special Projects.

Michael Lauer, M.D., FACC, FAHA, joined the National Heart, Lung, and Blood Institute (NHLBI) in July 2007 as Director of the Division of Prevention and Population Science; he now also serves as the Director of the Division of Cardiovascular Diseases. A board certified cardiologist, he received his M.D. from Albany Medical College in 1985 and underwent post-graduate training within the Harvard University system at Massachusetts General Hospital, Boston Beth Israel Hospital, the Harvard Graduate School of Education, and the Harvard School of Public Health. After completing specialized research training in cardiovascular epidemiology at the Framingham Heart Study, he joined the cardiovascular medicine staff of the Cleveland Clinic in 1993. During 14 years at the Clinic, he established a world-renowned clinical epidemiology research program with primary focus on diagnostic testing and comparative effectiveness. His research led to more than 200 publications in major medical journals (including the *New England Journal of Medicine, JAMA, Lancet,* and *Annals of Internal Medicine*), grant support from the American Heart Association and the National Institutes of Health, and election to the American Society of Clinical Investigation. Dr. Lauer has served as Contributing Editor for *JAMA*, Co-Director of the Cleveland Clinic Coronary Care Unit, Director of Cardiac Clinical Research, and as first Vice-Chair of the Cleveland Clinic IRB. He achieved distinction in medical education, leading the development of an award-winning clinical research curriculum at the newly founded Cleveland Clinic Lerner Medical College at Case Western Reserve University, where he was Professor of Medicine, Epidemiology, and Biostatistics. In November 2008, he was awarded the prestigious *Ancel Keys* lectureship at the annual meeting of the American Heart Association. In his current position at NHLBI, Dr. Lauer is leading a $1.5 billion per year research division that

oversees major programs in cardiovascular biology, translation, clinical research, epidemiology, and prevention.

Musa Mayer is a 20-year survivor, advocate, and author of three books on breast cancer, including *Advanced Breast Cancer: A Guide to Living with Metastatic Disease*. Her articles on breast cancer and advocacy frequently appear in magazines, newsletters, websites, and scientific journals, and she serves on a number of advisory and editorial boards, as well as steering committees for several clinical trials and registries. She frequently speaks and consults on advocacy and survivorship issues, and on advanced and metastatic breast cancer. As a teacher, Ms. Mayer has served as a faculty member and mentor in the National Breast Cancer Coalition's science training program, Project LEAD, as well as on the planning committee of the joint NCI-AACR-FDA-Duke University workshop, Accelerating Anti-Cancer Agent Development. As an independent advocate, she has worked with national and local breast cancer organizations, and has been a frequent keynote and plenary speaker at many conferences. Providing daily information and support online for women with advanced (metastatic) breast cancer on the largest Internet mailing list of its kind at www.bcmets.org has informed Ms. Mayer's work as a Patient Representative and Consultant for the FDA's Cancer Drug Development Program, enabling her to represent the patient perspective on a number of advisory committees at the FDA. She is currently serving as a member of the FDA's new Risk Communication Advisory Committee. In 2007, she completed work on "Understanding Evidence-Based Healthcare: A Foundation for Action," a six-module Web training course for advocates, developed with Dr. Kay Dickersin, Director of the U.S. Cochrane Center at Johns Hopkins, available free at www.cochrane.us. To date, over one thousand advocates and healthcare professionals from around the world have enrolled in this course. Ms. Mayer works as an advocate on a Department of Defense Center of Excellence grant on breast cancer and brain metastases, and in December 2007 launched a website for patients with brain metastases and their families at www.BrainMetsBC.org. In March 2008, Ms. Mayer offered a U.S. perspective at the first Africa Breast Cancer Conference, in Abuja, Nigeria, and has presented the global findings of a global survey of 900 metastatic breast cancer patients at the 2009 conference in Cairo, Egypt. Other projects include a needs assessment survey of women with advanced breast cancer for Living Beyond Breast Cancer, presented at the 2005 San Antonio Breast Cancer Symposium, at the American Psychosocial Oncology Society 2007 conference, and at the 2008 New Strategies in Breast Cancer Conference. Ms. Mayer also serves on the Institute of Medicine Forum on Drug Discovery, Development, and Translation. Her Web resource for women with advanced breast cancer can be found at www.AdvancedBC.org.

Jim McNulty is Vice President of Peer Support for the Depression and Bipolar Support Alliance (DBSA). McNulty collaborates with federal agencies and other organizations to develop recovery-oriented programs and to coordinate DBSA's federal policy initiatives. In Rhode Island, he serves as the President of DBSA MDDA-RI/Providence, where he has attended support group meetings for more than 20 years, and also as a board member of Mental Health Consumer Advocates of RI. Other positions that McNulty holds are Chair of the SAMHSA/CMHS National Advisory Council's Subcommittee on Consumer/Survivor Issues and board member of the American Association of Human Research Protection Programs (an accrediting body for research organizations). In addition, McNulty is a member of the APA's Task Force for the 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders*. McNulty's past positions include Director of the Office of Consumer Affairs for Rhode Island's Division of Behavioral Health as well as Director of Consumer & Recovery Services at Magellan Health Services. He has also served as President of the National Alliance on Mental Illness (NAMI) and as a member of the National Advisory Mental Health Council for the National Institute of Mental Health (NIMH).

Margaret M. Mooney, M.D., is the Chief of the Clinical Investigations Branch in the Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis, at the U.S. National Cancer Institute (NCI), National Institutes of Health (NIH). She was formerly the Interim Director of the Office of Evidence-Based Surgery at the American College of Surgeons in Chicago, Illinois. She received her medical degree from the University of Chicago Pritzker School of Medicine and her general surgical training at the Dartmouth-Hitchcock Medical Center in Lebanon, New Hampshire. She received board certification in surgery in 1997. She completed her surgical oncology fellowship training at the Roswell Park Cancer Institute in Buffalo, New York, where she was also a research fellow in the Department of Cancer Control and Epidemiology. Dr. Mooney also holds an M.S. degree in management from the Massachusetts Institute of Technology in Cambridge, Massachusetts. Dr. Mooney joined the U.S. National Cancer Institute in 2002 as Head of Gastrointestinal and Neuroendocrine Cancer Therapeutics in the Clinical Investigations Branch and was appointed Chief of the Clinical Investigations Branch in May 2009. As Chief of the Clinical Investigations Branch, she is responsible for the direction of the NIH Clinical Trials Cooperative Group Program. This program performs nearly all the phase III cancer treatment trials sponsored by NCI and is a primary vehicle for conducting large, definitive, practice-changing clinical trials. As branch chief, Dr. Mooney supervises a staff that collectively oversees, reviews, and coordinates more than 100 active phase III treatment trials in various cancer types.

William Z. Potter, M.D., Ph.D., Vice President, Translational Neuroscience, Merck Research Labs. Dr. Potter earned his B.A., M.S., M.D., and Ph.D. at Indiana University, after which he held positions of increasing responsibility and seniority over the next 25 years at the National Institutes of Health (NIH) focused on translational neuroscience. While at the NIH, Dr. Potter was widely published and appointed to many societies, committees, and boards; a role which enabled him to develop a wide reputation as an expert in psychopharmacological sciences and champion the development of novel treatments for central nervous system (CNS) disorders. Dr. Potter left the NIH in 1996 to accept a position as Executive Director and Research Fellow at Lilly Research Labs, specializing in the neuroscience therapeutic area and in 2004 joined Merck Research Labs as Vice President of Clinical Neuroscience, then the newly created position of Translational Neuroscience in 2006. His experience at Lilly and MRL in identifying, expanding, and developing methods of evaluating CNS effects of compounds in human brain cover state-of-the-art approaches across multiple modalities. These include brain imaging and cerebrospinal fluid proteomics (plus metabolomics) as well as development of more sensitive clinical, psychophysiological, and performance measures allowing a range of novel targets to be tested in a manner that actually addresses the underlying hypotheses. He has become a widely recognized champion for the position that more disciplined hypothesis testing of targets in humans is the best near term approach to moving CNS drug development forward.

Marc S. Sabatine M.D., M.P.H., is an Investigator in the Thrombolysis in Myocardial Infarction (TIMI) Study Group, an Associate Physician in Cardiovascular Medicine at Brigham and Women's Hospital, and an Assistant Professor of Medicine at Harvard Medical School. Dr. Sabatine graduated magna cum laude in biochemical sciences from Harvard College and received his medical degree magna cum laude from Harvard Medical School. He did his internal medicine residency and cardiology clinical fellowship at the Massachusetts General Hospital and his research fellowship at TIMI. He received an M.P.H. degree from the Harvard School of Public Health. Dr. Sabatine is an NIH R01-funded investigator whose research focuses on optimizing the treatment of patients with acute coronary syndromes through (1) clinical trials of novel pharmacotherapies, (2) application of proteomics and metabolomics for discovery of biomarkers for risk stratification, and (3) tailoring of therapy using pharmacogenetics. Dr. Sabatine has published extensively in these fields and has authored 100 original research articles. He has been awarded the American College of Cardiology Zipes Distinguished Young Scientist Award.

Jay S. Skyler, M.D., MACP, is currently a Professor of Medicine, Pediatrics, & Psychology, in the Division of Endocrinology, Diabetes, & Metabolism, Department of Medicine, University of Miami Miller School of Medicine, Miami, Florida. He served as Director of that Division from 2000 to 2004. He is Associate Director for Academic Programs, and Area Leader for Immunomodulation and Tolerance, at the Diabetes Research Institute, University of Miami. He was also Program Director of the University's General Clinical Research Center from 2001 to 2006. He is also an Adjunct Professor of Pediatrics at the Barbara Davis Center for Childhood Diabetes, University of Colorado at Denver. He is Chairman of the National Institutes of Health (National Institute of Diabetes and Digestive and Kidney Diseases)-sponsored Type 1 Diabetes TrialNet, an international network conducting clinical trials to prevent type 1 diabetes or interdict the type 1 diabetes disease process. His research interests are in clinical aspects of diabetes, particularly improving the care of type 1 diabetes through meticulous glycemic control, psychosocial and behavioral support, and immune intervention. He is widely acclaimed for developing "algorithms" for patient adjustment of insulin doses. He is a past President of the American Diabetes Association, the International Diabetes Immunotherapy Group, and the Southern Society for Clinical Investigation, and was a Vice-President of the International Diabetes Federation. He served as a member of the Endocrinology, Diabetes, and Metabolism Subspecialty Examining Board of the American Board of Internal Medicine, as Chairman of the Council of Subspecialty Societies of the American College of Physicians (ACP), and a member of the ACP Board of Regents. He was founding Editor-in-Chief of *Diabetes Care*, and currently is Scientific Editor of *International Diabetes Monitor* and Associate Editor of *Diabetes Technology & Therapeutics*.

Madhukar H. Trivedi, M.D., is currently a Professor and Chief of the Division of Mood Disorders in the Department of Psychiatry at the University of Texas Southwestern Medical Center at Dallas. He holds the Betty Jo Hay Distinguished Chair in Mental Health. Dr. Trivedi is an established efficacy and effectiveness researcher in the treatment of depression. Dr. Trivedi has focused his research on pharmacological, psychosocial, and other nonpharmacological treatments for depression. Dr. Trivedi has been a principal investigator in multiple clinical trials funded through the National Institute of Mental Health (NIMH) and the Texas Department of Mental Health. He has been involved with evidence-based depression guideline development since 1990, when he joined the Depression Guideline Panel of the Agency for Health Care Policy and Research (AHCPR). Dr. Trivedi has been the Director of the Depression Algorithm for the Texas Medical Algorithm Project (TMAP) since its inception. Dr. Trivedi has served as the chair of the Depression Work Group of the International Psychopharmacology Algorithm Project and as the scientific content expert for the San Antonio

Cochrane Center's evidence-based, AHCPR-funded efforts to update the Depression Guidelines. Dr. Trivedi spearheaded the rollout of best practices for the treatment of major depressive disorder (MDD) in various Mental Health and Mental Retardation (MHMR) centers across the state of Texas. Dr. Trivedi is also studying the effectiveness of treatments of depression in primary care. Dr. Trivedi is the Principal Investigator of the Depression Trials Network Combining Medications to Enhance Depression Outcomes (CO-MED) trial, which focuses on the use of specific antidepressant combinations to increase remission rates by treating a broader spectrum of depressed patients and by capitalizing on additive pharmacological effects. Dr. Trivedi is also Principal Investigator of three current NIMH grants titled CBASP Augmentation for Treatment of Chronic Depression (REVAMP), TReatment with Exercise Augmentation for Depression (TREAD), and Computerized Decision Support System for Depression (CDSS-D). Dr. Trivedi is also the Co-Principal Investigator of the Texas Node of the National Institute on Drug Abuse (NIDA)-funded Clinical Trials Network and was the Co-Principal Investigator of the NIMH-funded project titled Sequenced Treatment Alternatives to Relieve Depression (STAR*D). Dr. Trivedi has mentored multiple psychopharmacology post-doctoral fellows and research track residents over the past several years in Mood and Anxiety Disorders and is the Principal Investigator of an NIMH-funded post-doctoral T32 training program. Dr. Trivedi has received numerous awards including the Gerald L. Klerman Award from the National Depressive and Manic-Depressive Association Scientific Advisory Board-NDMDA and the Psychiatric Excellence Award from the Texas Society of Psychiatric Physicians-TSPP. Dr. Trivedi is or has been a member of several institutional review groups of the NIMH. Dr. Trivedi has published over 300 articles and book chapters related to the diagnosis and treatment of mood disorders.

Janet Woodcock, M.D., is the Director of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA). She also served as CDER Director from 1994 to 2005. Dr. Woodcock has held various positions within the Office of the Commissioner, FDA from October 2003–April 1, 2008. Prior to her 2008 reappointment to CDER, she served as Deputy Commissioner for Operations and Chief Operating Officer, where she was responsible for overseeing agency operations and cross-cutting regulatory and scientific processes. She previously served in other positions at the FDA, including Director, Office of Therapeutics Research and Review, and Acting Deputy Director, Center for Biologics Evaluation and Research. Dr. Woodcock received her M.D. from Northwestern Medical School, and completed further training and held teaching appointments at the Pennsylvania State University and the University of California, San Francisco. She joined the FDA in 1986.