Public Engagement and Clinical Trials: New Models and Disruptive Technologies: Workshop Summary

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PUBLIC ENGAGEMENT AND CLINICAL TRIALS

NEW MODELS AND DISRUPTIVE TECHNOLOGIES

WORKSHOP SUMMARY

Victoria Weisfeld, Rebecca A. English, and
Anne B. Claiborne, *Rapporteurs*

Forum on Drug Discovery, Development, and Translation

Board on Health Sciences Policy

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

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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:

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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.

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Acronyms

ACC	American College of Cardiology
ACTION	Analgesic Clinical Trials Innovation, Opportunities, and Networks
AHA	American Heart Association
CABG	coronary artery bypass graft
CBPR	community-based participatory research
CDER	FDA Center for Drug Evaluation and Research
CDRH	FDA Center for Devices and Radiological Health
CF	cystic fibrosis
CRO	contract research organization
CTSA	Clinical and Translational Science Awards
CTSN	Cardiothoracic Surgical Trials Network
CTTI	Clinical Trials Transformation Initiative
EHR	electronic health record
FDA	U.S. Food and Drug Administration
FURRThER	Families Undergoing Risk Reduction Through Educational Reinforcement
GIST	gastrointestinal stromal tumor
HRA	Health Research Alliance

IND	investigational new drug
IOM	Institute of Medicine
IRB	Institutional Review Board
LVAD	left ventricular assist device
NCATS	National Center for Advancing Translational Sciences
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NIMHD	National Institute on Minority Health and Health Disparities
PDUFA	Prescription Drug User Fee Act
PMA	premarket approval
RAIN	Rheumatoid Arthritis Investigational Network
REMATCH	Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure
STICH	Surgical Treatment for Ischemic Heart Failure
TEAR	Treatment of Early Aggressive Rheumatoid Arthritis
VA	U.S. Department of Veterans Affairs
WICER	Washington Heights/Inwood Informatics Infrastructure for Community-Centered Comparative Effectiveness Research

1

Introduction[1]

Experts believe well below half of medical treatments patients receive are supported by adequate scientific evidence (IOM, 2007). Discussions of health care quality over the past two decades increasingly have employed terms such as "evidence-based medicine" and "learning health care system." While these terms capture important concepts for professionals, they may come as a surprise to patients and the public, many of whom might assume medicine already *is* based on evidence and that the health system already *does* constantly learn of and implement new, better methods of treatment. Patients and the public might also believe that new therapies are tested in individuals similar to themselves (e.g., age, gender, race, ethnicity, disease state) when in reality there is a lack of diversity in clinical trial patient populations.

What the concepts of "evidence-based medicine" and "learning health care system" have in common is their reliance on the accumulation of medical knowledge based on science, not hope, and, further, that clinicians would take that knowledge out of the medical textbooks and laboratory notebooks and apply it in the care of individual patients and patient populations.

Clinical trials are the linking step that enables basic research findings to emerge at the patient's bedside and in physicians' examining rooms. The questions clinical trials seek to answer change over time, depend-

[1] The planning committee's role was limited to planning the workshop, and the workshop summary has been prepared by the workshop rapporteurs as a factual summary of what occurred at the workshop.

ing on advances in basic research and the population health problems they are intended to address. Potential new treatments must be tested in humans in order to find out whether they "work" and whether they cause harm (see Appendix B for an overview of the clinical trials process set forth in the workshop summary from an earlier Institute of Medicine [IOM] workshop in this workshop series). Clinical trials can comprise a series of rather elaborate steps, and the rationale for these trials may not be well understood by the public. An adequate infrastructure to support the efficient and effective conduct of the nation's clinical trials enterprise can help ensure that the system does not become too narrow a bottleneck, impeding the flow of discovery from science to practice.

Meanwhile, biomedical research is advancing rapidly, and certain significant problems in clinical trials have hindered their ability to keep pace with demands to translate discoveries into improved patient care. In short, as discussed at a 2009 workshop of the IOM's Forum in Drug Discovery, Development, and Translation, there is concern that "the current clinical trials enterprise in the United States is unable to produce the high-quality, timely, and actionable evidence needed to support a learning health care system" (IOM, 2010a). Among the broad categories of problems identified at that workshop were:

1. the length of time and high financial cost of clinical trials;
2. delays resulting from the many regulatory requirements for studies that involve human subjects;
3. the generally fragmented way clinical trials are prioritized and undertaken;
4. obstacles encountered within academic health centers;
5. lack of involvement of community physicians and their needs in the development and conduct of clinical trials; and
6. dwindling incentives for and attractions of a career as a clinical trial investigator.

A final significant problem cited at the 2009 workshop became the focus of this workshop: *the increasing difficulty of recruiting and retaining an appropriate human subject population for specific clinical trials*. As discussed at that meeting and in subsequent discussions of the IOM Forum, many clinical trials never recruit the number of people needed, and others accrue patients far too slowly, and the scale of need is substantial. In the United States in 2009, there were almost 11,000 clinical trials testing various medical interventions, mostly (59 percent) new drugs. Collectively, it was hoped these trials would enroll some 2.8 million people (IOM, 2010a).

In this workshop, titled "Public Engagement and Clinical Trials: New Models and Disruptive Technologies," the issue of participation in trials

was put in a large frame, with the more general problem seen as one of a lack of support for clinical trials by patients and families, by community leaders, by academic medical centers, and even by practicing physicians, who may not always seek out trials for their patients or encourage them to participate, and, in some cases, even discourage participation. Forum members have identified that successfully engaging these broad and diverse publics in the clinical trials enterprise is a substantial challenge.

The workshop covered the topics of recruiting and retaining people to serve as trial participants, increasing practicing clinicians' participation in and referrals to trials, and strengthening the public opinion climate in which clinical trials are carried out and, ultimately, brought into routine medical practice.

Workshop co-host Dennis Charney, Dean, Mount Sinai School of Medicine, set the tone for the meeting at its outset by saying that the ultimate success of his school and its new strategic plan will be based not on "how many papers we publish, or grants we get." Success, he said, will depend on the answer to the question, "Did we contribute to changing the practice of medicine for the better?" He added that a key element of that contribution will be the school's contribution to testing new medicines and therapies.

According to meeting chair Jeffrey Drazen, Editor-in-Chief, *New England Journal of Medicine*, testing medical treatments through clinical trials requires that people put themselves at risk. However, the evidence gained through successful clinical trials can ultimately reduce the uncertainty in medical decision making. Drazen pointed out that, several decades ago, the medical literature provided information on results of tests in very small groups of patients—10, 15, perhaps a hundred. Such small groups will show a therapeutic effect only if it is dramatic. For more subtle but meaningful effects and for refinements of existing treatments, a thousand, or even ten thousand, patients are needed for an effect to be apparent. Meanwhile, sophisticated statistical tools have been developed that enable much more refined hypothesis testing. Now, Drazen noted, the stumbling block is recruiting a sufficient number of patients for the trials themselves.

Medical progress needs more than a sound scientific idea that can be translated into clinical care in the form of an intervention, whether that is a drug, device, or behavioral intervention. Progress requires a population willing to put itself at risk. "The message of this meeting," Drazen said, "is that unless we can persuade more people to put themselves at risk, the rate at which we will be gathering knowledge will become smaller and smaller."

This is not easy, because it requires people to admit that the current medical system does not know the best answer to their problems. Drazen

commented that when patients say to him, "I don't want to be a guinea pig," he responds, "If I treat you based on what we know about your situation, you are a guinea pig anyway, because I don't know what works. At least this way, your therapy will teach us something." And, he adds, many other people may benefit from that knowledge in the future.

2

Framing the Problem

THE CURRENT LANDSCAPE OF CLINICAL TRIALS[1]

Over time U.S. investments in clinical research have grown substantially, despite the fact that the rate of increase in funding slowed between 2003-2007. Industry was the largest funder of biomedical research in 2008 ($38.4 billion) and within the public sector, the National Institutes of Health (NIH) invested $27.9 billion in biomedical research (Dorsey et al., 2010). The 2009 American Recovery and Reinvestment Act provided a one-time infusion of $1.1 billion in new funds for comparative effectiveness research, which includes pragmatic randomized trials;[2] and the 2010 Patient Protection and Affordable Care Act created a sizable trust fund to sustain this support.

Growth in funding and the ongoing rapid pace of scientific discovery have led to a major increase in the number of clinical studies, with

[1] This section of the summary is based on presentations by Deborah Ascheim, Associate Professor, Department of Health Evidence and Policy, Mount Sinai School of Medicine; Annetine Gelijns, Co-Chair, Department of Health Evidence and Policy, Mount Sinai School of Medicine; and Juan Lertora, Director, Clinical Pharmacology, NIH Clinical Center.

[2] *Explanatory* randomized trials generally measure the effects of a treatment (its efficacy) under ideal conditions, often using carefully selected individuals treated in a research setting. *Pragmatic* trials measure the effects of a treatment (its effectiveness) in the everyday clinical practice of community physicians, and their purpose is to provide information about the choice of treatments (Roland and Torgerson, 1998). Key features of pragmatic clinical trials include that they: (1) select clinically relevant alternative interventions to compare, (2) include a diverse population of study participants, (3) recruit participants from heterogeneous practice settings, and (4) collect data on a broad range of health outcomes (Tunis et al., 2003).

the number of randomized trials increasing 35 percent between 2005 and 2010.

The design, conduct, and analysis of clinical trials involves a broad range of public and private institutions, including academic medical centers, hospitals, community practices, pharmaceutical and medical device industries, voluntary health organizations, and contract research organizations (CROs). The NIH Clinical Center in Bethesda, Maryland, is a unique example of an organization wholly devoted to clinical trials. The Center conducts a robust program of intramural clinical trials, with more than 1,250 physicians and the bed capacity for 240 inpatients, all of whom are participants in one of the Center's more than 1,400 active research protocols. Most of the Center's intramural clinical trials are phase I or phase II research—that is, early, proof-of-concept studies, rather than later, confirmatory research, which is generally phases III and IV (see Appendix B: The Clinical Trials Process for definitions of phases 0 through IV).

Multiple Challenges to the Clinical Trials Enterprise

Despite increases in both funding and effort and an understanding of the requirements for successful clinical trials (see Box 2-1), the enterprise continues to falter, said Annetine Gelijns, Co-Chair, Department of Health Evidence and Policy, Mount Sinai School of Medicine. Some of the barriers to participation in clinical trials by key groups—patients, academic institutions, community physicians, and researchers themselves—and potential ways to overcome them are described in the succeeding paragraphs.

Barriers to Patient Recruitment

Clinical trials experience significant obstacles in patient recruitment.

BOX 2-1[a]
Elements for Successful Clinical Trials

- Well-defined clinical trial goals and target patient population
- Realistic patient accrual strategy
- Community outreach and education, *building trust*
- Community/patients advisory boards
- Well-informed community physicians and other health care professionals
- Effective patient retention strategy
- Protocol implementation support team

[a] Material presented by Juan Lertora, Director, Clinical Pharmacology, NIH Clinical Center.

For example, according to Gelijns, clinical trials funded by the National Cancer Institute encounter these stumbling blocks (IOM, 2010b):

- It can take more than 2 years from the time planning for a trial begins to enrollment of the first patient.
- The recruitment of qualified patients in clinical trials is often a slow process; insufficient patient recruitment can delay or cause a trial to be cancelled.
- Forty percent of trials end prematurely and are not published, a substantial waste of resources.
- Less than 5 percent of adult cancer patients are enrolled in clinical trials.
- Even fewer patients who are elderly, women, or minorities are enrolled.

As another example, trials involving a common cardiovascular disease, atrial fibrillation, also experience major issues in terms of slow accrual of patients. This holds for explanatory (phase I and II) trials and confirmatory (phase III) trials, but is perhaps even more salient for pragmatic trials that make head-to-head effectiveness and safety comparisons in a broad range of patients essential for developing the evidence base for everyday clinical decision making. Pragmatic trials are much less common than efficacy trials. The latter trials are clearly important to define the benefits of a novel intervention. However, the relative paucity of pragmatic trials has led to a situation where the evidence base underlying much of clinical practice is inadequate. A recent review of American College of Cardiology (ACC)/American Heart Association (AHA) guidelines found that a large proportion of recommendations in current cardiovascular guidelines were based on expert opinion or case studies, and not evidence from randomized clinical trials comparing therapies (Tricoci et al., 2009). According to Gelijns, factors contributing to problems in recruitment of both efficacy and effectiveness trials include

- lack of awareness among physicians and patients that relevant trials are available;
- lack of awareness of the benefits of engaging in clinical trials;
- maintaining clinical equipoise,[3] especially when treatment arms are very different and patients or physicians have strong preferences for one therapy over the other;

[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.

- maintaining equipoise is even harder for pragmatic trials as the treatment evaluated is typically available, and reimbursed for by payers, outside the clinical trial setting; and
- continued patient participation when the treatment is available outside the trial environment.

Gelijns noted that positive developments that may help overcome these barriers are

- greater collaboration between voluntary health organizations and clinical trial investigators to use centralized trial registries to reach out to patients with specific conditions and their physicians;
- outreach to community organizations (for example, the National Heart, Lung, and Blood Institute [NHLBI] has engaged in intensive community-based efforts to reach people with sickle cell disease);
- creation of user-friendly tools that can use data in the electronic health record (EHR) to identify eligible patients at the point of care;
- making the public aware that trial participants could receive superior care, as a result of increased follow-up and monitoring; and
- efforts to help people understand the current uncertainties about the relative benefits of various treatment options and the value that clinical trials provide to clinical decision making.

Weak Institutional Support

A number of disincentives to conducting clinical trials are found within academic medical institutions, Gelijns said, one result of which is a declining pipeline of new clinical investigators. Some of the reasons individuals do not pursue clinical investigation in the academic medical setting include

- economic disincentives such as inadequate reimbursement for trial activities and reduced time available to provide patient care;
- logistical disincentives that derive from a lack of infrastructure and support; and
- cultural disincentives, which manifest themselves in the decisions of tenure and promotion committees that often have a bias against clinical trials activity as a prestigious or beneficial academic pursuit.

Lack of Community Physician Involvement

There is also a lack of engagement on the part of community physicians. For example, the results of trials are often not generalizable

to the community physician's practice, as they are based on carefully selected patient populations and specialized delivery settings, Gelijns and Deborah Ascheim, Associate Professor, Department of Health Evidence and Policy, Mount Sinai School of Medicine, observed. However, Gelijns added, opportunities to create new partnerships and networks between academic and community-based physicians are being actively explored. Such networks could provide a "clinical laboratory" in which multiple trials can be conducted without having to create a new infrastructure for each individual trial. This structural approach would increase both the efficiency and the relevance of trials.

Another barrier for community physicians and patients, according to Gelijns, is a lack of third-party reimbursement for "experimental" therapies. More than a decade ago, Medicare agreed to cover the "routine care costs" for patients participating in qualified randomized trials (notably NIH-sponsored trials). However, private insurers' reimbursement policies remain highly variable. This constitutes a major obstacle to trial participation, according to Gelijns.

Trial Characteristics

Finally, some barriers to participation are inherent in the design of trials and are relevant to patients, researchers, and community physicians, said Gelijns. A review of more than 10,000 industry-sponsored trials found that the number and frequency of trial-related procedures such as laboratory tests or patient questionnaires has increased substantially over time (Getz et al., 2008). As the number and frequency of unique procedures patients must undergo have increased, and as the demands of protocol administration also have become much greater for investigators, Gelijns said, the resultant "trial execution burden" may be a major deterrent to participation for patients and potential researchers alike.

The analysis of trial results generally relies on statistical measures of "central tendency"—averages—and their strength, as measured by standard deviations and significance tests. An unavoidable weakness of this approach, Juan Lertora, Director, Clinical Pharmacology, NIH Clinical Center, commented, is that its generalizability is limited because the "real-world" patient population is heterogeneous, so results of a treatment are likely to be more scattered than in a study population of demographically and clinically similar individuals. Broadening analytic methods used in trials may make them more applicable to real-world populations and thus more useful for community physicians.

Innovations in trial design may simplify protocol design and speed the trials process, especially in the case of exploratory trials, said Gelijns. Such developments require close interaction between statisticians, inves-

tigators, and the Food and Drug Administration (FDA) to ensure they will generate evidence acceptable in the approval process. Gelijns concluded by noting that, while clinical trials are a critical link between scientific discovery and clinical practice and essential to ensuring that Americans reap the potential benefits of the nation's enormous investment in biomedical research, much can be done to improve the effectiveness of this system. She emphasized that a broad spectrum of stakeholders is involved in this process and will be critical to its success.

NIH Resources for Extramural and Intramural Researchers

Lertora noted that NIH can share with outside researchers some resources it has developed to support its own intramural clinical trials. These resources can facilitate protocol development and trial implementation for researchers who need support beyond what their home institutions can offer. Making such resources available is in line with the recommendation to have the Clinical Center open its doors to extramural investigators (NIH SMRB, 2010). Tools available to external researchers include the following:

- NIH Clinical Center staff developed a sophisticated computer-assisted protocol development tool called ProtoType[4] (Wanjek, 2008). The tool was created by NIH Clinical Center staff, including Philip Lightfoot, and with the support of Dr. Jon McKeeby and NIH Clinical Center Director, Dr. John Gallin. This web-based tool, 8 years in initial development and launched in 2008, allows for a standardized approach to protocol development, is flexible in terms of incorporating new "rules," increases the efficiency of Institutional Review Board (IRB) and scientific committee reviews, and creates a full protocol history. The paperless system can also import image libraries, reference databases, and so on. Furthermore, it supports collaboration and is helpful in training new investigators.
- A computer-based algorithm known as the "Investigational New Drug (IND) Wizard" is part of ProtoType and helps investigators determine whether an IND filing is required for protocol implementation, which is especially helpful for researchers investigating potential new indications for existing drugs ("drug repurposing").

[4] The ProtoType tool can be found at: https://prototype.cc.nih.gov/prototype10/contents/login/pw_login_screen.aspx (accessed October 10, 2011).

Intramural clinical investigators at the NIH Clinical Center are assisted by the NIH Office of Communications, Patient Recruitment, and Public Liaison regarding prescreening of potential patients, establishing contact with volunteers and physicians, and providing ongoing recruitment assistance. Another resource available to intramural investigators is the long-standing Clinical Center healthy volunteer program with a registry of over 50,000 people that serves as a source for control groups and for the study of basic human physiology, pathophysiology, and pharmacology.[5]

PANEL PRESENTATIONS AND DISCUSSION

"We need to create an environment in which the clinical study is no longer the patient's last resort, but the first resort, and participation in a clinical study becomes part of the standard of care."
—Angela Geiger, Alzheimer's Association

The workshop's first panel asked experts from diverse perspectives—regulators, payers, patients, and pharmaceutical companies—to comment on the problems and opportunities in clinical trials described in the opening presentations. Much of the discussion focused on drug development.

Clinical Trials and New Drug Development

At the outset, clinical trials' importance in the regulatory process was underscored by panelist Leslie Ball, Acting Director of FDA's Office of Scientific Investigations. Clinical trials produce the data that support FDA determinations whether a drug should be approved, and they determine what information will appear on the product label. While FDA regulations are designed to promote the public's health and protect people from unsafe, ineffective, or poor-quality drugs, the agency also has the mission of helping to speed innovations. As a result, according to Ball, FDA attempts to avoid rules and oversight practices that unintentionally introduce inefficiency and unnecessary resource use into the drug development process, and the agency recognizes that clinical researchers benefit from predictability all along the path of drug development: review, approval, and monitoring.

[5] Recently, a national registry for healthy volunteers for phase I clinical trials was proposed, in order to avoid overreliance on a small pool of individuals (some of whom treat trial participation, which pays from a few hundred to a few thousand dollars, as a profession). A limited volunteer pool poses excess risk to the individuals and may compromise a research study if treatment effects are confounded by recent exposure to another investigational agent (Resnik and Koski, 2011).

Evolution in clinical trials management is posing some new challenges for pharmaceutical manufacturers and regulators. Among them are trends toward globalization of clinical trials, recruitment of patients overseas, outsourcing trial components, and an increasing complexity of trial protocols. There is also a need to determine how best to integrate information from EHRs into a trial's analytic structure.

To create more efficiencies in this dynamic environment, Ball noted that FDA is engaged in efforts to

- increase dialogue among drug developers, academia, patients, and regulators;
- prioritize regulatory oversight activities and inspections based on evaluative assessments of risk and protocol implementation anomalies that really matter;
- foster a proactive quality risk management approach to the design, conduct, monitoring, data management, and reporting of clinical trials that builds quality in from the beginning of a trial's development;
- standardize and harmonize processes and regulations, both domestically and internationally;
- develop standards to facilitate use of EHRs in trials (Kush, 2011); and
- improve trial methodology through public-private partnerships (for example, the Clinical Trials Transformation Initiative [CTTI], https://www.trialstransformation.org/, and the Analgesic Clinical Trials Innovation, Opportunities, and Networks [ACTION] initiative).

One reason trials are increasingly difficult to conduct is that the U.S. standard of health care is generally high, commented Richard Murray, Head of Global Center for Scientific Affairs, Merck & Co. It is increasingly difficult to identify patients to participate in studies who have not yet had some type of treatment for their condition and, because new treatments are likely to represent only incremental improvements, large numbers of patients are needed to achieve statistical validity.

For the management of chronic diseases and conditions, studies may need to be relatively long in order to identify safety issues that could arise when a drug must be taken for months, years, or, possibly, a lifetime (IOM, 2011). Disadvantages of longer trials are that patients are harder to retain in the trial, the risk of investigator fatigue rises, and, from the manufacturer's point of view, the "clock is ticking" on the period of patent protection, said Murray.

According to Murray, recruitment barriers encountered include pub-

lic mistrust of clinical trials (and, in general, some mistrust of science and medicine by many Americans) and mistrust of the motives of the pharmaceutical industry. A horizon issue that might further erode trust, he said, is the use of foreign research subjects. This trend could be perceived as posing ethical problems, especially if the treatments being tested are not available in the overseas patients' own country.

Box 2-2 lists some of the principles and practices that workshop participants and discussants noted they have found helpful in recruiting and retaining patients in clinical trials. According to Greg Simon, Senior Vice President, Patient Engagement, Pfizer Inc., Pfizer has moved the "make it convenient" notion a large step forward with a new, online clinical trial, called REMOTE, which hopes to enroll about 600 patients in 10 states. The trial, which has FDA approval, will be testing a new drug and using mobile phone and Internet technology to facilitate participation, avoiding repeated visits to trial sites. Pfizer will compare results of this study to those of a similar traditional, center-based trial to determine whether

BOX 2-2[a]
Key Principles for Recruiting and Retaining People in Clinical Trials

- Develop a strong recruitment strategy involving community leaders.
- Start recruitment early—before time to start the trial.
- Respect local culture.
- Engage caregivers.
- Involve racially and ethnically diverse physicians in the recruitment process and in the trial itself (as a longer-term strategy, Merck has worked with the National Medical Association to increase clinical research training among African American physicians).
- Make it easier and more convenient for people to be part of the trial, through such practices as reducing the required number of blood draws and reimbursing for, or even arranging, travel.
- Give people credit for checking in and filling out some of their information remotely.
- Clearly explain the importance of the trial for the public's health, which makes it easier to overcome public skepticism and lack of understanding.

[a] Based on presentations by Carol Horowitz, Associate Professor, Department of Health Evidence and Policy, Mount Sinai School of Medicine; Robert Michler, Surgeon-in-Chief, Professor and Chairman, and Director, Center for Heart and Vascular Care at the Montefiore Medical Center/Albert Einstein College of Medicine; Richard Murray, Head of Global Center for Scientific Affairs, Merck & Co.; and Greg Simon, Senior Vice President, Patient Engagement, Pfizer Inc., and workshop discussions.

the mobile model can improve the access, timeliness, quality, and safety of its research.

A number of broader problems with the current clinical trials enterprise were described by Simon:

- Broken feedback loops. Trials produce knowledge that never reaches physicians, and physicians learn specifics about drug performance that never find their way back to researchers or become incorporated in future trials. Stronger feedback loops would help not only in identifying unexpected problems with a drug, but also in discovering unexpected positive outcomes.
- The need for greater coordination and data sharing among academia, government, clinicians, and industry, in order to encourage new innovation.
- Uncertain expectations regarding how much information is needed to get a drug to patients and what information should be collected once a drug reaches the market. Simon noted that even a 10,000-person trial cannot reveal how a drug will operate in millions of people.
- The need for increased funding for postmarketing surveillance, perhaps by allowing Prescription Drug User Fee Act (PDUFA) monies to be used for this purpose.[6]

In response to the discussion of whether private or public payers should increase their support for the clinical trials enterprise, Bruce Vladeck, Senior Advisor, Nexera, Inc., described the need for strong, meaningful trial standards to overcome the problem of trials of widely varying quality. He commented that criteria are needed to identify trials both of adequate scientific quality and sufficient importance, in terms of the public's health, to warrant public support. He also added that there needs to be strict compliance with research conflict-of-interest policies. Workshop participants discussed the respective roles of randomized clinical trials and observational studies in the generation of medical evidence and the assessment of a treatment's safety. Randomized clinical trials are useful for conditions that require small trials in subgroups of people with similar genetic mutations. In addition, randomized trials may still be the best way

[6] Enacted in 1992 and renewed in 1997 (PDUFA II), 2002 (PDUFA III), and 2007 (PDUFA IV), this law authorizes FDA to collect fees from companies that produce certain human drug and biological products and includes certain performance and other standards in connection with the regulatory process. In fiscal year 2010, FDA collected just under $552 million in PDUFA fees from manufacturers, and these fees provided more than 60 percent of financial support for the drug approval process (FDA, 2011a).

to assess the efficacy of new drugs, as opposed to providing a definitive safety assessment, Jeffrey Drazen, *New England Journal of Medicine,* said. Rare side effects or drug-drug interactions require time and large numbers of heterogeneous patients to discover. Because such events are relatively rare, Ball said, safety is being monitored through postmarketing surveillance that relies on patient registries and observational studies. FDA's Sentinel Initiative, for example, actively queries diverse automated health care data holders—EHR systems, administrative and insurance claims databases, registries, and the like—to track the safety of drugs, biologics, and medical devices once they reach the market (FDA, 2011b).

Patient Recruitment by Voluntary Health Organizations

Voluntary health organizations are proving effective in involving patients and the broader public in trials that involve relatively rare diseases for which cure remains unavailable. For example, there are only about 30,000 people living with cystic fibrosis (CF) in the United States. To reach this population, the Cystic Fibrosis Foundation has worked with the medical community to establish more than 110 CF care centers nationwide, about 80 of which now can conduct clinical trials, said Joan Finnegan Brooks, President, Patient-Focused Market Research, and a person with CF. This network has successfully reached out and engaged the CF community to participate in clinical trials, resulting in several new therapies to manage the disease.[7]

Similarly, the Alzheimer's Association has promoted patient involvement in clinical studies (Alzheimer's disease affects some 5.4 million Americans). The Alzheimer's Association's FY 2009-FY 2011 strategic plan explicitly includes patient participation in clinical studies as a part of the strategy to accelerate research progress. The Alzheimer's Association has taken a number of concrete steps in accord with this strategy, said Angela Geiger, Chief Strategy Officer, Alzheimer's Association. The organization has developed a health care provider outreach campaign to increase awareness of Alzheimer's trials, and in July 2010 it launched TrialMatch, a web- and telephone-based service that has connected more than 2,500 people with some of the 131 Alzheimer's clinical trials under way around the country, resulting in at least 115 people enrolled. Almost half of those who complete a TrialMatch profile are caregivers who say they "want to give something back" by participating in studies; the next biggest group is healthy volunteers. The desperation many patients and families feel

[7] Additional information on CF and the work of the Cystic Fibrosis Foundation can be found at: http://www.cff.org/.

makes them willing to participate in a trial, even if they understand it will not help them, said Geiger.

According to Simon, in an environment where scientists are many and trial participants are scarce, patient groups are starting to organize their own clinical trial networks and offer them to scientists, "because they realize their registries, their tissue banks, their biobanks, and their experience are the key resources."

3

Recruitment Challenges in Clinical Trials for Different Diseases and Conditions

"The one constant in trial recruitment is it will always change, and you must adapt." —Nina Bickell, Mount Sinai School of Medicine

The case studies in this chapter, which describe patient recruitment challenges for a range of medical conditions, illustrate the role of stakeholders' perspectives in shaping their engagement with the clinical trials enterprise. Several speakers noted that the stakeholders involved in clinical trials have unique points of view; for example, researchers are focused on answering the clinical question at hand as well as on their own career development, institutions guard their reputations and their resources, and referring physicians have multiple concerns that could include losing control of their patients' care, as well as, in some cases, professional liability. Many workshop presenters emphasized that patients worry about a great number of issues, their health being only one of them, and every aspect of a trial protocol that makes it harder to understand, less relevant to them, and less convenient diminishes the likelihood of participation.

CARDIOVASCULAR SURGERY[1]

From an institutional and investigator perspective, not meeting enrollment numbers in a timely way can cause a clinical trial to lose momentum and can lead to other negative conditions such as investigator burnout. In the worst cases, low enrollment can cause a trial to be

[1] This section is based on the presentation by Robert Michler, Surgeon-in-Chief, Professor and Chairman, and Director, Center for Heart and Vascular Care at the Montefiore Medical Center/Albert Einstein College of Medicine.

abandoned—a costly outcome that can harm the credibility of individual investigators and their institutions. The public and private organizations that fund trials look to a researcher's and an institution's prior history when making grant awards, and they take notice when investigators fail to meet their anticipated enrollment goals. From the investigator's perspective, then, patient recruitment is a significant responsibility and not doing it effectively may lead to frustration, institutional concern, and even embarrassment.

Three major clinical trials in which Robert Michler, Surgeon-in-Chief, Professor and Chairman, and Director, Center for Heart and Vascular Care at the Montefiore Medical Center/Albert Einstein College of Medicine, actively participated all involved patients with serious heart disease for which surgery was a treatment alternative: Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial, Surgical Treatment for Ischemic Heart Failure (STICH) trial, and NHLBI–funded Cardiothoracic Surgical Trials Network (CTSN).

REMATCH evaluated whether a left ventricular assist device (LVAD)[2] would reduce mortality compared to optimal medical management.[3] Trial participants, who were primarily Medicare patients, needed but were ineligible for heart transplants. REMATCH investigators hoped to show that an LVAD could reduce 2-year mortality by one-third to one-half, compared to optimal medical management. The investigators planned to enroll 140 patients over eight calendar quarters. After eight quarters, no more than 80 patients had been enrolled. Michler noted that enrolling centers could not meet the expense of this complex trial and the federal government would not provide additional funding to complete the study. Additional funding from the trial's industry sponsor helped the trial investigators complete the enrollment of 128 patients over 13 calendar quarters—suggesting the high cost and length of time it can take to achieve enrollment goals.

STICH, the largest surgical trial ever conducted, involving 2,135 patients enrolled in 127 sites across 26 countries, compared coronary bypass surgery with and without ventricular reconstruction of the left ventricle to optimal medical therapy in patients with significant heart

[2] An LVAD is a surgically implanted pump that helps pump blood from the heart's lower left chamber (the left ventricle) to the rest of the body.

[3] Optimal medical management included adherence to guidelines developed by a medical committee with the goals of optimizing organ performance and minimizing symptoms of congestive heart failure. The medical committee provided specific guidance on the appropriate drug therapies for this severely ill patient population. Patients also received monthly follow-up when they were out of the hospital (Rose et al., 2001).

failure.[4] Enrollment began with 32 study sites in 2002 and expanded to 171 sites by 2005 because of low patient enrollment. Eventually, 44 of the sites deactivated—at great expenditure of time, energy, and some $10,000 apiece—without ever enrolling a single patient. Originally, the trial was planned for Canada and the United States, but insufficient subject enrollment in these two countries prompted expansion worldwide. The enrollment of 576 patients in Poland ultimately provided the level of patient participation to meet enrollment goals. One of the lessons learned here, said Michler, is that additional sites should be added early in the trial timeline if a trial is not meeting expected enrollment targets.

The NHLBI-funded CTSN is conducting several clinical trials concerning the surgical management of cardiovascular disease in adults. Two trials focusing on the effectiveness and safety of currently available surgical approaches to ischemic mitral valve disease plan to randomize 550 patients.[5] Again, enrollment initially was sluggish, with less than one-third of the patients eligible per month actually enrolled. That rate has improved significantly, to almost half of those eligible now randomized. However, there is a range of site productivity with some of the 14 study sites enrolling three-fourths of their eligible patients, while other sites are enrolling only a fifth or a sixth of their eligible patients. Identifying, in advance, which proposed trial sites will be more assiduous in their enrollment efforts, prior to final site selection, would be of great benefit, Michler said.

According to Michler, recruitment lessons from these three trials fall into several categories:

1. *Protocol issues:* Enrollment may be affected if a treatment is available outside the trial. For the REMATCH trial, the investigational LVAD technology was accessible only within the trial, which served as a powerful incentive for participation for those who wished to have access to that technology.

   Unanticipated costs arising from difficulties in enrollment can negatively affect other parts of the trial protocol. For example, the STICH trial protocol originally included imaging studies to measure the size of the heart, but the trial sponsors made the decision to remove them from the protocol in order to increase enrollment

[4] The STICH trial involved heart failure patients in tests of (a) whether coronary artery bypass graft (CABG) surgery plus medical treatment is better than medical treatment alone and (b) whether CABG plus left ventricular volume reduction (making the heart smaller) in patients with left ventricle dysfunction is better than CABG alone.

[5] The alternative treatments for mitral valve disease in the CTSN moderate ischemic mitral regurgitation trial are CABG surgery with mitral valve repair versus CABG alone (300 patients). In the severe ischemic mitral regurgitation trial, alternative treatments are mitral valve replacement versus repair with or without CABG surgery (250 patients).

efforts by using the money saved to pay clinical sites for their trial expenses.

If the protocol design is too complicated or suggests that different arms of the trial are unequal (and thus that the trial lacks equipoise), these conditions might discourage physicians from referring patients to the trial.

2. *Site issues:* The clinical culture at a site may affect enrollment. Examples are lack of a site champion, weak institutional interest in clinical trials, and bureaucratic hurdles (legal issues, IRB inflexibility, and so on).
3. *Surgeon and referring physician issues:* Education and communication are critical during recruitment and throughout a trial and communicating openly and effectively with physicians about the state of knowledge aids enrollment. Physician toolkits are useful in building the knowledge base for referring doctors (and their patients).

   The stronger the referral relationships are at the outset, the better off the investigator is when initiating a new clinical trial, Michler noted. Relationships can be strengthened by keeping referring physicians informed about the progress of the trial, finding ways for them to participate without it being burdensome to them, and, when feasible, including them in publications, Michler said.
4. *Communication:* During discussion it was mentioned that continued communication not only aids physician involvement but also may aid in retaining trial participants. For instance, in a later discussion, workshop speaker Bernadette Boden-Albala, Co-Director, Irving Center for Clinical and Translational Research, Community Engagement Core Resource, Columbia University, said that dissemination of trial results to patients is critical. She suggested that all studies should end with dissemination of trial results back to the community in which the cohort or the trial participants were from as well as more broadly to the public. When patients are in the communication loop during and after their participation in a clinical trial, this can increase positive feelings associated with trial participation and convey that their contribution was of value. A workshop participant also noted that some people who drop out of clinical trials are convinced to do so by a family member who is a health professional—a physician, pharmacist, or nurse. The participant questioned whether health professionals are being trained to think positively about advising patients (and friends and family) to participate in trials. In many cardiovascular trials the treatment effect may appear underwhelming, Michler said, because the new treatment may not improve greatly upon what is already surgically available, instead the study results define when a specific surgical

therapy is most appropriately employed. Although in cardiovascular trials family members often become the strongest advocates for participation, many of the same issues that make it difficult for clinicians to become involved in trials also make it hard for them to recommend them to their families, he noted.

5. *Participant issues:* There is a need to take into account people's motivations to participate in trials, which can include earlier access to experimental treatments, having closer clinical monitoring, and a sense of altruism. Patients from different racial and ethnic groups and socioeconomic strata have different levels of trust in the medical community. Spending time with the patient and family, and providing educational materials that are culturally and linguistically relevant is "the only way to deal with the trust problem," said Michler (see next section).
6. *Funding and reimbursement:* In this era of increasingly constrained and uncertain hospital budgets, the costs of a trial may prevent hospitals from serving as trial sites. For example, a decade ago, the average cost per patient borne by hospitals in the REMATCH trial was $63,000 (excluding the costs of the device and the surgery, which were funded by the sponsors). Although since 2000 Medicare has covered the costs of treatment for participants in NIH-funded trials, other insurers may not, and not all costs borne by the institution are deemed treatment costs and thus reimbursable. Michler offered his suggestions to trial administrators to improve management of patient recruitment, listed in Box 3-1.

WORKING WITH UNDERSERVED COMMUNITIES

Principles of Community-Based Participatory Research (CBPR)[6]

The U.S. population groups referred to in shorthand as "racial and ethnic minorities" by 2060 will constitute the majority of the nation's population. Bringing adequate representation of diverse societal groups, especially vulnerable populations, will be essential if all Americans are to benefit from improvements in the prevention and treatment of serious medical conditions.

Accomplishing this requires an understanding of why people want to participate in trials. "For that, we need help from insiders," Carol Horowitz, Associate Professor, Department of Health Evidence and Pol-

[6] Based on the presentation by Carol Horowitz, Associate Professor, Department of Health Evidence and Policy, Mount Sinai School of Medicine.

BOX 3-1[a]
Targeted Strategies to Manage Patient Recruitment

Steps for trial leadership:

- Refine the patient eligibility criteria.
- Understand the preparation time necessary before a trial can start.
- Meet early with the IRB and legal department to try to expedite approvals.
- To assess site enrollment capabilities prior to selection, review previous trial screening logs from each site.
- Train investigators in strategies to maximize enrollment.
- Rapidly increase the number of clinical sites if enrollment lags.
- Establish and maintain strong communication, through frequent visits and regular meetings with all sites and principal investigators.

And, at the site level:

- Identify a strong leader willing to champion the trial in the institution.
- Create partnerships with referring physicians and surgeons.
- Consider identifying multiple principal investigators, who can reach out as a colleague to a variety of physician specialists (e.g., a cardiologist as well as a cardiac surgeon) or to different population groups (e.g., a physician who is also a community leader).

[a] Based on the presentation by Robert Michler, Surgeon-in-Chief, Professor and Chairman, and Director, Center for Heart and Vascular Care at the Montefiore Medical Center/Albert Einstein College of Medicine.

icy, said, because the perspective potential participants will have on a proposed trial is likely very different from the researcher's (see Table 3-1).

Researchers believe their projects involving diverse and underrepresented populations are valuable and urgent. Potential participants, however, have an earned skepticism, based on the many failed medical and social experiments of all kinds that have been conducted in their communities. According to Horowitz, when people believe they or their communities will not benefit from a study, the risk of participation rises to unacceptable levels. She remarked that the legacy of the Tuskegee syphilis study—the culmination of a long list of unethical and immoral research and treatment practices to which blacks were subjected—is neither easily dismissed nor forgotten (Washington, 2006).

Rather than sharing the perception that "this is an evidence-free world," giving rise to an urgent need for more clinical trials, minority community members often believe that "we know why we are sick, and

TABLE 3-1 Comparison of Researcher and Patient Perspectives on Clinical Trials

	Researcher Perspective	Participant Perspective
Purpose	Clear, important	Dubious ("Earned Skepticism")
Timeline	now, Now, NOW!	What's the hurry?
Benefit	Obvious (career, grants, knowledge, health, it's for their own good)	Unclear (drive-by, or helicopter research)
Risks	Minimal (no biggie, and Tuskegee was ages ago!)	Unacceptable if benefit iffy, historic abuses
Attitude to Research	Needed to gain knowledge	Problems apparent, resources lacking. Where did it come from?
Participants Should	Agree, comply	Question, contribute

SOURCE: Horowitz and Bickell, 2011.

we don't have the resources to do anything about it," said Horowitz. To these communities, the researcher's description of the planned study, which often might focus on a very narrow question that will benefit practitioners in a particular discipline, simply does not resonate.

Horowitz noted that there is a social obligation to approach the recruitment of minority patients into trials with ample forethought and a commitment to community engagement, in addition to the typical practical requirements of implementation of a protocol. Engagement should go beyond and may even precede the recruitment of participants in a particular study and, ideally, would consist of a long-term commitment to create a research-friendly community. This requires involvement with all those directly and indirectly affected by and involved in the trial: communities of patients, their clinicians, leaders of community organizations, and local opinion leaders. The latter are the hubs for social networks and the cultural insiders and thus are the people who can reach potential participants. This approach is commonly called "community-based participatory research" (CBPR).

Horowitz described three strategies that have proved useful in engaging a community in clinical research:

- *Emphasize effective communication*, taking into account literacy levels, vision (especially with elderly patients), and language, and ensure that information given is no more complicated, jargon-laden, or

legalistic than it absolutely needs to be.[7] Effective communication requires recognition of the gap in subject-matter knowledge between researchers and prospective participants and appreciation of attitudes toward research, clinical trials, and health care providers.

- *Build relationships in the community* and ensure there is a mutual benefit, so that communities and participants see that the trial represents a "win-win." Fundamentally, it means conducting trials that people want to be part of and believe is important *for them*.
- *Anticipate practical matters*. As examples, the choice between having a device implanted and taking a pill may not be an equivalent one from the point of view of patients; the study may involve costs in personal time or money that dissuade would-be participants; there may be excessive requirements for completing forms; participants may need transportation or dependent care; or the study site may be hard to get to or have limited hours. There is a need to simplify requirements and reduce burdens on participants to the extent possible.

In the discussion panel it was mentioned that while some investigators are becoming more aware of CBPR principles and how these principles could be effective in aiding participant recruitment, research sponsors do not necessarily understand them yet, said workshop participant Karriem Watson (HHS, 2011).

The National Institute on Minority Health and Health Disparities (NIMHD) has encouraged the development of CBPR, presenter Nina A. Bickell, Director, Center to Achieve and Sustain Health in Harlem, Mount Sinai School of Medicine, responded, and NIH funded the prediabetes grant Horowitz described for the workshop (see the case study on prediabetes care in the next section). The understanding was that the investigators would use CBPR methods to select the topic and create and implement a pilot study.[8]

A significant need in making CBPR work effectively is to build the capacity of community residents (and patients) to be grant reviewers. This requires training and a foundation of relevant information in order for CBPR to maintain robust research. For example, workshop participant Ronnie Todaro of the Parkinson's Disease Foundation, said her organization supports patient participation throughout the research process, from study

[7] The average American reads at an 8th-grade level; 40 percent of elders and half of African Americans and Hispanics read at or below the 5th-grade level (Partnership for Clear Health Communication, 2006).

[8] See, for example, NIMHD's CBPR initiative: http://www.nimhd.nih.gov/our_programs/communityParticipationResearch.asp (accessed October 10, 2011).

design, to recruitment, to dissemination of results. It also offers a 3-day learning institute for people with Parkinson's disease, to prepare them to serve as FDA advisors, serve on IRBs, review study protocols, and educate other community members about the importance of clinical trials.

The Clinical and Translational Science Awards (CTSA) institutions also are committed to community engagement, Horowitz said.[9] And, in places where there is a lot of institutional support for CBPR, there reportedly is parallel interest on the part of funders.

Case Study: Prediabetes Care

Nearly 26 million Americans have diabetes, with substantially higher rates among Hispanics and non-Hispanic blacks, compared to non-Hispanic whites (CDC, 2011). An East Harlem diabetes prevention trial is testing whether a successful, but expensive, hospital-based strategy of identifying people with prediabetes and helping them lose weight can be adapted to be delivered at the community level, using peer-led interventions. A substantial "pre-recruitment effort" began with an educational initiative, which Horowitz said was intended to (a) help area residents recognize that diabetes could lay in store for them even if they did not yet have it and (b) sensitize them to the threat of diabetes to a point at which they demanded action.

In contrast to most clinical trials, it was not the researchers, but their community partners, who chose diabetes prevention as the focus of the study. The partners selected many of the research methods and strategies; they made sure the study would resonate with the community, building trust and motivation and the relationships needed to support the research down the road; and they determined the incentive participants would receive. For its part, the research provided the community with a tangible benefit, including jobs for local people.

The community partners developed the following recruitment strategies:

[9] Resolving infrastructure issues in academic medicine has been one of the concerns of the NIH-funded CTSA consortium and its 60 participating academic medical research institutes. In late 2010, NIH announced plans for a new $722 million National Center for Advancing Translational Sciences (NCATS), a proposal before Congress in summer 2011. The purpose of the new NCATS is "to catalyze the generation of innovative methods and technologies that will enhance the development, testing, and implementation of diagnostics and therapeutics across a wide range of diseases and conditions" (Collins, 2011). The CTSA consortium will be incorporated into this new Center.

- Recruitment "where the people are," such as at major community events, in churches, food pantries, senior centers, and schools
- Holding "Stop Diabetes Day" recruitment parties
- Asking community-based organizations to champion the cause
- Leading the recruitment effort themselves (which proved the most effective)
- Asking clinicians to refer people (the least effective strategy)

Potential participants were required to fast, undergo various tests, and commit to being in a workshop and coming for follow-up. That they were willing to do this (despite not having diabetes) suggests to Horowitz that they were reasonably confident of the study's value before actual recruitment began.

The study was a success, both in terms of recruitment and its outcomes. In three months it recruited 99 "hard-to-reach" people, most of whom were nonwhite, Spanish-speaking, unemployed, undereducated, low-income, and uninsured. The group achieved significant weight loss, which they maintained for a year.

Throughout, the researchers worked to create an upbeat environment at the study site that would make participants feel welcome and part of the team. As the researchers routinely told study participants, "This is brought to you by you."

Case Study: Continuity of Breast Cancer Care[10]

An example of a trial exploring continuity of breast cancer care was presented to illustrate strategies for engagement of physicians in clinical trials. The goal of this trial was to make sure that breast cancer patients who had surgery made it back to their oncologists to obtain the adjuvant treatment that can improve survival rates. The trial subjects were breast cancer surgeons practicing in six unaffiliated New York City hospitals, for whom the researchers developed a tracking and feedback registry.

The researchers obtained the name of a key breast cancer surgeon in each hospital from its chair of surgery. They wanted to identify surgeons whom other surgeons looked up to and who could work across disciplines. These individuals were asked to be the principal investigators for the study at their specific hospital.

To convince these already-busy physicians to take on this job, Bickell said, the researchers worked to help them understand the extent of

[10] The breast cancer care case study was presented by Nina A. Bickell, Director, Center to Achieve and Sustain Health in Harlem, Mount Sinai School of Medicine.

underuse of adjuvant therapy, especially among minority women.[11] The researchers documented that these patterns of underuse persisted across hospitals and *across surgical practices*, which, according to Bickell, made the problem very salient to the surgeons and helped motivate participation.

In addition, the trial offered the surgeons a service—patient tracking—they could not otherwise have. Finally, the study team followed the "make it convenient" rule by streamlining demands on the surgeons and their practices, such as by communicating with a point person for each surgeon.

Surgeon recruitment and study outcomes were strong. Of surgeons who operate on women with breast cancer in the target hospitals, 97 percent agreed to participate, and the overall rate of adjuvant underuse dropped from 23 to 14 percent between 1999-2000 and 2004-2006 (Bickell et al., 2008).

Working with health professionals does not obviate the issue of trust, Bickell said. In this study, surgeons were particularly concerned about confidentiality and malpractice. Just as when working with a patient population, these issues had to be dealt with up front, through the trial design and recruitment processes.

MENTAL HEALTH[12]

Sixty years ago, clinical trials on the first drugs to treat schizophrenia and depression found such robust positive effects that the studies could be conducted with small numbers of patients. In recent decades, the situation has changed dramatically, said Kenneth Davis, President and CEO, Mount Sinai Medical Center and Professor of Psychiatry, Mount Sinai School of Medicine. The failure rate in clinical trials of new treatments for mental illnesses is disappointingly high:

- New treatments produce only small positive effects.
- Large numbers of participants respond as well (or better) to the placebo.
- Enrollment of participants is excruciatingly slow.

[11] The percentages of women who needed postsurgical adjuvant therapy and did not receive it were 34 percent among black women, 23 percent among Hispanic women, and 17 percent among white women.

[12] This section is based on the presentation by Kenneth Davis, President and CEO, Mount Sinai Medical Center and Professor of Psychiatry, Mount Sinai School of Medicine.

Similarly, while early trials of drugs for Alzheimer's disease proceeded smoothly—with robust effects, small placebo responses, and short enrollment periods—the situation has again reversed.

In recent years, trials of treatments for mental disorders have faced a number of difficulties in patient recruitment that are exacerbated with respect to psychiatric conditions:

- The stigma of the condition and, in some instances, the treatment (in part a result of lurid media depictions of both mental illnesses and their treatment)
- Ethical issues, when dealing with patients at high risk of suicide

Researchers have puzzled extensively over the difficulties with clinical trials related to mental disorders and have produced several hypotheses to explain them, said Davis. Perhaps mental illnesses differ to a much greater degree than previously thought, in which case much more needs to be learned about their underlying biology so that individual patients can be linked to the correct therapy. Unfortunately, this approach has not worked for patients with Alzheimer's disease.

It is also possible that based on new knowledge about the diagnosis, spectrum, and progression of these diseases, inclusion criteria for clinical trials have evolved to reflect these nuanced understandings of various mental illnesses. Another possible explanation for the difficulties facing clinical trials in mental health is that perhaps it was easier to recruit patients into clinical trials when there were no legitimate competing treatments. Today's trials in mental health might attract patients who have not had relief from the now-established treatments and whose disease is more difficult to treat. Or, as workshop participant Michael Parides, Professor of Biostatistics, Department of Health Evidence and Policy, Mount Sinai School of Medicine, suggested, the design of confirmatory trials might be flawed due to weaknesses in the design and objectives of early-phase trials.

Several recent trends have changed the research environment. One such trend is the growth of CROs, which in 2010 performed an estimated $20 billion in outsourced research tasks and support for the pharmaceutical and biotechnology industries. These firms vary markedly in their ability to execute studies and their commitment to quality, rigorousness, and even speed, Davis said. Another trend is the increased use of study sites outside the United States, some of which have less experience with conducting clinical trials than do U.S. institutions.

It is sometimes difficult to know *how* to test new treatments for mental disorders, particularly treatments having novel mechanisms that may require novel trial designs, said Davis. Sponsoring companies and FDA

often end up at an impasse, he remarked, with the companies wanting to know what kind of trial designs FDA will accept, and FDA waiting for companies' proposals.

Ultimately, what will be needed for successful trials for mental conditions will be to invest substantially more time in drug development, said Davis. U.S. patent law, however, fails to incentivize lengthy drug development efforts. Davis said these laws will have to be reconsidered if they are to best meet public health needs and enable real clinical breakthroughs for treatment—and especially prevention—of psychiatric conditions.

4

Models for Public Engagement

"Multiple communities require multiple approaches."
—Paul Harris, Vanderbilt University

LOVE/AVON ARMY OF WOMEN[1]

The Avon Foundation for Women has a strong commitment to breast cancer research, and, in the past 5 years, has supported some 350 research studies. In October 2008, the Foundation joined with the Dr. Susan Love Research Foundation to launch the Love/Avon Army of Women project.[2]

Because recruiting even 50 volunteers for a clinical trial can be a lengthy process, the Army of Women was conceived as a way to create a large, demographically diverse pool of women interested in participating in breast cancer research, said Marc Hurlbert, Executive Director of the Global Breast Cancer Programs of the Avon Foundation for Women and the Avon Breast Cancer Crusade. By making it easier for researchers to recruit study participants, project managers hoped that more prevention studies will be conducted overall and more will be conducted in women, rather than in mice or *in vitro*.

As of July 2011, the Army of Women project has attracted more than 356,000 registrants, adding approximately 1,500 new recruits each month. In its first two and a half years, the Army of Women has helped investigators recruit volunteers for 44 research studies, and 24 research teams are using the Army of Women website for participant recruitment.

[1] Material in this section is based on the presentation by Marc Hurlbert, Executive Director of the Global Breast Cancer Programs of the Avon Foundation for Women and the Avon Breast Cancer Crusade.

[2] See: http://www.armyofwomen.org/.

Those who join the Army of Women receive an email every few weeks describing research participation opportunities. If they are interested and meet the eligibility criteria, they contact the Army of Women, answer brief screening questions, and, if appropriate, their names are provided to the researcher for follow-up. Scientists must apply to the Army of Women for the opportunity to recruit volunteers from its pool, and every study undergoes a rigorous scientific, safety, and ethical review. When the study is over, researchers are required to present their results via a video or blog on the Army of Women website.

The demographic profile of the women who have volunteered is as follows:

- 86 percent have never had breast cancer.
- 74 percent have no family history of breast cancer.
- Half are between ages 40 and 59.
- 86 percent are Caucasian.
- Some 10,680 are African American, an equal number are Hispanic, and about 3,560 are Asian.

Hurlbert reported recent examples of how researchers are using the Army of Women database to recruit participants, including

- a study of methylation in breast tissue hormones, which needed 300 healthy women for core biopsies (an invasive procedure) and other tests; this request generated responses from 739 women, and the study has already recruited 425;
- a study looking for biomarkers in breast milk, which needed 250 lactating women who had been asked by their physician to have a breast biopsy to assess "something suspicious" (a relatively rare occurrence); the request generated such a large response that the researchers were able to quickly recruit 334 women, shorten the study's recruitment timeline from 6 months to less than a week, add to the study questions, and expand the recruitment target to 2,000; and
- a third study needed to recruit 100 Latina women for a study of breast cancer survivors' quality of life; it received responses from 125 Army of Women volunteers, only 5 of whom were ineligible, enabling the researchers to expand the study 20 percent.

23ANDME[3]

23andMe is a for-profit company that describes itself as a "direct [to] consumer genetics company" that customers interact with through a website.[4] A customer sends a saliva sample to the company for analysis, and, in 6 to 8 weeks, receives information about the genetic variants in his or her genotype and their implications for health. Customers are encouraged to share the results with their physician, said Brian Naughton, Founding Scientist, 23andMe, and genetic counseling is available. 23andMe builds "site stickiness" by providing engaging tools and information people can use in the analysis and understanding of their genetic information.

23andMe also engages with its customers through online surveys focused on everything from exercise and lifestyle to the presence of specific diseases, said Naughton. When customers answer a question such as, "Have you ever taken a nonsteroidal anti-inflammatory drug?" they receive immediate feedback about how many people in the database answered as they did.

More than 100,000 people are in the 23andMe database (as of July 2011), and more than 60,000 of them have taken at least one survey. People who have taken any surveys have taken, on average, 10, for a cumulative 20 million data points. They receive no reward for completing surveys, but participate out of an apparent desire to be part of a community.

The web is a convenient platform for administering long surveys because the answer to one question can automatically eliminate a whole series of questions that would be irrelevant to that individual. Although there are likely to be errors in data self-reporting, the size of the sample may in some cases minimize that. (The statistical power lost from self-reporting is highly dependent on the phenotype being studied, and for some conditions, such as schizophrenia, self-reporting may not work very well, said Naughton.)

According to Naughton, 23andMe is becoming useful for several types of clinical research. The surveys provide a rich database of potential associations that may reveal information about how environment, behavior, and other factors can affect gene expression. The genetics database enables efficient identification of people with specific genetic profiles. Or, studies can start with a pool of people having a known disease and look for previously unrecognized shared genetic characteristics.

23andMe has found that the most effective way to recruit its customers, particularly when it is trying to increase the pool of people with cer-

[3] This section is based on the presentation by Brian Naughton, Founding Scientist, 23andMe.

[4] See https://www.23andme.com/.

tain diseases, is to work with disease advocacy groups, Naughton said. For example, the firm worked with the Michael J. Fox Foundation for Parkinson's Research and, with its help, has now recruited some 5,000 people with Parkinson's disease, more than 85 percent of whom have completed the Parkinson's disease survey. It now has the world's largest database of people with the LRRK2 genetic mutation (which greatly increases the likelihood of developing Parkinson's disease). This resource is enabling tentative identification of potentially new genetic associations that may increase understanding of the disease.

As examples of how 23andMe can work, according to Naughton:

- When a pharmaceutical company requested research on dry eye syndrome, 23andMe posted a survey on its website to find people in its database who have this condition. It received 900 responses in one week and 8,000 responses to date. Now, 23andMe is able to contact those who reported severe dry eye symptoms to ascertain whether they would be interested in taking part in a clinical research study on the condition.
- For a pharmaceutical company interested in the genetic factors contributing to skin aging, 23andMe obtained 1,600 responses to a nontargeted survey within 90 days.
- For a study on hair loss, 23andMe analyzed data from 13,000 customers; the analysis replicated all known genetic associations, found three novel ones associated with male pattern baldness, and identified a suggestive association that may predict drug response. Administering the survey online was especially helpful, because it could show respondents pictures of different degrees of hair loss, in order to obtain more precise results.
- For a study of people over 80 who are carriers of the APOE e4 mutation for Alzheimer's disease, 23andMe recruited 127 patients in the first week.

As with the Army of Women project, 23andMe provides its community members with information on the results of studies in which they participated. This feedback is believed to be very important in creating incentives for future participation and for building the patient, or customer, base. For example, Naughton said that in just a few days after results of the Parkinson's disease research were released, 100 more Parkinson's patients joined 23andMe.

23andMe researchers have compared their results with those of large, multicenter trials. For example, two NIH-funded trials (Neumann et al., 2009; Sidransky et al., 2009) found that having a mutation in the GBA gene

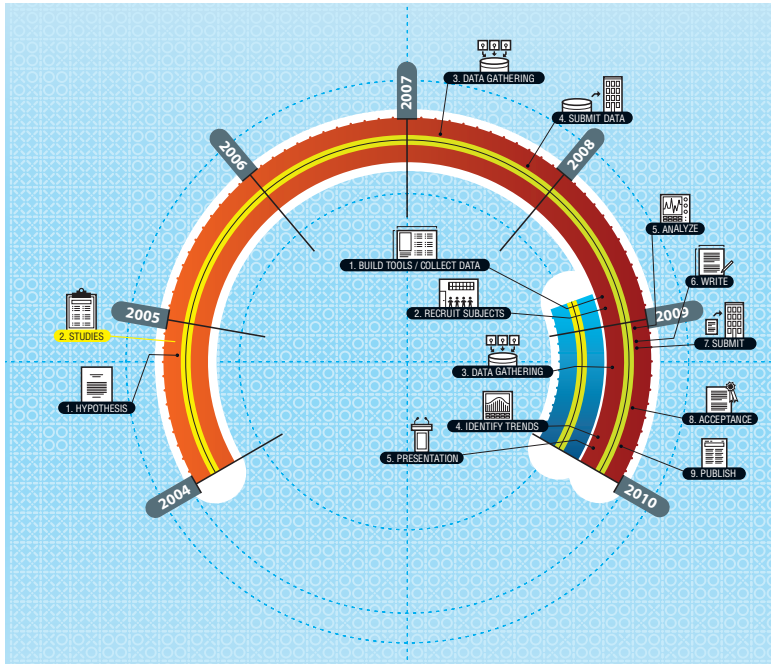

FIGURE 4-1 A timeline comparing a conventional NIH clinical trial versus the 23andMe research model. The orange and red semi-circle depicts a conventional NIH trial from hypotheses generation (step 1) through publication of trial results (step 9). The blue circle segment depicts the 23andMe research model from the building of tools and collecting of data (step 1) through presentation of research results (step 5). The conventional NIH trial took 6 years as compared to just over 1 year for the full application of the 23andMe research model in this example.
SOURCE: Goetz, T. 2010. Sergey Brin's Search for a Parkinson's Cure. *Wired Magazine*. http://www.wired.com/magazine/2010/06/ff_sergeys_search/all/1 (accessed September 7, 2011). Reprinted with permission from *Wired Magazine* and Dominik Schulz.

increases the risk of Parkinson's disease by a factor of 5. Analysis of the 23andMe database reached the same conclusion. The two NIH-funded trials took 6 years from inception to publication (Figure 4-1). Using 23andMe, recruitment of patients, analysis of saliva samples, and attainment of results took 8 months. Of course, said Naughton, the 23andMe study uses self-report, versus clinician testing, and it only needed statistical power sufficient to replicate existing knowledge rather than to

discover new information. But, he said, it is a tantalizing foretaste of how a trial can happen more quickly—and less expensively.

Naughton added that 23andMe has sufficient data to make new genetic associations, as it did for Parkinson's disease, not merely replicate existing studies, depending on the phenotype, and the number of people in the database with a particular condition.

RESEARCHMATCH[5]

Vanderbilt University and its sister CTSA institution, Meharry Medical College, use a number of web-based approaches for patient recruitment, engaging faculty and staff and creating public awareness of clinical studies. Among them is a collaboration project called ResearchMatch (www.researchmatch.org), which, said Paul A. Harris, Associate Professor, Department of Biomedical Informatics, Vanderbilt University, was born out of the simple philosophy that there are people in the community who want to be involved in trials. Although traditional methods often can enroll people in studies and trials only with great difficulty, Vanderbilt staff recognized that there was an unmet need to connect people who want to participate in clinical trials with researchers looking for volunteers.

The Vanderbilt team started by building a local registry, and in the past few years they have expanded it nationwide to serve the entire 61-member CTSA program. ResearchMatch is free to both volunteers and researchers, and it complements, but does not replace, other recruitment methods.

A potential volunteer who finds out about ResearchMatch registers on its website. Adults can register their children or elderly relatives living in their home. The registrant is asked basic intake information, about common inclusion and exclusion criteria, and about medical history and medications. One data point entered is street address, from which the software automatically calculates the registrant's distance from CTSA-participating institutions. People can type in their responses in their own words and the system translates it into a structured vocabulary. For example, the person's "heart attack" becomes the system's "MI."

Investigators must go through a specific process to gain approval to use the ResearchMatch database for recruitment. Once an investigator has received permission to recruit for a particular study, ResearchMatch's

[5] This section is based on the presentation by Paul A. Harris, Associate Professor, Department of Biomedical Informatics, Vanderbilt University.

simple filtering mechanism provides information about how many candidates fitting the specific criteria are in the database.

When this anonymized pool of registrants is deemed sufficient, the researcher sends an IRB-approved message to each individual in the pool. If prospective participants agree to participate, their identity is revealed, and the consent and educational processes proceed as in any other study.

As of July 2011, approximately 16,000 people were in the ResearchMatch database. Race and ethnicity data were similar to the population as a whole, although the ratio of women to men was approximately 3:1. About half the enrollees reported no health conditions and thus are potential controls. As of July 2011, 743 researchers were using ResearchMatch resources in the conduct of 268 active studies. Not only has the system worked at Vanderbilt, but, Harris said, comments from CTSA sites indicate the system is also working elsewhere.

The next step for the project is to evolve it from a disease-neutral-only framework to one that includes subsets of people with specific diseases. In addition, the development team is looking at the stakeholders' unmet needs. For example, patients and families may need information about an illness, they may need direction, or they may want a voice in the research community. Similarly, researchers also may need more information and may be able to serve as a source of information for participants and families. Finally, there may be additional stakeholders that are not involved yet—foundations, advocacy groups, and others—with needs that a simple-to-use tool like ResearchMatch could meet. Conceptually, the ResearchMatch system need not be limited to CTSA institutions. Because the service currently is offered at no cost, expansion to other institutions would require some consideration of whether it can be scaled out effectively. In the long term, said Harris, the impact of ResearchMatch will depend on investments at the institutional level—especially support for liaisons and development of community relationships built on trust that will encourage people to register.

5

Messages and Methods for Public Engagement

"The problem of the language used in describing clinical trials is the one problem that is exquisitely fixable." —Christina Zarcadoolas, CUNY School of Public Health at Hunter College and Mount Sinai School of Medicine

MESSAGES

Engaging vulnerable populations in clinical trials calls for sensitive messaging and wise choice of messengers. According to Carol Horowitz, Mount Sinai School of Medicine, what seems to work best is engaging people in what they perceive (and is truly) a cooperative enterprise. She used a baseball analogy:

> What's the difference between a baseball team and a pickup game? In a team, you know people need you to be there. You know you're important. You know you matter. We need to build that team—that family mentality—to get (underrepresented) people into our research and to get people into our research community.

In a discussion session of the workshop, this theme reemerged when Ann Bonham, Chief Scientific Officer, Association of American Medical Colleges, suggested that reluctance on the part of the public to participate in clinical trials may be because investigators have not made them feel like partners. Instead, the messages that are delivered (and received) tend to reinforce the gaps in knowledge between scientists and the public, a point effectively made in the following section.

Messages[1]

After 30 years of research on health literacy, the problem still has not been solved. Half of U.S. adults have low health literacy. That means, in the simplest case, they do not understand how to read a prescription label or what the dosing means, nor do they know what their cancer treatment is, beyond the most general statement. If they do not understand these things, they certainly do not understand what a research protocol is.

Christine Zarcadoolas, Associate Professor, CUNY School of Public Health at Hunter College and Mount Sinai School of Medicine, defined health literacy as "the wide range of skills and competencies that people develop over their lifetimes to seek out, comprehend, evaluate, and use health information and concepts to make informed choices, reduce health risks, and increase quality of life" (Zarcadoolas et al., 2006).[2]

The age group with the lowest level of health literacy is those 65 and older. Disproportionate numbers of racial and ethnic minorities and other underserved populations are health illiterate. The problem of health illiteracy is compounded by the high rate of *fundamental* illiteracy in the U.S. population, with the average American reading at an 8th-grade level. But even if health information is written at a 5th- or 8th-grade level and people can read and understand it, if they do not use it and cannot apply it in making decisions, they may not have health literacy. Four types of literacy are fundamental literacy (reading, writing, working with numbers), science literacy, civic literacy, and cultural literacy. The general public often does not have science literacy. Even people who have high fundamental literacy may not take their medications correctly, understand their physiology, take actions to protect their health, or distinguish among health advice based on science, pseudoscience, or hope.

Clear language is necessary but not sufficient to create understanding. Americans generally do not know, or they have great difficulty understanding, the underlying concepts embedded in health informa-

[1] This section is based on the presentation by Christina Zarcadoolas, Associate Professor, CUNY School of Public Health at Hunter College and Mount Sinai School of Medicine.

[2] An IOM workshop summary report defines health literacy as "the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions" (Ratzan and Parker, 2000). However, health literacy goes beyond the individual obtaining information. Health literacy emerges when the expectations, preferences, and skills of individuals seeking health information and services meet the expectations, preferences, and skills of those providing information and services. Health literacy arises from a convergence of education, health services, and social and cultural factors (IOM, 2004).

tion. About 20 years ago, researchers in the health literacy field began studying the effectiveness of "simple language" health messages, Zarcadoolas said. The researchers found that, even if the messages were linguistically clear, they often assumed more scientific knowledge than people have. For example, the message not to take an antibiotic when you have a cold may be clearly stated, but it will not make sense unless the target audience also knows that colds are caused by viruses and that antibiotics are ineffective against viruses. According to Zarcadoolas, at least 63 percent of Americans do not know that viruses and bacteria are different. So in this example the language in the delivered message will not be internalized without some underlying scientific understanding. Lack of science understanding has potentially life-threatening consequences. For example, in a study of people's reactions to the H1N1 pandemic of 2009, only 40 percent of Americans understood the risk sufficiently to plan to have their children immunized against H1N1, and almost 30 percent definitely planned *not* to (30 percent were unsure). Interviews with average New Yorkers found they did not understand why this new virus was so dangerous. Meanwhile, public health messages about the virus described flu in pigs and birds, gene reassortment, and so on—topics of intense interest to influenza researchers, perhaps of academic interest to clinicians, but of no perceived salience to the population at large.

The National Science Foundation has assessed public understanding of science for more than 30 years. Between 5 and 15 percent of the U.S. population is considered to be science literate, which is defined as knowing anything about the scientific process, such as what a research protocol might be or why a protocol is necessary. Even the word "trial," as in clinical trial, is laden with confusing meanings. When Zarcadoolas's team asks people what they think a "trial" might be, subjects often respond that a trial involves a judge; a trial is what the Lord places upon us; and there's "trial and error." To the ordinary person, all meanings of the term "trial" carry a negative connotation.

In the clinical trials context, where the underpinning of the whole enterprise is complex and speculative and carries some potential risks, and where many diverse sociocultural factors come into play, effective communication is even more difficult—starting with the fact that consent forms are typically written at the 17th-grade (post-college) level or higher. (In fact, most health information that hospitals and public health departments produce are written at the 10th- or 12th-grade level, which may help perpetuate health illiteracy, Zarcadoolas said.)

Zarcadoolas remarked that NIH's ClinicalTrials.gov should be a major source of information for people asked to participate in a clinical trial. The site has a frequently asked questions (FAQ) section, intended for potential

trial participants, called "Understanding Clinical Trials,"[3] and the first question is, "What Is a Clinical Trial?" The answer, she found:

> Although there are many definitions of clinical trials, they are generally considered to be biomedical or health-related research studies in human beings that follow a pre-defined protocol. ClinicalTrials.gov includes both interventional and observational types of studies. Interventional studies are those in which the research subjects are assigned by the investigator to a treatment or other intervention, and their outcomes are measured. Observational studies are those in which individuals are observed and their outcomes are measured by the investigators.

Zarcadoolas explained that the readability level of this passage is between the 12th- and the 15th-grade level. It is full of science concepts: biomedical, protocol, interventional, observational, subjects, assigned, investigator, intervention, measurement, and outcomes. A health-literacy load analysis reveals many opportunities for misunderstanding; many of the words have other meanings in everyday life.

The site also includes a glossary, hyperlinked to the FAQ. Clicking on the word "protocol" displays this definition (excerpt):

> While in a clinical trial, participants following a protocol are seen regularly by the research staff to monitor their health and to determine the safety and effectiveness of their treatment.

Zarcadoolas asked some of the patients she works with, who are generally low-literacy, low health literacy, and underserved, what they believed this statement means. She said that their interpretation was, "you're in this research project and then they decide if it's safe for you." It is possible that researchers' conscientious attempts to be explicit about the inherent uncertainty of clinical trials are an unintentional source of some of the confusion.

In the past two decades, Americans have seen many changes in science recommendations that have affected their daily lives. Nutrition advice keeps changing. New drugs are developed, then withdrawn. Interviews with the general public revealed three opinions about the recent market removal of children's cold medications:

- Why can't they get it right the first time?
- The scientists are just arguing with each other.
- I'm going to do what I think is right for me and my family.

[3] See http://clinicaltrials.gov/ct2/info/understand (accessed October 10, 2011).

Unless people appreciate that science knowledge is a moving target, they see it as providing conflicting advice and no sure guidance. Even the NIH definition of clinical trials starts with ambiguity: "Although there are many definitions of clinical trials."

Much work may be needed in order to create more meaningful public messages about science, research, and clinical trials, but many of the current problems are fixable. However, they are not fixable by merely simplifying language, Zarcadoolas said. It will take community participation, careful attention to health and science literacy, and using technology to change how and to whom vital information about biomedical research is disseminated.

The Love/Avon Army of Women project, among others described during the workshop, demonstrates that demographically diverse Americans *will* volunteer for clinical trials. It takes high "civic literacy" to understand that such volunteer participation is for the greater good, said Zarcadoolas, and it shows that the American public is altruistic and will contribute to the greater good. But they need to understand the reason for the trial and believe it is being done with and for them and their communities, not *to* them.

MESSENGERS[4]

Even if more meaningful messages about health and participation in clinical trials were devised, much will still depend on the choice of messenger. Americans rely predominantly on health professionals for information on many important aspects of health care: diagnosis, prescription drugs, alternative treatments, and recommendations for a specialist or medical facility (Kuehn, 2011), according to a 2010 Pew Research Center survey.

When respondents in a 2010 Capstrat survey were asked who was most influential "the last time you needed information on a health issue," respondents chose physicians (44 percent) over other health professionals and sources, said Janet Tobias, Ikana Media and Adjunct Assistant Professor, Mount Sinai School of Medicine. The second most influential source of information was a Google search (22 percent), although the survey did not ask about the kinds of resources the search led to (Albritton, 2010).[5]

These two surveys also suggest some of the circumstances in which

[4] This section is based on the presentation by Janet Tobias, Ikana Media and Adjunct Assistant Professor, Mount Sinai School of Medicine.

[5] The survey was conducted by Capstrat and Public Policy Polling, April 28-29, 2010, and included 678 adults 18 and older; 13 percent of the survey population was African American (approximately 88 individuals).

people find online guidance most valuable. The primary reason people seek information from online sources is the 24/7 access they offer, and they find the Internet more helpful than professionals when they want to reach out to fellow patients, friends, and family for emotional support or need a quick remedy for a common health problem. Respondents considered health professionals and nonprofessionals equally helpful when seeking "practical advice for coping with day-to-day health situations" (Kuehn, 2011).

African American respondents in the Capstrat survey rated Google higher than did the survey population as a whole, with respect to both reliability and influence. They also rated physicians less reliable than did the population as a whole (50 percent versus 74 percent overall) and less influential in their search for information (36 percent versus 52 percent overall).

Thus, while physicians may still be primary sources of information regarding participation in clinical trials, they are no longer the only one. Online sources of information about clinical trials are increasingly available. But if a curious person searches Google to find information regarding "clinical trials," Tobias asked, what does he or she find, and is it understandable?

The information sources that appear on the first page of Google results range from the NIH-sponsored registry of all clinical trials, ClinicalTrials.gov, discussed previously, to nonprofit and for-profit trial matching sites, to a Wikipedia entry, to a Medline resource, to recent news stories, which often focus on problems arising from clinical studies. Even if prospective trial participants choose an authoritative site, they may not understand what they find there, Tobias said.

Message Structures[6]

A person's decision to participate in a clinical trial is subject to all the individual considerations, vagaries, and complexities of any other decision about behavior. Because behavioral decisions are complex, said Bernadette Boden-Albala, Columbia University, they are best facilitated through structure.

Among the professional disciplines that have carefully studied individual behavior and decision making are the behavioral economists. Richard Thaler, a behavioral economist at the University of Chicago, has said, "There's no reason to think that markets always drive people to do what's good for them." In other words, humans sometimes make biased decisions that run counter to their interests, one of which might be partici-

[6] This section is based on the presentation of Bernadette Boden-Albala, Co-Director, Irving Center for Clinical and Translational Research, Community Engagement Core Resource, Columbia University.

pating in a clinical trial, Boden-Albala said. Thaler's is one explanation for why health-related behavior changes are difficult to achieve, even if they would increase the likelihood of better health and prevention of disease.

Another aspect of behavior is "preparedness"—preparedness to take some kind of action or make some decision. Systems and structures can prepare people for a wide array of challenges that may require only short-term skills (e.g., call 911) or long-term training (e.g., undertake a graduate education). For example, preparing people to recognize stroke, treat it as an emergency, and acquire the minimal skills to deal with it (call 911 and navigate to an emergency room) is relatively straightforward, and such preparedness efforts have markedly decreased the time-to-arrival at emergency rooms in communities where they have been implemented.

For people to respond adequately to an opportunity to participate in clinical trials also requires preparedness. Part of that preparation will require a better understanding about the nature of clinical trials, in general—the science literacy Zarcadoolas described—and the significance of specific concepts that may be unfamiliar: randomization, placebo, risk. They may still say no, but it should be an informed "no."

Boden-Albala explained that researchers need to consider that their prospective trial participants live in a web of social connections. Participating in trials requires a degree of science literacy on the part not just of potential participants, but their family, friends, and coworkers, who can encourage or discourage them from signing on initially and staying in the trial over its course, said Boden-Albala. Their physicians likewise need information about the specifics of the trial. She cited another University of Chicago behavioral economist, Nobel Laureate Gary Becker, who has said, "It doesn't matter what you or I do, it's how the whole group behaves."

Behavioral economics again would suggest that people want to be prudent (eat properly, exercise, contribute to science that might help future generations), but, said Boden-Albala, "They just don't want to do it right now." Social scientists have shown large differences in participation in certain programs depending on whether people must opt into the program or opt out (e.g., organ donation programs or 401[k] plans). If people must take a concrete action to participate ("explicit consent"), they may not get around to doing it. But if they must take an action *not* to participate ("presumed consent"), they do not get around to that, either (Thaler, 2009).[7] Under some circumstances, opt-out rules, or "presumed consent," for clinical research might be considered, Boden-Albala suggested.

Social networks and peer support have been shown to influence

[7] A third choice, which Thaler prefers at least with respect to organ donation, is "mandated choice," in which people are required to indicate their preference, and the process is made as simple as possible (Thaler, 2009).

BOX 5-1[a]
An Urgent Case for Clear Messaging

A clinical study conducted in East Africa to evaluate fluid resuscitation in children with severe infections (severe malaria, sepsis, or others) and shock came to a surprising conclusion: the treatment—fluid boluses—which has been the standard around the world, actually decreased survival (Maitland et al., 2011). The trial overturned several decades of pediatric recommendations that are taught in pediatric life-support training and followed worldwide. Six clinical centers in Kenya, Tanzania, and Uganda participated in the clinical study.

This study faced several messaging challenges from its outset. The study required approval to obtain "emergency consent." A lengthy consent form read to parents holding a critically ill child was neither feasible nor humane. Yet parents needed to understand (and subsequent research shows they did) that they could refuse to participate in the study without jeopardizing their child's treatment in any way.

As the research was being designed, opportunities to involve the community in discussions about the study might have been desirable, but were somewhat limited, inasmuch as the hospitals involved were regional facilities serving dispersed populations and had no real "community." To help address this, the research team developed and distributed explanatory brochures about the project.

Once the trial was stopped, it was important that health care providers not misinterpret the results as suggesting that *no* intravenous fluids should be given. Children who cannot drink for themselves still must receive sufficient fluids intravenously to maintain normal levels.

Dissemination efforts for the trial results include a paper in the *New England Journal of Medicine*; a YouTube video about the trial and its findings; and in-person presentations as well as distribution of a DVD about the trial to pediatric societies and academic institutions in East Africa. Finally, an ongoing effort is under way to advise the World Health Organization and other health policymaking bodies to develop policies and guidelines that take into account the results of this important study.

[a] Based on the presentation by Kathryn Maitland, Professor of Medicine, Imperial College.

health behavior—in positive and negative ways. As an example of a positive influence on health behavior, if your friends give up smoking or alcohol, you are more likely to do so also (Christakis and Fowler, 2008). Reflecting the influence of social networks and peer support on negative health behavior, if your friends are overweight, you are more likely to become overweight as well (Christakis and Fowler, 2007). It is important to work with the leaders in a social network and help them understand how a particular project benefits the community. Obtaining their support opens doors. See Box 5-1 for an international case study.

According to Boden-Albala, examples of how these concepts can be put into practice include the following:

- A study attempting to harness the strength of networks for health, called Families Undergoing Risk Reduction Through Educational Reinforcement (FURRThER), works with the entire family-friends network of a person who has had a stroke. The aim is to help them, collectively, reduce blood pressure—an accomplishment that will benefit each network member's health and, potentially, that of the patient at the center of the network.
- The Washington Heights/Inwood Informatics Infrastructure for Community-Centered Comparative Effectiveness Research (WICER) study is attempting to enroll 12,000 New York City residents in a registry that can move people quickly into randomized blood pressure trials. In eight focus groups, community members advised on study design, suggesting questions, and recommended the reward for registration ($25 in food coupons). As a recruitment strategy, the researchers used "snowball" techniques, asking people who registered to tell their friends and family about the registry. A thousand people registered in the first 7 weeks, as a result of contacts made by only 150 people.

Social media, such as Facebook, have the potential to serve as social networks in somewhat analogous ways. Although social network participation is heavily skewed toward the younger generation, a 2010 survey showed rapid growth in use among older adults: almost half of people 50 to 64 use social networking sites, as do more than a quarter of those 65 and older (Pew Internet and American Life Project, 2010). Already researchers have used Facebook announcements to advertise clinical trials. In addition, there are many websites that are more targeted to health topics or to specific diseases and conditions.

An example is the website Patients Like Me (http://www.patientslikeme.com/), which has enrolled almost 113,000 patients, collectively having more than 500 conditions. It has developed a clinical trials matching tool, conducts surveys of registrants that can be useful in trial design, has a pool of patients for observational studies, and, similar to the Army of Women and 23andMe both discussed in Chapter 4, is committed to publication of results of studies involving its members.

Boden-Albala cited the following as challenges to be aware of in using social networks:

- Avoiding coercion in using personal networks
- Ensuring reliability of the data and accuracy of self-reports
- The risk of unblinding studies where participants share "too much" information

6

The Media

"The landscape is filled with landmarks now because so many of them have been declared." —Peggy Peck, MedPage Today

Americans use a wide range of media and most people (59 percent) obtain information from both online and offline sources. The number of outlets for medical and health news has expanded markedly, with the inception of dedicated online medical news services. Traditional news outlets—broadcast and cable networks and newspapers and news magazines—now have robust online presences that provide additional content and background to stories appearing on air or in print. A panel of journalists from national broadcast media, an online medical news source for professionals, and a patient-focused market researcher discussed the challenges facing news organizations in covering the medical research beat and provided some ideas for how journalists might respond.

BALANCED COVERAGE

Getting medical research stories right is vitally important, because many Americans obtain much of their health information from the media—television, radio, print, and the Internet, said Heather Won Tesoriero, Medical Producer, CBS News. Media coverage of medical advances, particularly by broadcast news, is often criticized for emphasizing the "good news" in medical research and underreporting the "bad news"—when, for example, a previously touted advance does not pan out, she said. Media organizations are criticized for being overly enthusiastic about the results of clinical trials, for underplaying the preliminary nature of the results or the small size of the study population, and for

underemphasizing the long time between the trial and a marketable treatment, said Won Tesoriero.[1]

Panelists discussed that reporting on research and on clinical trials focuses on potential benefits for several reasons: the constant preoccupation with what is "new"; audience interest in stories that affect them, which requires reporters to extrapolate findings to a tangible end point ("what this means is that there may someday be a cure for"); researchers' growing tendency to inflate the significance of their work; and for broadcasters, especially, the limited time (and space) for news stories, which does not allow for extensive context and caveats.

Roger Sergel, Managing Editor, Medical Unit, ABC News, suggested that one approach would be for journalists to analyze studies' confidence intervals and not report on those with weak significance levels, or report only cautiously on studies that rely on associations, since audiences likely do not understand that an association does not prove cause and effect.

Particularly helpful, said Peggy Peck, Vice President and Executive Editor, MedPage Today, was including patient histories in the story package presented to the news media. These personal stories engage viewers, listeners, and readers and help provide context and, at times, a more complete picture. To maintain a balance between what is "new" and what is "important," journalists have to carefully evaluate the real significance of the medical information that comes to them.

RELATIONSHIPS WITH RESEARCHERS

Researchers tend to want journalists to report on what they themselves are interested in—that is, the *process* of research, Sergel said—but journalists believe the public does not understand and is not very interested in the research process. Instead, reporters want to know how a set of trial results will affect their audience.

The panelists discussed that universities and research centers—as well as some individual researchers—have learned the value in aggressively promoting research results. Greater visibility enhances the prospects for obtaining additional grants, career advancement, and institutional prestige. As a result, Sergel said, news releases that an institution's public relations department writes about a study typically suggest the results are very exciting and newsworthy. At the same time, investigators have learned to speak in hyperbole and use words like "landmark," "practice-changing," and "grand slam," said Peck.

[1] A recent FDA user's guide for communicating risks and benefits includes a discussion of health care news coverage and strategies for improving the accurate representation of scientific findings by the media (FDA, 2011c, Chapter 18).

Researchers have become "too media savvy," Peck continued. "They're looking to give you the perfect sound bite." Editors and journalists, she said, "have to train our colleagues to take a giant step back from language like that."

Reporters would find it helpful if researchers and institutions were more realistic about the broader significance of their findings—in terms of number of people affected or size of the advance in knowledge—when deciding to pitch a story. "But if it really could be a potential game changer down the road, that's enough too," said Won Tesoriero.

Some editors have become cautious of stories where there seems to be too much excitement, because of the possibility that the story will be overblown. Sergel believes that researchers are responsible for making sure that news releases, public relations statements, and researchers' own statements do not overstate the study findings or their significance.

RELATIONSHIPS WITH THE AUDIENCE

Unlike some other news beats, health is very "selfish." People can be broadly interested in politics or economics with no particular stake in the coverage, Sergel said, but, for most people, a health story immediately raises the question, "How will this affect me or my family?"

He further suggested that there may be too much reporting on medicine, including a lot of early, inconclusive, and unclear studies that fall into a gray area. Reporting could be much more selective, because the more equivocal information is likely to be lost on people. However, Americans tend to want more health and science news. It might be more useful, Sergel suggested, to concentrate on stories about the care people receive, as was the news focus during the debate on health care reform.

Americans' low health and science literacy, discussed throughout the workshop, affects the way that research news is covered and health information is presented. Many in the advocacy community, for example, recognize that communications materials intended for patients, family members, and caregivers must be written at an 8th-grade level, said Joan Finnegan Brooks, Patient-Focused Market Research. CF advocates, for example, have included patient representatives on their communications committees to ensure that medical information is clear and not open to misinterpretation.

Broadcast reporters, especially, try to avoid jargon, such as words like "randomized" or "placebo," which they believe alienate viewers. Although the report might cover a study that finds interesting associations, that term might not be used; instead, the limitations of that type of research finding might be described. Having to distill stories in both time

and language creates some frustration for journalists who do not want to reduce them to the point they lose their meaning, said Won Tesoriero.

But even if a reporter cannot use jargon, a workshop participant said, "you have to tell people the truth," and the truth does not reside only in multisyllable words.

CONFLICT OF INTEREST

Journalists have an essential occupational preoccupation with the reliability of their sources. Situations that reflect on the credibility of researchers—most notably, potential conflicts of interest that arise when medical researchers receive funds from drug companies or other sources that may try to influence research outcomes—are looked at carefully by major news organizations, as Peck described.

As a result, journalists may report explicitly on those conflicts or adopt other strategies to let their audiences know where financial support for a project originated. *MedPage Today*, for example, includes a box at the bottom of articles that includes financial disclosures.

Financial disclosure—"following the money"—is crucial if people are to understand the factors that may be driving the science. However, journalists recognize that conflicts of interest are not necessarily black and white, Won Tesoriero said. Where does a conflict begin? It is not surprising when researchers receive grants from a number of corporate sources—particularly if they are field leaders. Receiving corporate support for research projects is different from being part of a company's speaker's bureau or participating in other compensated activities. And, if there is an apparent conflict, is that affecting what the researcher says? It takes a certain level of sophistication to understand the range of conflicts before making a judgment, she said.

Sergel pointed out that there are differing views even among journalists about what is a conflict, and sometimes it is difficult to sort out whether a story should be dismissed simply because of a potential conflict. It is not possible to lay down an absolute rule, inasmuch as the funding of many lengthy clinical trials may have come from multiple sources over time.

Although the public at large may not be interested in industry-researcher relationships, clinicians—the people who will use the information in the care of patients—should be aware when they exist, said Peck. Reporting on them alerts clinicians to look deeper.

Often journalists learn about potential conflicts a scientist may have from other researchers, and, increasingly, institutional ethics committees' insistence on greater transparency gives journalists additional information.

From the point of view of a disease advocacy organization, having key researchers and clinicians involved with industry is a positive, if that creates the opportunity to advise biotech or pharmaceutical companies about a particular disease. Finnegan Brooks said that these industry-researcher relationships are how interest in diseases—especially diseases with relatively few patients (small markets from the pharmaceutical company's point of view)—gains traction.

If conflict-of-interest rules are too stringent, it "knocks out everybody that we would want at the table," said Finnegan Brooks.

7

Novel Clinical Trial Designs

"Our clinicians engage in research now. It's the usual care of the patient, and we generate research information from it."
—Louis Fiore, VA Boston Healthcare System

The workshop session on innovations in trial design began with a series of challenging questions by the moderator, Michael Krams, Vice President, Head of Neurology Franchise, Johnson & Johnson. How can we conduct clinical trials such that actionable results come from them? How can we translate the creation of knowledge into impact for society? Will innovative trial designs let us emulate the stunning performance improvements that have been accomplished in computing? And, as was mentioned by Bram Zuckerman, Director, Division of Cardiovascular Devices, Center for Devices and Radiological Health (CDRH), FDA, from a practical standpoint, can we create a library of case studies so that people can see how these methods work?

ADAPTIVE CLINICAL TRIAL DESIGNS[1]

While the annual number of new drug approvals in the United States has remained relatively flat for the past several decades—hovering more or less between 18 to 25—what has not been constant are the costs of drug trials, which have been increasing at about triple the inflation rate. Part of the problem stems from the success in genomic sequencing and the explosion in the number of new, less well validated targets, with their resultant high failure rates.

[1] Material in this section is based on the presentation by Michael Parides, Professor of Biostatistics, Department of Health Evidence and Policy, Mount Sinai School of Medicine.

These rising costs can be considered not as the price of success, but the price of failure—an insight credited to Robert Hemmings.[2] If clinical trial designs could detect failure sooner, in phase I or even phase II, then trials would not proceed to the later phases, where costs have been increasing most dramatically.

There are many ways for a trial to fail, said Michael Parides, Mount Sinai School of Medicine. Perhaps the compound simply does not work, or not at the dose being tested, or not in the expected patient population. Sometimes the study design is not optimal or the entire drug development plan is flawed. Many phase III trials that fail have problems that can be traced to phase I and II trials that did not produce the quality of information needed for the confirmatory trial to be designed appropriately.

Improved clinical trial designs hold great promise for making the clinical trial enterprise more efficient, primarily by earlier detection of inadequate benefit. At the same time, treatments that do offer benefit need to be accurately recognized, so that they are not prematurely abandoned, he said. Reliably discarding compounds that do not work and keeping those that do increases the overall trial success rate.

A promising approach to improving trial design is "adaptive design." Adaptive design is not a new idea, but it is becoming increasingly interesting to researchers. In general, adaptive designs use interim data to modify an ongoing trial without undermining its validity and integrity or introducing bias. Modifications might include correcting inaccurate assumptions or reestimating the sample size. The adaptations are carefully planned in advance and are prespecified, such that, while the trial design is flexible, it is not completely open-ended. There are numerous variations on the adaptive design theme, some more accepted than others.

Recent developments have made adaptive trial designs more feasible. Perhaps most important is the increased use of Bayesian statistical methods, made feasible by desktop computing power. Bayesian approaches allow continual reassessment of trial findings with respect to, for example, maximum tolerable dose. Rather than assigning patients to trial doses according to an algorithm that does not make dose-limiting toxicity explicit, in the Bayesian approach, the researcher makes an assumption about the relationship between dose and toxicity; data are collected; the relationship is reassessed; and the process repeats through some number of cycles. The key element, Parides said, is the notion of continuous learning: Each new patient has the benefit of what was learned from each previous patient. Most such applications require simulations, an approach

[2] Dr. Hemmings is Statistics Unit Manager of the U.K. Medicines and Healthcare Products Regulatory Agency.

that fits the drug development paradigm well, as a series of revisions of an original idea, updated with additional information. This is a useful model for exploratory trials.

A second new element is the bolder nature of some types of adaptive design, for example, unblinded sample size estimation, changing the primary end point, patient enrichment (that is, once a trial starts, the investigator perceives there may be subgroups for which the treatment works better and stops randomizing people outside of those subgroups), and seamless phase II/phase III designs. Strategies such as these require rigorous statistical management.

Information gained from the use of these statistical methods allows researchers to abandon a trial arm or curtail an entire trial early in development if it is not expected to work. For example, "adaptive dose-finding randomization" helps the researcher decide to drop treatment arms based on initial responses, whether due to toxicity, efficacy, or both; and even in a phase III confirmatory trial, where adjustments must be made cautiously, group sequential procedures are an accepted way to gain information that can lead to midcourse corrections or even trial termination.

A real-world trial conducted in LVAD recipients—people with end-stage heart failure surgically implanted with mechanical heart pumps—provides an example. The investigators wanted to know whether the trial was generating enough information to warrant continuation. Parides showed how the trial data would look if there were 20 patients each in the control group and the active therapy group. The number of treatment failures in the two groups was 13 (controls) and 10 (treatment). Conventional statistical methods would make it hard to judge whether the trial should be continued. The p value is 0.52, with a wide confidence interval. However, the customary reliance on p values in this case would be misguided, Parides said. When the same data are analyzed using Bayesian approaches, the first step is to assess the success probability for both groups. Due to the assumptions of clinical equipoise, these probabilities are the same, albeit unknown. After the data are collected, they are refitted to the model, revealing that the probability that the treatment is better than control is 75 percent. In this case the Bayesian analysis was a much more accurate way to present the data and one that made the decision to move forward with the trial clear.

At the more controversial end of the spectrum of potential trial adaptations is changing the study's primary endpoint. Serious problems can arise, as occurred a decade ago in the CAPRICORN trial, a multicenter, multinational, randomized, double-blind, placebo-controlled trial of whether beta-blockers plus routine medical management performed better than routine management alone after a heart attack (Colucci, 2004). The initial primary endpoint was all-cause mortality. As the trial was

under way, the mortality rate was lower than expected, but, because the study was blinded, the investigators did not know whether that was because one of the interventions was working very well, or whether both were effective. At that point, the researchers elevated a prespecified secondary endpoint—cardiovascular hospitalization—to be the coprimary endpoint. Unfortunately, it turned out that the result for this combined endpoint was not statistically significant, while the original would have been (a 23 percent reduction in all-cause mortality).

While adaptive designs undeniably have appeal, Parides said, they are not always better and not necessarily logistically simple or less expensive. On a trial-by-trial basis, adaptive designs may cost more, but they save money overall, he said, by preventing investment in futile exercises.

Motivating researchers to change the way they work and methods they use is difficult, Krams said. "As we all know, in the clinical R&D environment, culture eats strategy for lunch." When the number of scientists in academia, industry, and at FDA who are familiar with adaptive research methods gradually increases, these new methods may become more acceptable, said Parides. Methodological problems will be resolved, some approaches will fall by the wayside, and some will eventually become second nature.

Currently, researchers do what is feasible because it *is* feasible, rather than because it will produce the most useful endpoints, Krams said. The incentives are geared toward obtaining results as quickly as possible. Krams advised looking beyond an individual trial to an entire research program and assessing how many times a second trial is needed because of inconclusive answers to the research question. A more productive way of framing the incentives, therefore, is to work toward achieving the best information value per research unit invested.

USING POINT-OF-CARE CLINICAL TRIALS TO CREATE A LEARNING HEALTH CARE SYSTEM[3]

Randomized clinical trials remain the gold standard for determining a treatment's safety and efficacy, but their high costs and extended timelines and the delayed integration of their results into clinical care are problematic. Observational studies are less expensive and produce quicker results, but their findings are less reliable. Louis Fiore, Assistant Professor, VA Boston Healthcare System, described an initiative to meld the two methods, called "point-of-care clinical trials," which uses randomization

[3] This section of the report is based primarily on a presentation by Louis Fiore, Assistant Professor, U.S. Department of Veterans Affairs (VA) Boston Healthcare System.

to remove selection bias in an observational study. The method is being tested within the VA and led by the Boston VA Healthcare System. The long-term goal of this new research approach is to create a true learning health care system,[4] he said.

In most medical facilities, research and clinical departments are completely separate. Poorly funded researchers raise their own money and not until some years after their project ends do their findings become adopted by the clinical side of the house. A point-of-care approach would speed up adoption of treatment improvements and allow researchers to leverage the resources of the clinical services.

The VA is well positioned to try this approach for several reasons: its clinicians are interested in it; VA patients continually return to the system over a period of years; and the VA has a sophisticated EHR system, which allows patient records to be accessed from any VA facility.

According to Fiore, point-of-care clinical research is a quality improvement strategy, and it has a number of advantages over traditional research methods:

- The studies compare existing approved drugs with known toxicities and therefore do not involve IND applications or require IRB approval—they ask "which is better?" questions.
- They are designed so that a substantial portion of their operations can be conducted by clinical staff as part of routine care delivery, with study data captured passively in the EHR.
- They do not disrupt regular clinical care, require lengthy and repeated discussions with patients, or demand unusual data collection.
- Participating patients are drawn from the day-to-day caseload of the VA hospital, with minimal exclusion criteria, and thus are a generalizable population.
- Minimal extra outpatient visits are required; when participants are discharged and return as outpatients, the next set of data is captured.
- The researcher has access to real experiences and outcomes, not surrogate ones, and follow-up can continue as long as desired.
- The research is low cost, even through the follow-up phase, costing only an estimated 10 to 30 percent of the cost of an industry-sponsored trial.

[4] The learning health care system can be defined as the seamless and continuous development and application of evidence in the course of patient care. In such a system, each patient care experience naturally reflects the best available evidence, and, in turn, adds seamlessly to learning what works best in different circumstances (IOM, 2008).

- Finally, since the research is being done in the same health care system that is going to use the results, physicians are more likely to have confidence in them. In fact, they have generated the results themselves.

In short, this is a pragmatic approach to study design that produces very pragmatic results, germane to a hospital's specific patient population (see Box 7-1). Generalizing to a different facility requires analyzing differences in the health care systems and patients served, not the treatment being tested, Fiore said.

Administratively, point-of-care research is facilitated by what Fiore terms a "rational approach" to regulatory oversight and obtaining informed consent. The question of whether clinicians are participating in a trial, versus merely going about their regular business, is an important

BOX 7-1[a]
Point-of-Care Clinical Trial Pilot Study

To test the feasibility of point-of-care research, VA investigators at the eight VA hospitals in the six-state New England region are comparing weight-based versus sliding-scale determinations of insulin dose in non-intensive care unit patients with diabetes. VA physicians and the clinical literature have been divided on which approach is best. The study's primary endpoint is hospital length-of-stay, and the secondary endpoint is glycemic control and readmission within 30 days.

When patients enter the hospital needing insulin, physicians (via EHR) are presented with three options. This is the "point of care." Options 2 and 3 provide an insulin regimen according to usual weight-based or sliding-scale protocols. The first option is "no preference" and invites clinicians to enroll their patients in a study comparing the two protocols. If they choose the study, the patient is automatically randomized to one or the other treatment, a nurse obtains consent, and a progress note about the study is automatically entered in the record.

From there the computer takes over, writing the orders for the clinician to sign. The study is fully integrated into the hospital's informatics system, with the EHRs tracking which of the two treatments produces the best outcomes. Using adaptive randomization and Bayesian approaches, randomization may start out 1:1, but as one arm of the trial becomes statistically superior, randomization will change to 60:40, 70:30, and so on. Eventually, new patients will be randomized 99:1 to the effective arm, and the study will conclude. In effect, the more successful treatment will become the standard of practice in the facility "directly as the study is happening," Fiore said.

[a] Based on the presentation by Louis Fiore, Assistant Professor, VA Boston Healthcare System.

one. Declaring them "researchers" might impose regulatory requirements related to, for example, serious adverse-event reporting. If drugs are well established (like warfarin), Fiore queried, is it really necessary to report adverse events (like bleeding)? Similarly, is written informed consent needed for low-risk comparison studies—for example, one insulin type versus another—or will oral consent suffice? Ideally, Fiore believes, when a patient is admitted to a VA facility and provides the usual consent to care, the form would include consent to participate in this type of research. This blanket "opt-in" consent would be documented in the EHR.

The electronic record is key to the efficiency and national scalability of point-of-care research. Researchers work with information technology staff to modify the record to incorporate tools and bits of code that allow it to randomize, extract data, and create notifications. At the end of the study, the randomization node can be easily changed to a decision-support node. And, economic analyses are simple because all the costs are already recorded in the health system.

Because VA patients' electronic records are available at any VA facility nationwide, additional opportunities to participate in trials present themselves. For example, a veteran at a VA facility remote from any research center might have prostate cancer (or other tissue) analyzed, with the results recorded in the EHR. At another VA site engaged in prostate cancer research, a drug trial might be under way for which the patient would be an appropriate participant. Mining the EHR data allows that patient to be identified and facilitates the patient's engagement in the trial. Fiore said this would move research to the patient, rather than the patient to the research.

Another potential benefit of point-of-care trials would be to create a culture change in the way clinicians and patients think about treatment trials. If doctors and patients want treatments based on the best medical knowledge, with strategies that have been tried and tested—in other words, if they want to provide and receive evidence-based medicine—then they need to be part of the evidence-gathering process.

A fundamental challenge to the diffusion of point-of-care research is the lack of appreciation and reward for collaborative work within academic medicine. The days of lone investigators owning data and carrying out projects in isolation are numbered in the clinical sciences, Fiore believes. Yet, the academic infrastructure has not even begun to dismantle these silos. Additionally, Zuckerman mentioned that the training environment needs to change, so that medical schools produce physicians who are clinical trialists and clinical research courses become a standard part of the curriculum.

The point-of-care model requires a reconsideration of the relationship between clinical care and research. Clinical effectiveness research is "engineering," and as much as it is needed, there are too many research

questions, too few investigators, and too little funding. Clinical care dollars, being spent in any case, can generate the data. If the health care system used point-of-care research methods to learn from its experiences, it could, Fiore said, "make taking care of patients a whole lot quicker, more effective, and probably cheaper."

THE FOOD AND DRUG ADMINISTRATION PERSPECTIVE[5]

FDA leaders perceive a role for the agency in encouraging innovation and promoting efficient development of new and improved medical products, said Douglas C. Throckmorton, Deputy Director for Regulatory Programs, CDER, FDA. FDA staff attempt to make researchers' jobs easier by designing clear and thoughtful rules and interpretations, publishing guidances regarding them, and ensuring they are applied equally to everyone. The goal is to help innovation, he said, not hinder it (FDA, 2010, 2011d). For example, draft FDA guidance on the use of adaptive trial designs has been released. The document starts with adaptive designs that are used regularly and would be rather easy to accept and ends with some of the more complicated and problematic adaptations that might take a fair degree of discussion.

Promoting an efficient process for medical products development means more than waiting for researchers to submit their trial applications, Throckmorton said. It means supporting appropriate collaborations, building opportunities, developing standards that enable efficient drug development, and building support for academic science. FDA staff frequently engages in partnerships, collaborations, and consortia, such as CTTI, a public-private collaboration with Duke University. CTTI members, drawn from government, industry, academia, and patient groups, are examining and prioritizing the major challenges in the conduct of clinical trials, with the goal of increasing their quality and efficiency.

In addition, FDA is attempting to make its own operations more efficient, Throckmorton said. The agency is working to focus the clinical trials monitoring program on trial sites where the most problems are likely, rather than treating all sites equally. In an effort to build quality into a clinical trial from the beginning, Pfizer and FDA staff are conducting a pilot test in which they are simultaneously designing a phase III study and its monitoring program.

A wide range of regulatory approaches is necessary to carry out FDA's regulatory authority over devices, which include everything from

[5] This section is based on the workshop presentations of Douglas C. Throckmorton, Deputy Director for Regulatory Programs, Center for Drug Evaluation and Research (CDER), FDA; and of Bram Zuckerman, Director, Division of Cardiovascular Devices, CDRH, FDA.

sterile gloves to LVADs. The most stringent regulations cover the Class III, high-risk, life-supporting products that require premarket approval (PMA), which in many ways is similar to the approval pathway for a new drug.

The agency's challenge is to ensure the safety and effectiveness of medical devices even as science is continually evolving, devices are becoming increasingly complex, and the existing regulatory pathways to market were established in 1976. In the meantime, Zuckerman said, some of the distinctions between "drug" and "device" have blurred.

A practical consideration for device developers is the need to engage with the FDA's CDRH "early and often" regarding its clinical trial strategy, Zuckerman noted. Adaptive designs may be particularly helpful to device developers, as many of them are small companies with correspondingly small research budgets. But even large device manufacturers may want trial results quickly, because a device's life cycle is often relatively short. An estimated 10 to 15 percent of device applications currently include some combination of Bayesian or adaptive designs.

8

The Health System's Structure and Culture

BUILDING A SUPPORTIVE CLINICAL TRIALS ENVIRONMENT IN ACADEMIA[1]

Clinical trial organization is typically one-off. There is no guiding structure or organizational infrastructure. Everyone involved in a trial is brought together around the conduct of that single trial, then the group disbands. Little learning about "best trial practices" is carried forward, particularly in light of the high dropout rate among investigators.

Fundamental obstacles hindering the academic clinical trials enterprise in the United States, as cited by Eric Rose, Chair of the Department of Health Evidence and Policy, Mount Sinai School of Medicine, are cultural, economic, and ethical. These obstacles are responsible for

- the slow pace of designing and implementing trials;
- declining patient enrollment at trial sites;
- loss of clinical investigators to other work; and
- the failure to produce evidence for optimal clinical practice.

Evidence of our current difficulties is apparent in a range of data on trial experience. An estimated 20 percent of principal investigators fail to enroll a single patient, and another 30 percent under-enroll in a given trial. Moreover, the proportion of people randomized into a trial who complete

[1] This section is based on the presentation by Eric Rose, Chair of the Department of Health Evidence and Policy, Mount Sinai School of Medicine, and workshop discussions.

it is declining—less than half, in 2003-2006. Finally, 38 percent of principal investigators who participated in clinical trials between 2000 and 2005 did not return to conduct another clinical trial within the next 3 years.

Cultural Obstacles

More than 90 percent of trial delays are caused by overambitious timelines and difficulties with patient enrollment. Timelines turn out to be too optimistic in large part because investigators encounter administrative and institutional hurdles, such as protracted budget negotiations, slow IRB review and approval, and, as noted, poor patient recruitment. At

BOX 8-1[a]
Building Connections Between Community Physicians and Clinical Trials: Challenges and Potential Solutions

Community physicians play a key role in the clinical trials enterprise. In discussing the need to bring clinical trials to where the patients are, workshop participants noted that community physicians are important stakeholders and partners in conducting clinical trials. Community physicians can engage in a number of points across the lifecycle of a clinical trial—from the generation of research questions, service as the principal investigator, facilitating the recruitment and retention of patients, and community-focused dissemination of trial results. Panelists and workshop participants discussed a number of challenges and potential solutions to facilitate the development of effective connections between community physicians and researchers conducting clinical trials in academic medicine.

Challenges discussed at the workshop for community physician engagement in clinical trials:

- Significant time constraints due to busy clinical practice and the concern that it will take the physician extra time to locate an appropriate clinical trial for a patient and explain the value of the trial to the patient.
- Information overload (e.g., a physician receiving "100 emails per day" concerning clinical trials, but none of those coming from an entity or individual the physician knows or trusts).
- Failure of communication with researchers throughout the lifecycle of the trial—including concern that physicians will be caught by surprise or will be unaware of treatments and side effects their patients experience as part of the trial.
- General lack of physician knowledge as to the array of clinical trials available and how the trial might help their patients.
- Heterogeneous patient mix and a diversity of patient medical needs that may or may not be solved or improved through care received in a clinical trial.

least some of these problems might be remediated with a stronger institutional infrastructure that could support investigators as they navigate the approval process.

Nor are there strong incentives for investigators to participate in research. Trial involvement earns little currency within the culture of academia when decisions about appointments and promotions are made.

Finally, Rose noted that a minority of the physician population is actively engaged in recruiting and enrolling patients in clinical trials (see Box 8-1 for additional discussion of physician engagement in clinical trials). Encouraging participation is not part of their routine practice or their hospital departments' priorities, quality plan, or metrics. The opportunity

- Need for consideration of patients' insurance coverage, or lack thereof, which could determine whether a clinical trial would make financial sense.

Methods and potential solutions discussed at the workshop to improve community physician engagement in clinical trials:

- Prioritize timely, two-way communication among community physicians and researchers throughout the course of the trial.
- Educate and assist the community physician in distilling information on currently available clinical trials and the importance of particular trials for the physician's patients.
- Simplify and improve the clinical trials infrastructure so that patients can participate in a trial in their community (e.g., a cancer patient in Cincinnati can receive a novel agent as part of a clinical trial at his/her oncologist's office, instead of driving to Indianapolis three weeks each month).
- Partner with community physicians early in the development of a clinical trial to develop research questions that are of value to them and clinical trial protocols that can be implemented in the clinical practice setting without major difficulties.

[a] Based on the panel discussion with Rafat Abonour, Chairman, Hoosier Oncology Group, Associate Dean for Clinical Research, Professor of Medicine, Professor of Pathology and Laboratory Medicine, Indiana University; Sanford Friedman, Associate Clinical Professor of Medicine of Cardiology, The Mount Sinai Hospital; Carol Horowitz, Associate Professor, Department of Health Evidence and Policy, Mount Sinai School of Medicine; Ramon Murphy, Clinical Professor of Pediatrics and Preventive Medicine, Vice-Chair of Department of Pediatrics, Voluntary Affairs, Associate Director, Mount Sinai Global Health Center, and Director, Off-Site Pediatric Residency Program at the Mount Sinai School of Medicine; and Hugh Sampson, Professor of Pediatrics and Immunology, Mount Sinai School of Medicine, Director of the Jaffe Food Allergy Institute, Dean for Translational Biomedical Research, and Principal Investigator and Director, Conduits, Institutes for Translational Sciences, Mount Sinai Medical Center. This box provides an integrated summary of each of their remarks and discussions with workshop participants during the panel, and should not be construed as reflecting consensus or endorsement by the planning committee, the Forum, or the National Academies.

to enroll patients is neglected despite the apparent willingness of many Americans to participate in trials, if asked. Kenneth Davis, Mount Sinai School of Medicine, noted that metrics and criteria are needed for evaluating the performance of clinicians who engage in clinical trials during promotion and tenure discussions. People who design and conduct clinical trials should not be regarded as all the same; they may be on different tracks. They may be coming up with the new ideas and, therefore, are on a research track; or, they may be skilled at developing creative ways to implement trials and, therefore, are on a clinical educator track. However, a third group includes people doing clinical trials who are not developing the ideas, nor are they innovators with respect to developing new methods, measures, biomarkers, and the like. In that case, they may not be on a tenure track in academic medicine, said Davis.

Economic Obstacles

Economic disincentives appear at every stage of trial design and implementation.

Clinical departments, hospitals, medical schools, and academic medical centers have little or no budget to support trial infrastructures. However, the CTSAs are one unique example of a clinical research mechanism that supports and funds the development of trial infrastructures.

Enrollment payments are typically given to physicians after patient enrollment. But the capital to support trial infrastructure needs to be in place prior to enrollment. Patients randomized to control groups that do not receive a billable procedure generate less clinical revenue for physicians and hospitals than if those patients were not in the trial and received the procedure, thus creating enormous resistance to using control groups.

Finally, Rose said, specialists frequently perceive randomization of patients referred to them by physicians for a treatment as a threat to their referral relationships and their standing in that community.

Ethical Obstacles

Among the ethical obstacles a researcher must overcome are those involving perception and misperception; for example, the perception that trial participants are being treated as guinea pigs or that randomization is a threat to the physician's unfettered exercise of clinical judgment. A more tangible worry may be a concern or perception that the investigators or clinical community lack equipoise with regard to the trial hypothesis. An underlying dilemma is that most trials are designed to help bring a product to market, Rose said, not to identify the best options for patients.

The latter issue reemerged in the panel discussion, led by the state-

ment that not all clinical studies are equal. "Do we really need another study of the tenth variation on the same theme, or another lookalike drug?" a panelist asked.

Potential Solutions

The key cultural change, Rose believes, has to be to reenvision quality measurement. Current metrics for determining quality in medical care are substantially poorer than those in other high-risk industries where quality is measured, monitored, and improved more rigorously. Quality metrics that would make sense in health care involve patient characterization, phenotype definition, process definition and monitoring, and outcomes. Processes and outcomes should be benchmarked against peers and against past performance, and they should be iterative, not static.

The competencies required to assess patient care quality in this way go well behind those that have traditionally defined the "good doctor." Some such competencies identified by the Accreditation Council for Graduate Medical Education are system-based practice, practice-based learning, communications skills, and professionalism (ACGME, 2007). Reinforcing the "learning organization" goal articulated in an earlier session, Rose said that "medical quality measurement is essentially a broad array of ongoing observational clinical trials," and he further argued that an academic medical center that is not managing quality, using the tools and skills integral to observational trials is, by definition, not a high-quality institution.

Enrolling patients in clinical trials is typically not used to measure individual academicians' divisional, departmental, or institutional performance. In the past 5 years, the percentage of patients enrolled in clinical trials was made a performance metric for clinicians in Columbia University Medical Center's department of surgery. Chiefs of divisions that were not enrolling at least 10 percent of their patients in clinical trials were considered to be underperforming. Performance metrics like this will create a culture vastly more supportive of clinical trials.

PUBLIC-PRIVATE PARTNERSHIPS IN CANCER TRIALS[2]

Cancer is not a monolith but has been revealed as thousands of different genetically distinct and molecularly driven diseases. New technology that over the past few years has permitted researchers and

[2] This section is based on the presentation by George D. Demetri, Senior Vice President for Experimental Therapeutics, Dana-Farber Cancer Institute and Director, Ludwig Center at Dana-Farber/Harvard Cancer Center, and workshop discussions.

pathologists to examine tissue at the chromosomal level has revealed significant differences among cancers once thought to be single entities. Without the ability to differentiate cancer types and treat them with specific therapies, treatment has taken place in one of those "evidence-free zones," said George D. Demetri, Senior Vice President for Experimental Therapeutics, Dana-Farber Cancer Institute and Director, Ludwig Center at Dana-Farber/Harvard Cancer Center.

Understanding the differences among cancer types leads to the question: How do we personalize therapy and guide patients into the right trial at the right time for the specific cancer they have? According to Demetri, patients' interest in personalized approaches is rekindling their interest in clinical studies. However, referrals are slowed because many clinicians have come to believe that their patients will not be eligible for a trial until none of the existing treatments work for them. The result is that patients referred to trials can be among the most difficult to treat, making it increasingly difficult to achieve the next advance.

Demetri described several research projects that have taken advantage of new insights about the unique genetic characteristics of specific cancers involving sarcomas. Two similar but rare sarcomas (gastrointestinal stromal tumors [GISTs] and leiomyosarcoma) are cancers of the smooth muscle cells that had previously been undistinguishable but are now recognized as separate diseases. Laboratory scientists studying mutant cells in the gut found a causative target for GISTs, and further research showed that, if an abnormal enzyme is shut down, the GIST cells die. Previously, there was little to offer these patients, but the treatment developed from these observations works perfectly, according to Demetri.

To recruit patients for an early study of this drug, the researchers designed a website that would appear in response to Google searches for either GIST or leiomyosarcoma, since the chance for conflating the two was so high. This helped the team educate both patients and clinicians to reexamine previous diagnoses of these cancers.

The study of rare cancers poses several patient recruitment problems. Because the number of cases is so small, one strategy is to recruit patients across multiple centers, either in the United States or through collaboration with researchers in other countries. Recruitment (and operation of an international study) is costly, and, he said, the National Cancer Institute has requirements for regulatory review of multicenter international trials that preclude application by a single U.S. cancer investigator. Demetri reported that in multiple instances, drug sponsors have helped to overcome obstacles related to managing and implementing a trial. For example:

- A trial originally being conducted in two centers was able to expand to 365 centers across the world once the drug sponsor, Pfizer, contributed to its management.
- For another trial, Demetri wrote the phase III application and is the principal investigator, but Bayer Oncology is handling implementation in several hundred sites around the world.

In the latter case, Bayer Oncology had supported earlier phases and was willing to participate in the phase III trial because it believed that if the company did the work on its own it would require "an extra seven years and $50 million," Demetri said.

Although sarcomas collectively account for only 1 percent of human cancer cases, the knowledge gained through identification of successful molecularly targeted therapies appears applicable to other kinds of cancers and has shown the real value of public-private collaboration.

Underscoring this point, Gail Cassell, Department of Social and Global Medicine, Harvard Medical School, noted that other countries "have figured out why the United States has been so successful in biomedical research, and it is the collaboration between the public and private sectors." Moreover, Cassell pointed to a survey that indicates that Americans strongly support cross-sector and cross-institutional collaboration (Research!America, 2010).

ENGAGING COMMUNITY PHYSICIANS IN RHEUMATOID ARTHRITIS RESEARCH[3]

The Rheumatoid Arthritis Investigational Network (RAIN) began in 1989, in part due to perceived problems with rheumatoid arthritis drug trials sponsored by industry, specifically:

- Patient groups studied were not representative of or generalizable to the whole population
- Active therapies were not compared to each other
- Placebos were used liberally
- Patients and their clinicians often did not know which arm patients were assigned to, even long after trial completion
- Investigators were believed to have severe conflicts of interest
- There was a bias toward publication of only those trials that have a positive (statistically significant) result

[3] This section is based on the presentation by James O'Dell, Rheumatoid Arthritis Investigational Network (RAIN), Larsen Professor, Vice Chair Internal Medicine, Chief of Rheumatology, University of Nebraska.

- The trials had an underlying objective of maximizing the effects of the sponsor's product, not producing maximum benefit to patients

RAIN is housed at the University of Nebraska and involves some 40 practicing rheumatologists from six states—mostly in the Midwest. It specializes in investigator-initiated trials that are conducted in the offices of physicians in private practice. The university provides both infrastructure and trial experience so that the private clinicians are not burdened with responsibilities for trial startup. For example, about half of them do not have their own IRBs, in which case they become offsite investigators of the university; for the remainder, the university IRB coordinates with the physician's IRB. As a trial proceeds, communication and interaction with physicians, trial study coordinators in different sites, and the nurses involved are scrupulously maintained, said James O'Dell, RAIN, Larsen Professor, Vice Chair Internal Medicine, Chief of Rheumatology, University of Nebraska.

The first RAIN trial, results of which were published in the *New England Journal of Medicine*, took 7 years to reach publication (O'Dell et al., 1996) but has been credited with popularizing combination therapies for rheumatoid arthritis. (RAIN also was the first to publish information on genetic associations with treatment responses.)

From the beginning, RAIN projects have been designed to relate to how clinicians actually take care of patients. To accomplish this, the organizers meet with RAIN clinicians (and patients) and together decide the questions the trial will attempt to answer and details of the research protocol. Examples of questions of direct relevance to practicing clinicians that O'Dell cited are:

- How much improvement has the patient experienced, regardless of starting point?
- Can we predict, based on studies of first-degree relatives of patients, who will develop rheumatoid arthritis in the next 2 to 5 years?

In RAIN's first trial, the protocol design responded to clinicians' concerns that their patients not be kept on a therapy that did not work for them. As a consequence, the protocol specified that if patients were not having good results, the team would increase medication dosages, and if they still did not experience at least a 50 percent improvement, they would come out of the trial after a year.

RAIN also participated in a collaborative trial called TEAR (Treatment of Early Aggressive Rheumatoid Arthritis) out of recognition that, even with approximately 40 physicians in its network, running a clinical trial

is so complicated that it must work with other teams. As a result, O'Dell said, RAIN has engaged in a number of research consortia and collaborations with academic institutions and VA. In several of these trials, RAIN was the primary enroller of patients, indicating the participating physicians' ongoing commitment to the network. When RAIN physicians enroll a certain number of patients they are named as authors in trial-related publications.

During the workshop discussion period, a participant suggested that, as the United States moves toward accountable care organizations, all of the incentives will be against physicians taking the time necessary to adequately inform patients about research projects. That difficulty may be counterbalanced in the future if it becomes feasible to collect study data directly from EHRs.

O'Dell attributes RAIN's success to having recruited the right investigators. By involving these clinicians from the start of its studies, they have shared ownership of protocols, trial implementation, and results. Because they understand why the trial was designed as it was, they are more effective at keeping their patients involved. Finally, they are much more likely to have confidence in and adopt the therapeutic approaches the trials show to be more effective, because, in many cases, this greater effectiveness has been demonstrated in their own patients.

9

Toward a Patient-Centered Strategy for Clinical Trials

THE CHANGING POLITICS OF CLINICAL TRIAL ENGAGEMENT[1]

Many people, perhaps especially those in the medical profession, think of the term "health politics" as an oxymoron, said Larry Brown, Professor of Health Policy and Management, Mailman School of Public Health at Columbia University, and that the one should have nothing to do with the other. However, the challenges and strategies involved in "politics" are those of managing deep conflicts in values and interests. Such issues are intrinsic to the clinical trial enterprise, which must ask itself questions like:

- What kinds of trials are worth doing, or more worth doing than others?
- What kinds of patients and what categories of diseases should be addressed in trials?
- Who ought to pay for them? And from whose budget should the funds come?

Thus, the goals of clinical trials have important and inescapable political dimensions because of the choices that will be made about which trials will be done and the parameters under which they will be carried out.

[1] This section is based on the presentation made by Larry Brown, Professor of Health Policy and Management, Mailman School of Public Health at Columbia University.

Goals of Clinical Trials

Society wants trials that will advance the cause of evidence-based medicine, improve the quality and effectiveness of care, and correct errors in past practice. Desired trial goals are to save money for the health care system, to identify what does not work, and to be a force for cost containment. While clinical trials should be robust and efficient and timely and accessible, they should also honor a lengthening list of social criteria and priorities: diversity of the study populations, meticulous patient safety, strict informed consent, rigorous institutional review, and, not least important, accountability with respect to investigators' conflicts of interest and the role of industry and private interests in sponsoring and shaping the trials.

Although it obviously would require heavier investment in clinical trials in order to achieve all these goals, Brown said, it is not so clear where that money should come from. Should it derive from new public money at a time when government budgets are under intense pressure? Should it be public money rechanneled from basic research to clinical evaluations? Should it be private money? Should institutions bear more of the costs of running trials? Should it come from a combination of these sources?

In part because of multiple goals, competing internal priorities, and funding uncertainties, over time researchers have not only increased the number of trials but also asked more of them, by making them more complex, and, in some ways, more internally conflicting. Researchers have complicated the design and execution of trials—essentially for political reasons—because trials stand at the center of converging, yet often incompatible, public and professional priorities and expectations.

The NIH Example

Managing the kinds of conflicts and tensions faced by trial researchers ought to be possible. Indeed, the lustrous history of biomedical research in the United States since the end of the Second World War, primarily under the auspices of NIH, suggests that is so.

NIH has developed an impressive list of political resources and strategies that might offer clues and cues for managing the current clinical trials enterprise. Brown provided a checklist of these NIH resources and strategies, along with some of the notable individuals involved, including the following:

- Strong entrepreneurial energies by **citizen advocates** of great skill and tenacity, such as Mary Lasker, known for her unflagging support of biomedical research, especially cancer research,

and Florence Mahoney, a colleague of Lasker's in the support of research, who developed a keen interest in aging and mental health. They and many other advocates put enormous skill and energy into supporting research over the long haul.

- Skillful advocacy for more research money by **disease groups**, which prompted growth in the number of NIH Institutes and Centers that focus on specific diseases, conditions, and treatment approaches, as well as increases in the total NIH budget over time.
- **Medical leaders** in specialty associations, faculty of academic medical centers, and academic medical center deans who have been dependable research champions when the need arose to discuss research needs with members of Congress, testify at congressional hearings, and make the case to the news media.
- Cultivation of **congressional champions**, for example, the late Senator Lister Hill (D-AL) and Representative John E. Fogarty (D-RI),[2] as well as numerous successors, rewarded for their efforts by public recognition and good press.
- Engagement of **prominent public figures and celebrities** in research advocacy. Recent examples include Elizabeth Taylor in HIV/AIDS research and Michael J. Fox in Parkinson's disease research.
- NIH's skillful use of the **news and information media.** A principal touch point with advocates and the news media has been NIH's insistence on the **integrity of the research funding process**, which employs peer review to award federal funding to leading scientific researchers.
- Finally, NIH responsiveness to **emerging groups and movements.** For example, when it became clear there was strong interest among Americans and important members of Congress in complementary and alternative medicine, NIH launched a small investigational program that now has grown to a Center with almost $1.3 billion in the President's fiscal year 2012 budget request.

Despite (or perhaps because of) these impressive efforts, expectations of how quickly biomedical science can "solve" major health issues have been unrealistic. In 1965, when President Lyndon Johnson launched the quest for a fully implantable artificial heart (which he wanted to have signed, sealed, and delivered by Valentine's Day, 1970), he said

[2] For whom were named, respectively, the Lister Hill National Center for Biomedical Communications (est. 1968), an intramural research division of the National Library of Medicine, and the John E. Fogarty International Center for Advanced Study in the Health Sciences (est. 1968), at the NIH.

what he wanted was results, not research, Brown noted. Other bumps in the road have appeared as well: ongoing disputes about the relative balance between basic and applied research, the best management and organization of NIH, the famous battle over an independent cancer institute, and the relationship between burden of disease and priorities for research funding. Nevertheless, over the years, the nation's federally funded research establishment has weathered such political challenges successfully.

Are these precedents transferable, translatable, and adaptable to new challenges? Clearly, the clinical trials enterprise faces some different, more complicated problems than does basic research, which, Brown remarked, is in some ways the easy case. For basic research, Congress appropriates money, the money goes to NIH, and it is allocated to leading research scientists who carry out studies in their laboratories. Research results are the ends of this process, and research is the clearly understood means to those ends. The importance of clinical studies is somewhat more difficult to communicate; it is harder to explain their rationale, legitimate their activities, and justify spending money on them.

Reasons for this difficulty include the culture of academic medical centers, which are more attuned to basic research than to clinical trials and less inclined to reward those who commit the enormous amounts of time and labor that trials require. Other reasons involve the challenges of site selection and management and the need for identification of local champions who will be effective politically, organizationally, and scientifically. But one of the biggest difficulties is recruiting and retaining people in trials, and whether the supply of participants is, or can be made, adequate to the demands of the increasing number of complex trials.

Challenges for Consumer Organizations

Brown put forth a number of factors that contribute to this recruitment and retention problem, including when people

- distrust the research enterprise, out of a generalized concern that researchers (or research sponsors) do not have patients' best interests at heart;
- fear that if they participate in a trial, something bad might happen to them, or they will not obtain beneficial treatment because they are in the wrong arm of the trial;
- believe it is advantageous, or at least not harmful, to wait and obtain the benefit of new treatments without going through the inconvenience of trial participation (free-rider problems);
- lack information about trials for which they might be eligible;

- have clinicians who do not know about relevant trials or do not encourage (or even discourage) their patients' participation;
- will incur costs for the treatments that insurance may not cover;
- are daunted by the complexity of enrollment and continued compliance and participation;
- experience burnout, fatigue, or boredom with the trial;
- lack either general literacy (including non-native speakers of English) or health literacy (affecting foreign-born and native speakers alike); and
- come from cultures within the United States that might be important to a trial for diversity reasons, but that have either no tradition of trial participation, or a negative experience with trials (see, e.g., Washington, 2006).

These dilemmas have no single response, and there is no obvious formula for moving forward in resolving them, Brown said. What may be needed is a concerted effort by a range of organizations acting as networks with carefully coordinated strategies to raise the prominence and secure the legitimacy of the clinical trials enterprise. Following the successful example of patient organizations, such as those for CF, Alzheimer's disease, and breast cancer, these crucial groups need to take on the challenge of forging links with medical specialty associations, academic medical centers, community physicians, and other relevant community organizations and leaders. This will help them present a united front of support for research to their patient and family constituents.

At the same time, consumer-oriented organizations must cultivate congressional and state-level champions. Attention at the state level is crucial, since roughly half the states mandate at least some insurance coverage for the cost of "routine care" received in clinical trials.[3] Such state-level opportunities should not be overlooked in a narrow focus on the federal government.

Finally, consumers and researchers must ally and make a clear case for clinical trials with the news and information media. It is a formidable translational challenge, Brown said, but one that might draw on the NIH political playbook.

[3] The Patient Protection and Affordable Care Act enacted in March 2010 requires health insurers to pay the cost of routine care delivered in phase I-IV clinical trials. The requirement will take effect in 2014 and will offer a baseline of insurance coverage for clinical trial participants in all 50 states and the District of Columbia (NCI, 2010).

Challenges for the Research Community

Clearly, clinical trials need a large number of effective champions. More and more strategic coordination among important organizations and the application of their collective leverage would support public-sector research efforts at the federal and state levels and foster robust public-private partnerships.

Brown offered some cautions. Because of the extraordinary demands of clinical trials, researchers must resist the temptation to overload trial protocols with multiple questions, variables, and population groups. If there are opportunities to use other kinds of research, including observational research, that will answer a research question just as well, those alternatives should be sought so as not to drive the clinical trials enterprise into the ground. Trials should be saved for when they truly offer a comparative advantage.

Given that the promotion of clinical trials is highly labor-, time-, and capital-intensive, is it worth the effort? Or a lost cause? A very good case, he said, can be made that it is indeed worth the effort, perhaps now more than ever.

In the nearly 7 decades since World War II, which encompass the major expansion of NIH, the United States has energetically pursued the technological imperative—striving to conquer numerous diseases—and has fairly consistently accepted the notion that "more is better." Remarkable results have accrued, except in the realm of health care costs. This nation now spends more than 17 percent of its gross domestic product on health care. With the country in the midst of an economic crisis, the implications of this current rate of health spending are disconcerting. Economists increasingly talk about the unsustainability of Medicare, Medicaid, and private health care spending, and Congress is at loggerheads over the way forward. In all domains of health care, cost concerns make this a serious and difficult time.

Research simply must figure out which treatments work (and work better) and which do not, and for whom. The country no longer has the luxury of assuming that more is truly better or taking a cavalier attitude toward evaluation, Brown said. That imperative is not solely because of cost containment, although reining in costs is a strong driver. It is also motivated by questions of quality. Increasingly, surveys show Americans realize that more health care does not necessarily mean better health. They recognize there are negative health consequences of overuse and overexposure to the system, that treatments have risks, medical errors occur alarmingly frequently, and imperfectly understood drugs may interact in dangerous ways or cause negative side effects.

People—often armed with Internet search results—increasingly ask their doctors for evidence. "You're recommending this treatment; what is the evidence it works and that it will work *for me*? Compared to what?" What these trends imply is that, in the overall portfolio of NIH and other research funders, both public and private, it only makes sense to expand investments in evaluative clinical studies that can answer such questions.

Concluding Remarks

In his concluding observations, Brown remarked that the nation has not moved faster in solving problems with clinical trials for a number of reasons, including, perhaps, because "clinical trials are means to the means to the end—that is, cures and solving medical problems." Meanwhile, many more immediate items crowd the agendas of patient groups, payers, academic medical centers, NIH, and others. Clinical trials simply have not risen high enough to motivate the investment of political and budgetary capital that would bring the supply of resources for trials into line with the growing demand for trial results. It takes time and effort to elevate an issue on any organization's agenda. It involves tradeoffs, he said, and it requires an organizational decision to expend the political capital, use the leverage, and deploy scarce human and monetary resources.

In the strategic portfolios that reflect the roles and missions of the key organizations to which NIH and other policy makers respond, it is simple common sense to raise the priority of clinical trials—to find out "what works" in health care. In the last analysis, the choices we make about clinical trials speak to how we as a society are willing to expend our political capital and what we really care about, Brown said.

CLOSING PANEL[4]

The workshop's final panel began with an overarching note by Jeffrey Drazen, *New England Journal of Medicine*, that this workshop was concerned with how to enhance the process for developing and testing clinical intervention strategies. Human capital is needed in order to translate ideas about strategy into treatments that can actually be used in clinical practice. New treatments may be readily integrated into clinical care, or they may require a reengineering of the whole process of care delivery, or they may land anywhere between these two poles.

[4] Participants in the summary panel were Jeffrey Drazen, Editor-in-Chief, *New England Journal of Medicine*; Juan Lertora, Director, Clinical Pharmacology, NIH Clinical Center; Greg Simon, Senior Vice President, Patient Engagement, Pfizer Inc.; and Nancy Sung, Senior Program Officer, Burroughs Wellcome Fund.

There is a fundamental misunderstanding of what constitutes scientific objectivity, said Greg Simon, Pfizer, Inc., that began when the investigator—"the man in the white coat"—was deemed the most important person in the room, that is, the objective observer. Unfortunately, there is no such thing. Objectivity is a social phenomenon.

Bringing the patient experience into research as a valued component is not "an act of charity," Simon said, it actually improves the social objectivity of the research. When patients are constantly an afterthought, researchers miss the substantial contribution that patients could make. As one example, involving patients would mean that the mind-body relationship, which is responsible for much of the confounding nature of placebos (a rock on which many costly trials have foundered), finally would have to be unraveled. Additional principles of public engagement in clinical trials discussed during the workshop are listed in Box 9-1.

The "learn-and-confirm" paradigm used in clinical trials—learning in the early stages and confirming in the later ones—could be aptly applied to the history of clinical trials itself, said Juan Lertora, NIH Clinical Center. At present, the research enterprise probably does not learn enough from trials that have failed. Was failure caused by questions posed incorrectly? he asked. Was implementation flawed? Did it result from lack of communication with and engagement of the community? Or, from the need for more financial or logistical help from the sponsor? Researchers can learn from failures as well as successes, said Lertora.

Experiences such as those of 23andMe and the other consumer-oriented websites described at the workshop suggest the depth of public interest in participating in clinical trials. Use of a web interface to provide registrants with instant feedback on survey questions is in striking contrast to the lack of information that participants in conventional trials—and their physicians—receive, according to Nancy Sung, Senior Program Officer, Burroughs Wellcome Fund. It helps explain why these customer-oriented sites have achieved the continued participation and active engagement of so many of their registrants. Working to ensure patient satisfaction for those participating in clinical trials is an independent goal that could also improve patient recruitment and retention.

People may be more willing to participate in trials when they see individuals who they believe will understand their culture and concerns. A long-term strategy to increase participation of minorities in clinical trials, said Sung, would be to continue efforts to increase preparation of underrepresented groups to be faculty and investigators.

Meanwhile, many patient groups have established research foundations that support targeted clinical research and encourage participation

BOX 9-1[a]
Principles of Public Engagement Discussed During the Workshop

- Even a relatively small patient group can ally itself with strong and visible partners. The CF community in the United States is small—only about 30,000 patients—but has teamed up with more than 110 clinical centers around the country to encourage CF research. These relationships also give the disease—and the people affected—greater visibility, attention, and influence.
- Highly visible events, such as the Alzheimer's Association's national Walk to End Alzheimer's, raises awareness of Alzheimer's disease (as well as funds) among large numbers of the public.
- Increasingly, websites offer numerous ways for families and volunteers not just to passively learn about health conditions, but also to actively participate in research.
- Voluntary health organizations can work with a resource people trust—their doctors—who can act as information conduits and legitimate participation in trials and other disease advocacy activities.
- Multicenter clinical research projects find that different trial sites enroll patients at markedly different rates, indicating that concerted efforts to reach out to the community and to persuade referring doctors to enroll their patients in a trial could make a difference.
- It is important that researchers be clear with both patients and doctors about the state of the science and the purpose of the trial, bearing in mind the vast differences in health and science literacy that impede effective communication.
- A more effective communication will present trial information within the framework of the patient's motivation to participate in research, not in terms of the researcher's goals.
- It takes time and energy to gain community input and forge communication links.
- Partnership with community representatives in the trial planning permits addressing of the issues *they* want to know more about and helps ensure the community will benefit from the research effort.

[a] Based on workshop panel discussions and presentations. Statements, recommendations, and opinions expressed are those of individual presenters and participants and are not necessarily endorsed or verified by the Forum or the National Academies, and they should not be construed as reflecting any group consensus.

in it. The Health Research Alliance (HRA) is a consortium of nearly 50 nonprofit, nongovernmental funders of biomedical research and includes numerous patient groups.[5]

[5] The HRA fosters open communication and collaboration among its members; provides data and analysis about the funding of biomedical research and training by HRA member organizations; identifies gaps in funding and facilitates innovative grant making; and addresses key issues in accelerating research discovery and its translation. For more information, see http://www.healthra.org/pdfs/HRA_fact_sheet_6_17_2011.pdf (accessed October 10, 2011).

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Appendix A

Workshop Agenda

PUBLIC ENGAGEMENT AND CLINICAL TRIALS:
NEW MODELS AND DISRUPTIVE TECHNOLOGIES

June 27-28, 2011
Conduits and Department of Health Evidence and Policy
Mount Sinai School of Medicine
Goldwurm Auditorium
Icahn Medical Institute, 1st Floor
1425 Madison Ave. (at the NE corner of East 98th St.)
New York, NY 10029

Background:
Rapid advances in biomedical research have drawn attention to the critical need for an effective clinical trial system that can generate the evidence needed to translate discoveries into improved patient care, and illuminate targets for further innovation. There is growing recognition, however, that the U.S. clinical trial enterprise is unable to keep pace with the national demand for actionable research results, and inefficiencies in the clinical trial enterprise limit our ability to realize the clinical benefits of scientific discovery. Many clinical trials never meet their recruitment goals and others are accruing patients far too slowly. In addition, the divide between clinical research and clinical practice is growing wider—physicians working in real world clinical care settings are removed from the clinical trials on which medical evidence and care choices are ideally made. Successfully engaging

the broader public (including patients and communities) and medical professionals (community physicians and those practicing in academic medical centers) in the clinical trial enterprise is a significant challenge.

In light of these current challenges to clinical trials in the United States, this collaboration between the IOM Forum on Drug Discovery, Development, and Translation and Mount Sinai School of Medicine seeks to engage stakeholders and experts in an open discussion of current challenges and potential solutions to improving the capacity for efficient conduct of clinical trials in the United States through enhancing public engagement.

Meeting Objectives:

- Define and discuss the problem of inadequate public engagement in clinical trials.
- Identify the structures and culture of health care systems and delivery organizations that fail to support or engage with the clinical trial enterprise and suggest potential solutions for how health centers can be engaged to support the clinical trial enterprise.
- Discuss how academic medical centers can create successful community partnerships to improve public engagement in clinical trials.
- Highlight and discuss models/methods, both proven and yet to be tried, of public engagement. Address the media's role in public engagement.
- Describe novel clinical trial designs (such as adaptive clinical trial designs) that minimize enrollment needs and address treatment assignment concerns of physicians and their patients.
- Involve stakeholders in a discussion of moving forward to create a comprehensive strategy for enhanced public engagement in clinical trials.

JUNE 27
SESSION I: FRAMING THE PROBLEM

Moderator: Jeffrey Drazen, Co-Chair, Forum on Drug Discovery, Development and Translation, *New England Journal of Medicine*

Session Objectives:

- Provide a definition of "engagement," both public and professional, in clinical trials.
- Survey the current landscape in terms of deficiencies in public and professional engagement, and discuss consequences of this lack of engagement.
- Identify gaps/areas of particular need, desired outcomes of enhanced engagement, and the challenges facing this progress.

12:00-12:10 PM	**Welcome** DENNIS CHARNEY, Dean, Mount Sinai School of Medicine JEFFREY DRAZEN, Co-Chair, Forum on Drug Discovery, Development and Translation, *New England Journal of Medicine*
12:10-12:25 PM	**Shaping an Effective and Efficient Clinical Trial Enterprise: What Are the Challenges?** ANNETINE GELIJNS AND DEBORAH ASCHEIM, Mount Sinai School of Medicine
12:25-12:45 PM	**An Effective Clinical Trial System: A Perspective from the NIH Clinical Center** JUAN LERTORA, National Institutes of Health
12:45-1:30 PM	**Panel Discussion: A Perspective from Industry, Patient Advocates, Payors, and Regulatory Agencies** LESLIE BALL, FDA JOAN FINNEGAN BROOKS, Patient-Focused Market Research ANGELA GEIGER, Alzheimer's Association RICHARD MURRAY, Merck GREG SIMON, Pfizer BRUCE VLADECK, Nexera

SESSION II: MODELS AND METHODS FOR PUBLIC ENGAGEMENT

Moderator: Nancy Sung, Burroughs Wellcome Fund

Session Objectives:

- Through case examples, discuss various stakeholder perspectives and efforts focused on public engagement. In case studies, identify

primary audiences, key messages, and success or lack of success in engaging the public.
- Present strategies that foster research interest and participation in diverse populations through innovative community partnerships.

1:35-1:50 PM	**Recruitment Challenges in Cardiothoracic Surgical Trials** ROBERT MICHLER, Montefiore-Einstein Heart Center
1:50-2:05 PM	**Diabetes, Clinical Trials, and Innovative Community Partnerships** CAROL HOROWITZ AND NINA BICKELL, Mount Sinai School of Medicine
2:05-2:20 PM	**Clinical Trials in Mental Health** WAYNE GOODMAN, Mount Sinai School of Medicine
2:20-2:35 PM	**Recruitment in Breast Cancer Trials, A New Approach: The Love/Avon Army of Women** MARC HURLBERT, Avon Foundation Breast Cancer Crusade
2:35-2:55 PM	**Panel Discussion** KENNETH DAVIS, The Mount Sinai Medical Center ROBERT MICHLER, CAROL HOROWITZ, NINA BICKELL, WAYNE GOODMAN, MARC HURLBERT
2:55-3:20 PM	**COFFEE BREAK**

SESSION III: TECHNOLOGIES AND NOVEL COMMUNICATION APPROACHES

Moderator: Janet Tobias, Mount Sinai School of Medicine

Session Objectives:

- Present innovative technologies/platforms that hold promise for achieving higher levels of public awareness (e.g., clinical trial matching; increasing adherence; online information efforts).

3:25-3:40 PM **23andMe**

BRIAN NAUGHTON, Chief Scientist, 23andMe

3:40-3:55 PM **Social Networks and Public Engagement in Clinical Trials**

BERNADETTE BODEN-ALBALA, Columbia University

3:55-4:15 PM **Panel Discussion**

SESSION IV: MEDIA AND PUBLIC ENGAGEMENT IN CLINICAL TRIALS

Moderator: Paul Costello, Stanford School of Medicine

Session Objectives:

- Discuss the role in public engagement of media, health care information portals, and public advocates.

4:20-4:35 PM **Survey of the Public Perception and Media Landscape**

CHRISTINA ZARCADOOLAS, CUNY and Mount Sinai School of Medicine

JANET TOBIAS, Mount Sinai School of Medicine

4:35-4:55 PM **A Recent Trial of Pediatric Fluid Resuscitation and Novel Methods for Physician Engagement**

KATHRYN MAITLAND, Imperial College

4:55-5:40 PM **Panel Discussion: Public Information and Public Advocacy**

JOAN FINNEGAN BROOKS, Patient-Focused Market Research

PEGGY PECK, *MedPage Today*

ROGER SERGEL, ABC

HEATHER WON TESORIERO, CBS

CHRISTINA ZARCADOOLAS, CUNY and Mount Sinai School of Medicine

JUNE 28
SESSION V: NOVEL CLINICAL TRIAL DESIGN

Moderator: Michael Krams, Johnson & Johnson

Session Objectives:

- Present novel clinical trial designs currently in use (e.g., adaptive trial designs), their strengths and weaknesses, and the desirability and/or feasibility of scaling up the widespread use of such designs.
- Discuss the ways in which novel clinical trial designs can enhance public engagement in clinical research and address treatment assignment concerns of physicians and their patients.

8:05-8:20 AM **The Promise of Novel Trial Designs**

MICHAEL PARIDES, Mount Sinai School of Medicine

8:20-8:35 AM **Trial Designs Addressing Treatment Assignment Concerns**

LOUIS FIORE, VA Boston Healthcare System

8:35-8:55 AM **Perspective of the Food and Drug Administration (FDA)**

BRAM ZUCKERMAN, Center for Devices and Radiological Health, FDA

DOUGLAS C. THROCKMORTON, Center for Drug Evaluation and Research, FDA

8:55-9:15 AM **Panel Discussion**

SESSION VI: HEALTH SYSTEM STRUCTURES AND CULTURE

Moderator: Harry Greenberg, Stanford University

Session Objectives:

- Present case studies that include a health system perspective on public and professional engagement methods and approaches and address broader culture and infrastructure/systemic issues.
- How can health systems develop a culture conducive to conducting clinical trials, including incentives for the careers of health professionals, systems approaches to better identify potential enrollees, engagement of referring physician community?
- For a health care delivery system, what are the suggested messages/approaches to enhance public support, understanding, buy-in, and ultimately participation in clinical trials? What organizations at the local level can be leveraged to achieve this?
- How can academic medical centers create effective community partnerships to improve public engagement in clinical trials?

9:20-9:35 AM **Building a Clinical Trials Culture in Academia**

ERIC ROSE, Mount Sinai School of Medicine

9:35-9:50 AM **Exploring Novel Institutional Models in Cancer**

GEORGE DEMETRI, Dana-Farber Cancer Institute and Harvard Medical School

9:50-10:05 AM **New Organizational Models in Rheumatoid Arthritis Trials**

JAMES O'DELL, Rheumatoid Arthritis Investigational Network (RAIN), University of Nebraska

10:05-10:20 AM **ResearchMatch.org and Other IT Solutions**

PAUL HARRIS, Vanderbilt University

10:20-10:40 AM **Panel Discussion**

10:40-11:00 AM **COFFEE BREAK**

11:00-11:45 AM **Building Connections Between Community Physicians and Academic Medicine: The Challenges**

Panel Moderated by: HUGH SAMPSON, Mount Sinai School of Medicine

SANFORD FRIEDMAN, The Mount Sinai Hospital

RAFAT ABONOUR, Indiana University Simon Cancer Center

RAMON MURPHY, Mount Sinai School of Medicine

CAROL HOROWITZ, Mount Sinai School of Medicine

SESSION VII: BUILDING A COMPREHENSIVE STRATEGY

Session Objectives:

- What are the most promising methods and messages for public and professional engagement that you heard during this meeting? What is the likelihood of action? How can they be prioritized?
- What would be the ideal technology to enhance public and professional engagement?
- What are the most pressing structural and cultural needs for a local health care system to enhance promotion of public and professional engagement and participation in clinical trials?
- What efforts aimed at physicians, researchers, patients, and the broader public will facilitate closing the gap between clinical researchers and clinical practitioners?

11:45 AM-12:05 PM **The Changing Politics of Clinical Trial Engagement**

LARRY BROWN, Columbia University

12:05-12:15 PM	**Building a Comprehensive Strategy: A Summary of the Meeting**
	JEFFREY DRAZEN, *New England Journal of Medicine*
12:15-12:30 PM	**Summary Discussion**
	JEFFREY DRAZEN, *New England Journal of Medicine*
	JUAN LERTORA, National Institutes of Health
	GREG SIMON, Pfizer
	NANCY SUNG, Burroughs Wellcome Fund
12:30 PM	**Adjourn**

Appendix B

The Clinical Trials Process

The following is an excerpt from Chapter 1: Introduction of Transforming Clinical Research in the United States: Challenges and Opportunities: Workshop Summary (IOM, 2010a).

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.

Appendix C

Participant Biographies

Rafat Abonour, M.D., is a Professor of Medicine, Professor of Pathology and Laboratory Medicine at Indiana University (IU). Dr. Abonour has been active in clinical research for the past 15 years at Indiana University and his work has been published in *Nature Medicine* and the *New England Journal of Medicine*, among others. His role as a leader of the Multiple Myeloma program has allowed him to participate in practice-changing research using IMiDs and proteasome inhibitors. He has been facilitating clinical research at IU Simon Cancer Center and IU School of Medicine for the past 4 years.

Deborah D. Ascheim, M.D., is an Associate Professor in the Departments of Health Evidence and Policy and Medicine/Cardiovascular Institute at the Mount Sinai School of Medicine in New York. She is the Clinical Director of Research and Director of the Clinical Research Unit at the International Center for Health Outcomes and Innovation Research (InCHOIR) at Mount Sinai. She was previously an Assistant Professor of Medicine (Cardiology) and Health Policy at Columbia University Medical Center and the Mailman School of Public Health. Dr. Ascheim is a cardiologist with expertise in heart failure and extensive experience in clinical investigation. Her research focuses on the measurement of clinical outcomes and on complex trials evaluating novel device or surgical interventions. She has particular expertise in the design, coordination, and analysis of such multicenter clinical trials. She is the principal investigator of the data coordinating center of a planning grant funded by NHLBI to develop a

confirmatory comparative effectiveness trial of hybrid coronary revascularization and the co-principal investigator of the coordinating center for the NHLBI Cardiothoracic Surgery Network. Her work has been published in such journals as the *New England Journal of Medicine*, the *Journal of Cardiac Failure*, the *Journal of Thoracic and Cardiovascular Surgery*, the *Annals of Thoracic Surgery*, and *Thyroid*. Dr. Ascheim has served on numerous clinical trial oversight and advisory committees for federally- and industry-funded trials. She presently serves as the Vice Chair of the Board of Directors of Physicians for Human Rights, and as a Trustee for the Brearley School in New York. Dr. Ascheim graduated from New York University School of Medicine and completed her internship and residency in internal medicine, as well as her fellowship in cardiovascular diseases, at the New York-Presbyterian Hospital/Weill Cornell Medical Center. She completed a postgraduate fellowship at Columbia University College of Physicians & Surgeons (Columbia P&S) and remained on faculty as an attending cardiologist in the Heart Failure Center at Columbia P&S and the Mailman School of Public Health from 1995 to 2008.

Leslie K. Ball, M.D., FAAP, is the Acting Director of the Office of Scientific Investigations (formerly known as the Division of Scientific Investigations [DSI]), Office of Compliance, CDER, FDA, where she has served in this role since 2008. While in DSI she has been active in developing a risk model for selecting clinical trial sites for inspection, collaborating with the European Medicines Agency and other international regulatory authorities, developing approaches to inspecting electronic data, and instituting process improvements for enforcement actions. Beginning in 2003 she served as branch chief of DSI's Good Clinical Practice Branch II. Dr. Ball joined FDA in 1996 as a medical officer in the Center for Biologics Evaluation and Research, Office of Vaccines Research and Review. From 2001 to 2003 she worked at the Office for Human Research Protections, Department of Health and Human Services (HHS), where she coordinated compliance investigations, participated in inspections of institutions and IRBs, and worked on children's research issues. Dr. Ball graduated with a B.S. in biology from Georgetown University. She received her M.D. from Georgetown University School of Medicine, where she also completed a residency in pediatrics. She completed a fellowship in pediatric infectious diseases at the Walter Reed Army Medical Center. She served as a pediatrician at the U.S. Naval Hospital, Subic Bay, Republic of the Philippines, in private practice in Maryland, and in the Department of Pediatrics at the National Naval Medical Center, Bethesda.

Nina A. Bickell, M.D., M.P.H., is Director of the Mount Sinai School of Medicine's NIMHD-funded Center to Achieve and Sustain Health in Harlem designed to improve care in minority communities. She is principal investigator (PI) of randomized trials to reduce disparities in breast cancer treatment using community-based patient assistance programs and a physician-centered tracking and feedback intervention. A practicing primary care general internist in the Mount Sinai Diagnostic and Treatment Center, she completed a primary care internal medicine residency at Montefiore Hospital and Medical Center in the Bronx, New York, a preventive medicine residency at the University of North Carolina at Chapel Hill where she received her M.P.H. in epidemiology, and a Robert Wood Johnson Clinical Scholars fellowship at University of North Carolina at Chapel Hill. In addition to academic appointments, Dr. Bickell served as a senior clinical research scientist at the NYS Department of Health in the Office of Quality Improvement. Dr. Bickell's research includes assessing underlying causes of racial and ethnic disparities in care and improving the quality of care; evaluating approaches to implement sustainable interventions in various clinical settings; access to care for vulnerable populations; determinants and effects of continuity and coordination of care; the relationship of physician beliefs, attitudes and practice; and patient and systems-level barriers to care.

Bernadette Boden-Albala, M.P.H., Dr.P.H., is an Assistant Professor of Sociomedical Sciences in Neurology and the Co-Director of the Irving Center for Clinical and Translational Research Community Engagement Core Resource at Columbia University. As a social epidemiologist her work has focused on disparities in risk factors for cardiovascular disease, obesity, and stroke in urban communities with an emphasis on social support and social networks. She has recently focused much of her efforts into understanding and testing the relationship between social networks and vascular disease by conducting an exhaustive investigation of social networks in the Northern Manhattan Study. Indeed this formative research is focused on using social networks to promote effective and sustainable strategies toward vascular wellness. Currently she serves as Director of the 12,000-community-based WICER survey, and PI on the FURRThER study, a complex family network intervention. Other work includes vascular epidemiology and intervention research among blacks in Washington, DC (ASPIRE), as well as among the Alaskan Yupik Native population in rural Alaska. She recently completed the SWIFT intervention study focused on acute stroke preparedness behaviors. She was the first recipient of the AHA Heritage Affiliate Women with Heart Grant and also received the Jack Elinson Sociomedical Sciences Award. Research

publications include topics such as metabolic syndrome and stroke risk among women and minorities, sleep and vascular risk, risk perception and health behaviors, social isolation, and outcomes poststroke. She is a board member of the AHA National Stroke Council, member of the National AHA behavioral working group, Chairperson of the Community Education Workgroup of the Northeast Cerebrovascular Consortium, and a longtime speaker for the AHA and National Stroke Association.

Joan Finnegan Brooks, President, Patient-Focused Market Research, has worked with organizations involved in CF care and research for over 25 years. She helps organizations develop improved strategies for the CF market environment by providing the voices of the patient, caregiver, and clinician communities in the process. Brooks has consulted for biotechnology and pharmaceutical companies, research institutions, and patient advocacy groups. Brooks has in-depth knowledge of CF and current scientific research, and specialized CF care center and clinical trial networks. Her market research background and contacts among patients, families, clinicians, and researchers in the CF community complements and leverages her clients' resources. She has created data-gathering instruments, designed surveys, and conducted interviews in the CF community. She provides key insights into drug development and marketing programs, and has developed "voice of the customer" outreach strategies. Brooks has worked with clients to maximize patient participation in clinical trials and made recommendations to ensure acceptability of new therapies. Brooks has volunteered for the Massachusetts/Rhode Island Chapter of the Cystic Fibrosis Foundation for 26 years and has been involved with the CF community all her life. She is a leader in many CF Foundation initiatives focused on clinical practice guidelines for patient care, CF adult issues, quality improvement efforts in CF care centers, and clinical trial participation. She was appointed co-chair of a task force focused on patient and family participation to improve patient outcomes at CF care centers. Brooks testified before Congress to appeal for increased support for CF research from NIH. She is past President of the Chapter Board of Directors and was a Chapter Trustee on the CF Foundation Board of Trustees. Brooks has been honored and recognized by the national CF Foundation and their chapter offices for exceptional volunteer efforts and achievements throughout the years. Brooks' story has been featured in many publications and websites. Always an advocate for people with CF and their families, Brooks is a patient representative on the Protocol Review Committee for the clinical trials network sponsored by the CF Foundation. She writes a column addressing the adult perspective for Homeline, a Cystic Fibrosis Services Pharmacy publication, and was a Director for the United States Adult Cystic Fibrosis Association. Brooks

has been a speaker at annual North American Cystic Fibrosis Conferences and the Biotechnology Industry Organization Convention, and served as a faculty member for an intensive training seminar hosted by the Institute for Patient- and Family-Centered Care. She regularly speaks at a Harvard University course focused on disease pathobiology and treatment. She is a sought-after and inspirational speaker at CF care centers across the country. Brooks graduated from Brown University with a B.A. degree in economics. Prior to establishing her consulting practice, Patient-Focused Market Research, in 2002, she had a 17-year career with a global financial services company. She was a securities trader and investment manager in Treasury, and a product manager in Marketing. BankBoston, now part of Bank of America, recognized Brooks in national press releases and publications as its 1998 Volunteer of the Year.

Lawrence D. Brown, Ph.D., is Professor of Health Policy and Management in the Mailman School of Public Health at Columbia University. A political scientist, he got a Ph.D. in government at Harvard University in 1973. After positions at Harvard, the Brookings Institution, and the University of Michigan, in 1988 he came to Columbia, where he chaired the Department of Health Policy and Management for 10 years and the university's Public Policy Consortium for 3 years. He is the author of *Politics and Health Care Organizations: HMOs as Federal Policy* (Brookings Institution, 1983) and of articles on the political dimensions of community cost containment, expansion of coverage for the uninsured, national health reform, the role of analysis in the formation of health policy, and cross-national health policy. Dr. Brown edited the *Journal of Health Politics, Policy and Law* for 5 years, has served on several national advisory committees for the Robert Wood Johnson Foundation, has an RWJ Investigators in Health Policy award, and is a member of the IOM.

Dennis S. Charney, M.D., is the Anne and Joel Ehrenkranz Dean of Mount Sinai School of Medicine and Executive Vice President for Academic Affairs of the Mount Sinai Medical Center. Dr. Charney's arrival at Mount Sinai in 2004 signaled a new era of innovation in research, education, and clinical care. Since joining the faculty, he has established a culture of excellence that has elevated Mount Sinai School of Medicine—an institution founded in 1968—to among the top medical schools in the nation. With an emphasis on translational research, Dr. Charney has accelerated the pace of change at Mount Sinai, streamlined collaboration across disciplines, and facilitated the integration of research, clinical care, and educational innovation. These efforts have produced remarkable results. The Mount Sinai School of Medicine now ranks 18th in NIH funding—an increase from 25th in 2004—and in the past 4 years, its position in *U.S. News &*

World Report has risen from 32 to 18. No other medical school in America has achieved this degree of improvement in such a brief period. Early in his tenure at Mount Sinai, Dr. Charney led the creation of the School of Medicine's Strategic Plan, an organizational restructuring that included the creation of 15 interdisciplinary research institutes. As a medical school embedded in a hospital, Mount Sinai has always integrated research and clinical medicine. These institutes—chosen in the areas where Mount Sinai can truly excel—embody the institution's mission as a leader in basic and clinical research. A leading investigator on neurobiology and the treatment of mood and anxiety disorders, Dr. Charney has made fundamental contributions to the understanding of neural circuits and neurochemistry related to human anxiety, fear, and mood. He has pioneered research related to the psychobiological mechanisms of human resilience to stress. In addition, his research team has made major contributions to the discovery of novel and more effective treatments for mood and anxiety disorders. Dr. Charney's distinguished career as a researcher and educator began in 1981 at Yale University School of Medicine, where, within 9 years, he rose from Assistant Professor to Professor of Psychiatry, a position he held from 1990 to 2000. While at Yale, Dr. Charney chaired the National Institute of Mental Health (NIMH) Board of Scientific Counselors, which advises the institute's director on intramural research programs. After nearly two decades at Yale, NIMH recruited Dr. Charney to lead the Mood and Anxiety Disorder Research Program—one of the largest programs of its kind in the world—and the Experimental Therapeutics and Pathophysiology Branch. That year he was also elected to the IOM of the National Academy of Sciences. His scientific research has been honored by every major award in his field. Dr. Charney remained at NIMH until he was recruited to Mount Sinai in 2004 as Dean of Research. Two years later, he was appointed Dean for Academic and Scientific Affairs for Mount Sinai School of Medicine and Senior Vice President for Health Sciences of the Mount Sinai Medical Center. In 2007, Dr. Charney became the Dean of the Mount Sinai School of Medicine and Executive Vice President for Academic Affairs of the Medical Center. The following year, he was named the Anne and Joel Ehrenkranz Dean of Mount Sinai School of Medicine. A prolific author, Dr. Charney has written more than 700 publications, including groundbreaking scientific papers, chapters, and books. He has authored a dozen books, including *Neurobiology of Mental Illness* (Oxford University Press, 3rd ed., 2009); *The Peace of Mind Prescription: An Authoritative Guide to Finding the Most Effective Treatment for Anxiety and Depression* (Houghton Mifflin Harcourt, 2004); and *The Physicians Guide to Depression and Bipolar Disorders* (McGraw-Hill Professional, 2006). In 2011, Dr. Charney plans to publish his 13th book, which addresses emotional resilience.

Paul Costello, M.S.W., is the chief communications officer for the Stanford University School of Medicine. Prior to joining Stanford in 2004, he was vice president of external affairs for the University of Hawaii System. In Hawaii, he hosted a weekly public affairs program on PBS Hawaii. In government and politics he served as a press spokesman to First Lady Rosalynn Carter, Ohio Governor Richard Celeste, Washington, DC, Mayor Sharon Pratt Kelly, and Kitty Dukakis during the 1988 presidential campaign. In the private sector, he was vice president of public affairs at the cable television company Home Box Office and at the Chicago retail company, Marshall Field. He was the managing director of the New York office of the global public relations company, Weber Shandwick. Now at Stanford, he leads the medical school's communication efforts, overseeing media relations, publications, and social and new media platforms.

Kenneth L. Davis, M.D., is the President and Chief Executive Officer of the Mount Sinai Medical Center, and Professor of Psychiatry, Mount Sinai School of Medicine. Dr. Davis received his bachelor's degree from Yale College, from which he graduated magna cum laude. He received his medical degree from Mount Sinai School of Medicine and was valedictorian. He completed an internship, residency, and fellowship in psychiatry and pharmacology, respectively, at Stanford University Medical Center, and thereafter won a career development award from the VA to pursue his research in cholinergic mechanisms and neuropsychiatric diseases. In 1979, Dr. Davis joined the faculty at Mount Sinai, becoming Chief of Psychiatry at the Bronx VA Medical Center. He spearheaded Mount Sinai's research program in the biology of schizophrenia and the therapeutics of Alzheimer's disease. In 1987 he was appointed Chairman of Psychiatry, Mount Sinai School of Medicine. In January 2003 he was appointed Dean of Mount Sinai School of Medicine and in March 2003 he assumed the additional position of President and Chief Executive Officer of the Mount Sinai Medical Center. Under his leadership, Mount Sinai entered a new era of innovation in research, education, and clinical care. He led what has been characterized as the "largest financial turnaround in academic medicine." The Medical Center grew in both scope and ambition, accelerating the momentum of translational research, intensifying collaboration across all disciplines, and providing the impetus to reach new heights of excellence through closer integration of the research, clinical, and educational dimensions of Mount Sinai's mission. In 2007, Dr. Davis, who had held the position of both Dean and CEO for 4 years, named a new Dean of Mount Sinai School of Medicine.

George D. Demetri, M.D., is the Senior Vice President for Experimental Therapeutics, Dana-Farber Cancer Institute (DFCI); and Director,

Ludwig Center at Dana-Farber/Harvard Cancer Center; Quick Family Senior Investigator in Medical Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, Massachusetts. Dr. Demetri received an undergraduate degree in biochemistry from Harvard University, followed by a Rotary Foundation Fellowship to do research at the Université de Besancon, France, after which he received his medical degree from Stanford University School of Medicine, California. After completing his internal medicine residency and chief residency at the University of Washington Hospitals in Seattle, Washington, he pursued a fellowship in Medical Oncology at DFCI and Harvard Medical School, where he has served as an attending physician since 1989. Dr. Demetri and colleagues at Harvard have developed a large research-focused multidisciplinary center of excellence for sarcoma patients at the Dana-Farber/Harvard Cancer Center, supporting a number of translational and clinical research projects in sarcomas and focusing on new drug development through the Ludwig Center at Dana-Farber and Harvard Medical School. He is also directing Dana-Farber's Center for Novel Experimental Therapeutics (C-NExT). Dr. Demetri's research and clinical interests have focused on mechanism-based drug development for solid tumors, with a particular emphasis on molecularly-defined subsets of sarcomas such as GISTs. Work from the multidisciplinary team at Dana-Farber/Harvard has contributed to the development of several new drugs for sarcomas and other malignancies, including imatinib (Gleevec), sunitinib (Sutent), trabectedin (Yondelis), and other new rationally designed therapies in development. Dr. Demetri serves as co-chair of the Medical Advisory Board for the Sarcoma Foundation of America as well as several scientific and editorial advisory boards. With an interest in Internet-based medical social network technologies, he also serves as an editor of CancerNet (www.cancer.net) from the American Society of Clinical Oncology.

Jeffrey M. Drazen, M.D., is the Editor-in-Chief of the *New England Journal of Medicine* and co-chairs the IOM's Forum on Drug Discovery, Development, and Translation. 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.

Louis Fiore, M.D., M.P.H., has worked for the Department of Veterans Affairs since his internship at the VA Boston Healthcare System in 1981. Following his hematology and oncology fellowships he became a clinical investigator for cancer consortiums and began writing clinical trial protocols. In 1998 he published the CHAMP trial, a 5,000-subject trial of combined aspirin and warfarin therapy in survivors of acute myocardial infarction. Dr. Fiore was "re-schooled" in clinical effectiveness at the Harvard School of Public Health and co-directed the Massachusetts Veterans Epidemiology Research and Information Center until 2004, when he founded the VA Cooperative Studies Program Coordinating Center in Boston. He has recently completed a sabbatical in biomedical informatics and is currently leading development of VA Informatics resources including clinical trials and translational medicine platforms.

Sanford J. Friedman, M.D., is an Associate Clinical Professor of Cardiology at the Mount Sinai Hospital (MSH). He is a graduate of Columbia College and Tufts University School of Medicine. Dr. Friedman conducted his internal medicine residency and cardiology fellowship at MSH. He subsequently was full-time head of the coronary care units at MSH. After 2 years he went into private practice. For over 30 years he has been in a two-man practice with Dr. Jose Meller. The practice is huge; they "accept assignment" and they understand the problems of private doctors in this environment. His focus has been 40 percent internal medicine and 60 percent general cardiology. He is known by his colleagues for his interest in preventative cardiology and cardiac rehab. He teaches fellows and residents one month a year in the CCU and supports the MSH cardiac rehab program with seminar sessions with the patients.

Angela Geiger is the Chief Strategy Officer for the Alzheimer's Association. In this role, she works across the nationwide organization to develop and implement strategy to maximize mission impact. In addition, she leads the effort to develop and deliver program services, marketing, and fundraising at the Association. Geiger has broad experience in strategic marketing and product development for nonprofits. Prior to joining the Alzheimer's Association, Geiger spent 8 years at the American Cancer Society in a variety of customer-focused leadership roles in the areas of mission delivery, fundraising, and marketing. Geiger also worked for

the American Lung Association and for higher education institutions. Throughout her career, Geiger has collaborated with field organizations to create and implement successful special events and grassroots programs that reach a wide range of diverse constituents. She has her B.A. and M.B.A. from the University of Pittsburgh and has contributed to a variety of publications and conferences.

Annetine C. Gelijns, Ph.D., is the Co-Chair of the Department of Health Evidence and Policy at Mount Sinai School of Medicine, New York, New York. Dr. Gelijns also holds the positions of Professor of Health Policy and Co-Director of the International Center for Health Outcomes and Innovation Research (InCHOIR) at Mount Sinai School of Medicine. Before coming to Mount Sinai in 2008, she was Professor of Public Health and Surgical Sciences in the Department of Surgery, College of Physicians and Surgeons, and the Division of Health Policy and Management of the Mailman School of Public Health, Columbia University, New York City. She was also a Division Chief in the Department of Surgery. Prior to her position at Columbia, she directed the Program on Technological Innovation in Medicine at the IOM, National Academy of Sciences. From 1983 to 1987, she worked for the Steering Committee on Future Health Scenarios and for the Health Council, the Netherlands. Dr. Gelijns has been a consultant to various national and international organizations, including the World Health Organization (WHO) and the Organisation for Economic Co-operation and Development (OECD). Her research focuses on measurement of the long-term clinical outcomes and economic impact of clinical interventions, patient safety research, and the factors driving the development and diffusion of medical technology. She has special expertise in cardiovascular disease, particularly in the design, coordination, and analysis of multicenter trials. She is the PI or co-PI of several Data Coordinating Centers for the NHLBI-sponsored trials, including CT Surgery Clinical Trials Network, the REMATCH trial, and several newer generations of LVAD trials. Dr. Gelijns has published, in such journals as the *New England Journal of Medicine*, *JAMA*, and *Health Affairs*, on the methodology and conduct of complex surgical and device trials, the assessment of quality of life and economic analysis of clinical procedures, and volume-outcome studies, as well as policy studies on technological change.

Wayne K. Goodman, M.D., was appointed Professor and Chairman of the Department of Psychiatry at the Mount Sinai School of Medicine in July 2009. He is the Esther and Joseph Klingenstein Professor of Psychiatry and Professor in the Department of Neuroscience. He has conducted research on the phenomenology, neurobiology, and treatment of obsessive-compulsive disorder (OCD) and is the principal developer

of the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), the gold standard for assessing OCD. He is co-founder of the Obsessive Compulsive Foundation, the international patient advocacy organization for this disorder. Dr. Goodman is a leader in the field of brain stimulation for intractable psychiatric disorders. A graduate of Columbia University with a B.S. in electrical engineering, Dr. Goodman received his medical degree from Boston University and completed his internship, residency, and a research fellowship at Yale University School of Medicine where he remained on faculty until 1993 as an Associate Professor. In 1994, he joined the University of Florida in Gainesville where he served as Chairman of the Department of Psychiatry for 9 years. Prior to joining Mount Sinai, he served as Director, Division of Adult Translational Research and Treatment Development, at NIMH from 2007 to 2009. Dr. Goodman has published more than 250 articles and is a member of the American College of Neuropsychopharmacology. He has served as Chair of FDA's Psychopharmacologic Drug Advisory Committee and is currently on FDA's Neurological Devices Advisory Committee.

Harry B. Greenberg, M.D., is the Senior Associate Dean for Research and the Joseph D. Grant Professor of Medicine and Microbiology and Immunology at the Stanford School of Medicine. Dr. Greenberg received his B.A. in history from Dartmouth College in 1966. He received his M.D. from Columbia College of Physicians and Surgeons in 1970. He did his internal medicine house staff and GI fellowship training at Bellevue Hospital and Stanford University, respectively. Dr. Greenberg spent 10 years at the NIH in the Laboratory of Infectious Disease as a tenured scientist before returning to Stanford in 1983. He is currently the Joseph D. Grant Professor of Medicine and Microbiology and Immunology and the Senior Associate Dean for Research at Stanford University School of Medicine. He is also a staff physician at the Palo Alto VA hospital. Dr. Greenberg is a member of a variety of scholarly societies, governmental committees, and editorial boards. He is the past President of the American Society of Virology, a consultant for a variety of vaccine manufacturing companies, and the director of Stanford's NIH-funded CTSA. He has been an active NIH-funded investigator for over 30 years during which time his studies have focused primarily on viruses that infect the GI tract, liver, or respiratory tree. He has published over 400 articles, chapters, and reviews during this time. His work has spanned the spectrum from basic studies of viral–host cell interaction to translation work on the immune response to important pathogens in both animal models and humans to clinical trials of vaccine safety and efficacy. He has trained a large number of M.D. and Ph.D. postdoctoral students who are now in independent careers in science and academic medicine. He has also carried out a variety of

other administrative roles at Stanford including being the Chief of the GI Division of the Department of Medicine, the acting Chairperson of the Department of Medicine (twice), and the ACOS for research at the Palo Alto VA. During a 2-year leave of absence from Stanford, Dr. Greenberg was the Chief Scientific Officer at a biotechnology company called Aviron (now MedImmune Vaccines), where he played a key role in bringing the live attenuated influenza vaccine to licensure.

Paul A. Harris, Ph.D., is an Associate Professor in the Department of Biomedical Informatics at Vanderbilt University with approximately 15 years' experience working in the field of clinical research informatics. Dr. Harris serves as director of Vanderbilt's Office of Research Informatics and leads the informatics operations unit for Vanderbilt's CTSA program. He earned his doctorate in biomedical engineering from Vanderbilt University in 1996 and has been very active at the national level in both the NIH GCRC and NIH CTSA programs. Dr. Harris' primary professional interest is the creation and optimization of informatics tools used to facilitate clinical and translational research. His teams are responsible for StarBRITE (Vanderbilt's online home for clinical and translational research services), Synthetic Derivative (Vanderbilt's de-identified research data warehouse), Research Derivative (Vanderbilt's identified research data warehouse), REDCap (a web-based data collection and management software platform), and ResearchMatch (a national web portal designed to match potential study volunteers with active research teams). These programs have earned a strong national reputation within the NIH CTSA program and in the broader clinical research informatics community. ResearchMatch is serving more than 15,500 research volunteers and scientific teams at 61 U.S. partner institutions. REDCap is serving more than 20,000 research end users at 216 academic and nonprofit institutions across six continents.

Carol R. Horowitz, M.D., M.P.H., is Associate Professor of Health Policy and Medicine at Mount Sinai School of Medicine, and a practicing general internist. Her research focuses on using CBPR to address health disparities and improve chronic disease prevention and control. She is the Principal Investigator of several NIH-funded community-based interventions, a CDC Center of Excellence to eliminate diabetes disparities and the Community Engagement and Research Core for Mount Sinai's CTSA Conduits. She has an M.D. from Cornell University, and received an M.P.H. from the University of Washington as a Robert Wood Johnson Clinical Scholar.

Marc Hurlbert, Ph.D., serves as the executive director of the global breast cancer programs of the Avon Foundation for Women and the Avon Breast Cancer Crusade. The Crusade, which has programs in more than 55 countries, provides more than $50 million to breast cancer philanthropy annually. Dr. Hurlbert develops the Crusade's overall strategy, sets funding guidelines, implements programs, and evaluates progress of grant recipients. Since the Crusade launched in 1992, Avon breast cancer programs in more than 50 countries have raised almost $700 million for research and advancing access to care, with a particular focus on the medically underserved. Dr. Hurlbert was elected by his peers in the nonprofit industry to serve as the Chairman of the Board (2010, 2011) of the Health Research Alliance, an alliance of 50 nonprofit organizations that collectively award $1.5 billion in annual grants to 5,500 research investigators. He also serves as Chairman of the Cancer Committee for Columbia University and New York Presbyterian Hospital. Dr. Hurlbert is an advocate member of the NIH/NIEHS Breast Cancer and the Environment Research Program Working Group. Dr. Hurlbert received his undergraduate degree in biochemistry from the University of Kansas and his Ph.D. in pharmacology from the University of Colorado Health Sciences Center. He completed his training with a postdoctoral fellowship at New York University Medical Center, Skirball Institute of Biomolecular Medicine.

Michael Krams, M.D., a neurologist by training, has been involved in planning, designing, and implementing adaptive clinical trials for more than a decade. Since 2004 he has—together with Brenda Gaydos—cochaired PhRMA's working group on adaptive designs. This group was put in place to facilitate a dialogue of statistical, regulatory, and clinical experts from industry, academia, and health authorities to share experience and shape recommendations related to statistical and operational aspects of adaptive designs (Gallo et al., 2006, *Journal of Biopharmaceutical Statistics* 16:275-283; Gaydos et al., 2009, *Drug Information Journal* 43:539-556). In 2006 Dr. Krams took on the role of building a scalable enabling infrastructure for adaptive designs, in particular in "Learn" at Wyeth. In 2010 Dr. Krams joined Janssen Pharmaceuticals, where he heads up the Neurology Franchise and continues to work for an increased use of adaptive designs.

Juan J. L. Lertora, M.D., Ph.D., has been Director, Clinical Pharmacology Program, Office of Clinical Research Training and Medical Education, NIH Clinical Center, since July 2006. Previously, he was Professor of Medicine and Pharmacology and Section Head of Clinical Pharmacology at Tulane University School of Medicine in New Orleans, Louisiana (1981-2006). He was Program Director, Tulane–Louisiana State Univer-

sity Charity Hospital General Clinical Research Center (1998-2005) and Principal Investigator, Tulane LSU Adult AIDS Clinical Trials Unit (1996-2005), both funded by NIH. Dr. Lertora is a graduate of the Faculty of Medicine, National University of the Northeast, Corrientes, Argentina, and the Graduate School, Department of Pharmacology, Tulane University. He received a Merck Sharp and Dohme International Fellowship in Clinical Pharmacology at Tulane, completed training in internal medicine at the University of Connecticut, and a clinical pharmacology fellowship at the University of Iowa. He was Assistant Professor of Medicine and Pharmacology, Clinical Pharmacology Center, Northwestern University in Chicago (1977-1981) and received a Faculty Development Award from the Pharmaceutical Manufacturers Association Foundation (now the PhRMA Foundation). Dr. Lertora serves on the editorial board of *Clinical Pharmacology and Therapeutics*, the FDA Advisory Committee for Pharmaceutical Sciences and Clinical Pharmacology, and the Board of Directors of the American Society for Clinical Pharmacology and Therapeutics (2007-2011). He is Adjunct Professor of Medicine at Duke University. Dr. Lertora conducted phase I and II safety and efficacy clinical trials and studied pharmacokinetics-pharmacodynamics, drug metabolism, pharmacogenetics, and drug interactions of antiretroviral drugs. Previous research included erythropoietin's role in the anemia of chronic renal disease, the dose-related cardioselectivity of practolol, the antiarrhythmic-inotropic actions of NAPA (N-acetylprocainamide), the cardiovascular actions of NAPADE (desethyl-N-acetylprocainamide), CYP2E1 and chlorzoxazone metabolism, and pharmacokinetics of ribavirin and peg-interferon alfa-2a in HIV-infected patients.

Kathryn Maitland, M.D., is based at the KEMRI-Wellcome Trust Programme in Kilifi, Kenya, and is a Professor of Paediatric Tropical Infectious Diseases and Honorary Consultant in Paediatric Infectious Disease, Imperial College, London; and Honorary Fellow at the MRC Clinical trials Unit, London. Over the past 11 years she has been based full time in East Africa, where she leads a research group whose major research portfolio includes severe malaria, bacterial sepsis, and severe malnutrition. Her work focuses upon understanding the pathophysiology of severe malaria and severe malnutrition and includes clinical trials of emergency interventions to improve outcome. Her research group has recently completed the largest trial of critically ill children ever undertaken in Africa (FEAST trial: http://www.feast-trial.org) examining fluid resuscitation, which is likely to lead to major changes in health policy in children with severe illness in sub-Saharan Africa.

Robert E. Michler, M.D., is Surgeon-in-Chief; Samuel I. Belkin Endowed Chair; Chairman and Professor, Department of Cardiovascular and Thoracic Surgery; Chairman and Professor, Department of Surgery; and Co-Director, Center for Heart and Vascular Care at the Montefiore Medical Center/Albert Einstein College of Medicine, New York, New York. Dr. Michler is a nationally noted heart surgeon who specializes in complex aortic and mitral valve repair. His research interest in repairing the injured heart has led to clinical trials in autologous skeletal myoblast and cardiac stem cell transplantation. He is an NIH-funded investigator and leader in clinical trial enrollment. Dr. Michler and his teams have advanced minimally invasive cardiothoracic surgery procedures and surgical robotics. This work led to FDA approval for selective cardiac robotic procedures including mitral valve repair and coronary bypass surgery. Dr. Michler has authored hundreds of peer-reviewed publications, recently publishing in the *New England Journal of Medicine*, *Circulation*, and the *Proceedings of the National Academy of Sciences*. He is a frequent editor on cardiac surgery topics and lectures extensively, both nationally and abroad. Formerly, he was the John G. and Jeanne B. McCoy Endowed Chair, Professor of Surgery, and Chief of Cardiothoracic Surgery and Transplantation at The Ohio State University Medical Center in Columbus, Ohio. Before joining The Ohio State University, Dr. Michler was a tenured Associate Professor of Surgery at Columbia University and served as the Director of the Cardiac Transplant Program, one of the largest cardiac transplant programs in the nation, at Columbia-Presbyterian Medical Center in New York. Dr. Michler received his undergraduate education magna cum laude from Harvard University. He received his medical education at Dartmouth Medical School where he was a Leopold Schepp Scholar. Dr. Michler completed his residency in general surgery, a fellowship in cardiothoracic transplantation, and a residency in cardiothoracic surgery at the Columbia Presbyterian Medical Center in New York. He was awarded the Blakemore Research Prize for 3 consecutive years. He completed a chief residency in pediatric cardiothoracic surgery with Dr. Aldo Castaneda at the Harvard Medical School, Boston Children's Hospital. Dr. Michler is the Chairman and Founder of a not-for-profit foundation, Heart Care International, which performs pediatric heart surgery in underserved regions of the world. To date, Heart Care International has helped over 1,000 children with heart disease and performed heart surgery on over 600 children. He has received numerous honors including "Person of the Week" by Peter Jennings of ABC *World News Tonight*, the Pace Humanitarian Award, and "The Order of Christopher Columbus" by Hippolito Mejia, President of the Dominican Republic.

Ramon Murphy, M.D., M.P.H., is a Clinical Professor of Pediatrics and Preventive Medicine; Vice-Chair of Department of Pediatrics, Voluntary Affairs; Associate Director, Mount Sinai Global Health Center; and Director, Off-Site Pediatric Residency Program at the Mount Sinai School of Medicine. Dr. Murphy trained in pediatrics and preventive medicine. Ramon Murphy is currently in charge of an eight-doctor private practice, closely affiliated with Mount Sinai School of Medicine. The practice, Uptown Pediatrics, has approximately 10,000 patients, 29 employees, and 4 pediatric residents who do all of their outpatient work there. The practice has electronic records and has a diverse population of patients from the entire New York community including East Harlem. He also serves as Vice-Chair of Pediatrics, Voluntary Affairs, and Associate Director of the Global Health Center at Mount Sinai which he founded in 2003. He is active in teaching at the practice, hospital, and medical school and has been listed in America's Top Doctors for the past 12 years.

Richard Murray, M.D., joined Merck & Co., Inc. in November 1994, where he was a founding member of the Regional Medical Director Program. Over the subsequent 17 years, he assumed increasing responsibility within U.S. Human Health Medical and Scientific Affairs, including head of U.S. Academic and Professional Affairs, and he was promoted to Vice President, External Medical and Scientific Affairs, in August of 2007. He became Head of the Global Center for Scientific Affairs in May 2010, including responsibility for the Merck Investigator-Initiated Studies Program. Dr. Murray, a native Washingtonian, graduated from Clark University (Worcester, Massachusetts) with an A.B. in psychology and a M.A. in chemistry. He graduated from Howard University College of Medicine (Washington, DC) and subsequently was an intern, medical resident, Chief Medical Resident, and Pulmonary & Critical Care Fellow at the University of Pennsylvania in Philadelphia. Prior to joining Merck, Dr. Murray was Assistant Professor of Medicine at the University of Pennsylvania where he was an investigator in the area of reactive airways disease, smooth muscle function, and calcium signaling. He was also Co-Director of the Adult Asthma Program at the Hospital of the University of Pennsylvania. Dr. Murray is Board Certified in Internal Medicine and Pulmonary Diseases. He is a Fellow of the American College of Physicians, a Fellow of the American College of Chest Physicians, and a Fellow of the College of Physicians of Philadelphia. He serves on the boards of directors for the Merck Childhood Asthma Network, and the Southeast Pennsylvania Chapter of the AHA. Dr. Murray has previously represented Merck at the IOM Clinical Research Roundtable and the Roundtable on Health Disparities.

Brian Naughton, Ph.D., joined 23andMe at its founding and over the past 5 years has drawn on his experience in bioinformatics, statistics, and genetics to analyze data, develop algorithms, and translate scientific research to drive the world's first personal genome service. Among other projects, he has worked on the design of the 23andMe custom chip, and the development of tools related both to risk estimation and ancestry. Dr. Naughton is a graduate of the Trinity College, Dublin, and received his Ph.D. from the Biomedical Informatics program at Stanford University, where he worked with Professors Doug Brutlag and Serafim Batzoglou. His thesis work included novel methods for the detection of transcription factor binding sites.

James R. O'Dell, M.D., is Larson Professor of Internal Medicine, Vice-Chairman of Internal Medicine and Chief of Rheumatology at the University of Nebraska Medical Center (UNMC) in Omaha. He also has served as Director of the Internal Medicine Residency Training Program at UNMC for the past 25 years, where he has directed the training of over 500 internal medicine residents. Dr. O'Dell received his undergraduate degree at the University of Nebraska-Lincoln in electrical engineering and his medical degree and completed a residency and chief residency in internal medicine at the University of Nebraska College of Medicine. He completed a clinical and research fellowship in rheumatology at the University of Colorado in Denver in 1984 and is board certified in both internal medicine and rheumatology. Dr. O'Dell founded and has directed RAIN for the past 22 years. RAIN is a group of rheumatologists who conduct investigator-initiated trials to find better treatments for rheumatoid arthritis (RA). This research network has pioneered the use of combinations of medications to treat RA, was one of the first groups to describe genetic factors that predict response to therapy, and has done extensive work with the use of minocycline in the treatment of RA. Dr. O'Dell is the PI of the large multinational RA research study based at the VA. This trial that also has NIH funding is comparative effectiveness research at its best in a double-blind placebo-controlled randomized trial. Dr. O'Dell has published extensively, mostly in the area of RA and recently authored "Drug Therapy: Rheumatoid Arthritis" for the *New England Journal of Medicine*. He has presented frequently at national and international meetings and has more than 100 published articles in top-level journals. He has received many awards for teaching excellence, was recently honored with the Nebraska ACP Laureate Award, and as a distinguished Scientist at UNMC. In 2008 he received the Department of Internal Medicine Career Research award. He has served on numerous American College of Rheumatology (ACR) committees over the past 20 years, including time on both the ACR and REF BOD, as well as a 2-year

term as President of the Research and Education Foundation of the ACR. He was recently Secretary of the College and is currently President-Elect.

Michael K. Parides, Ph.D., is Professor of Biostatistics in the Department of Health Evidence and Policy, and Director of the Center for Biostatistics at the Mount Sinai School of Medicine in New York City. Dr. Parides is an expert in the design, execution, and analysis of clinical trials; having advised academic, government, and industry sponsors for the past 25 years. He has spent his career focusing on quantitative methods in clinical and translational research, including the development and application of novel adaptive, Bayesian, and sequential approaches for both exploratory and confirmatory clinical trials. Dr. Parides has served as principal statistician and PI for many large multicenter randomized clinical trials in neurology, cardiology, cardiac surgery, HIV, and psychiatry, and on numerous NIH Data Monitoring Committees and clinical trial study sections. He is also dedicated to teaching and mentoring; teaching graduate students at Mount Sinai, and young clinical and statistical investigators through the National Institute of Neurological Disorders and Stroke (NINDS)-funded week-long Clinical Trials Methods Course, and through educational activities of the American Academy of Neurology and the Society for Clinical Trials.

Peggy Peck, Vice President/Executive Editor, MedPageToday.com, began her career in journalism at *The Record*, a New Jersey daily newspaper. In 1980, she started writing for the medical trade press with a column in *Physician's Management*. Since then, her byline has been ubiquitous, appearing in *Modern Medicine*, *Medical Tribune*, *Medical World News*, *Physician's Weekly*, *Internal Medicine News*, *Family Practice News*, *Pediatric News*, *Clinical Psychiatry News*, *Skin and Allergy News*, and *ObGyn News*. As a freelancer, she has contributed to a wide range of publications and websites including *WebMD*, *Medscape*, *Reuters Health*, *UPI*, *Good Housekeeping*, *Oncology Times*, *Neurology Today*, *Neurology Now*, and *AMNews*.

Eric Rose, M.D., is an academic physician and entrepreneur with interests in drug discovery, biodefense, clinical evaluative research, and health policy. Since 2007 he is the Executive Vice President for Life Sciences at MacAndrews & Forbes and CEO of Siga Technologies, Inc., a developer of antiviral drugs directed at potential agents of bioterror. He was appointed in 2007 to the National Biodefense Scientific Board which advises the HHS Secretary on biodefense, influenza, and emerging diseases. In 2008, he assumed the chairmanship of the Department of Health Evidence & Policy at the Mount Sinai School of Medicine. From 1994 through 2007, he served as Surgeon-in-Chief at New York-Presbyterian Hospital/Columbia

and Chairman of the Department of Surgery at the Columbia University College of Physicians and Surgeons, where he held a distinguished professorship. An accomplished heart surgeon, researcher, and entrepreneur, Dr. Rose grew one of the nation's premier departments of surgery while managing, investigating, and developing complex medical technologies ranging from heart transplantation and novel approaches to Alzheimer's disease to bioterrorism. He has authored or co-authored more than 300 scientific publications and has received more than $25 million in NIH support for his research. Dr. Rose pioneered heart transplantation in children, performing the first successful pediatric heart transplant in 1984, and has investigated many alternatives to heart transplantation, including cross-species transplantation and man-made heart pumps. Siga has received more than $100 million in federal research support since he joined the company, developing antiviral drugs for smallpox, dengue, and Lassa fever. In May 2011, Siga was awarded a $433 million contract to provide 2 million courses of its novel oral smallpox antiviral drug to the Strategic National Stockpile to protect the civilian population in the event of a smallpox outbreak, a recognized material threat to U.S. national security. He received both his undergraduate and medical degrees from Columbia University.

Hugh A. Sampson, M.D., is a Professor of Pediatrics and Immunology at the Mount Sinai School of Medicine in New York, and is the Director of the Jaffe Food Allergy Institute, Dean for Translational Biomedical Research, and PI and Director of Conduits; Institutes for Translational Sciences at the Mount Sinai Medical Center. Dr. Sampson's research interests have focused on food allergic disorders including the immunopathogenic role of food hypersensitivity in atopic dermatitis and anaphylaxis, characterization of food allergens, and immunotherapeutic strategies for treating food allergies. Dr. Sampson's group is conducting a number of clinical trials to treat food allergy and to understand basic immunologic mechanisms accounting for the eventual development of tolerance. His research has been funded continuously by a number of grants from NIH and private foundations. He has published over 350 articles and 60 book chapters on food allergic disorders and co-edited 4 books, and was elected to membership in the IOM of the National Academies for his work on food allergies.

Roger Sergel is the Managing Editor of the Medical Unit for ABC News. In the role, he oversees ABC News' Medical Unit and provides editorial guidance for all medical reporting on *World News Tonight*, *Good Morning America*, *Nightline*, and *20/20*, as well as other broadcasts and platforms. Sergel has more than 36 years' experience in broadcast journalism and

nearly 30 years' experience in medical reporting. In 1996, Sergel created the ABC News Medical Unit, which evaluates medical information for all broadcasts and also develops story ideas. As part of that unit, Sergel established a unique system of e-mailing doctors and public relations contacts throughout the medical field in order to obtain feedback about developing stories. The e-mail network today includes over 4,000 doctors in 200 specialty areas and over 1,000 public relations professionals at the federal government health agencies, medical centers, hospitals, specialty organizations, pharmaceutical companies, and managed care companies. No other news organization covering medicine has a comparable network of contacts. The Medical Unit also produces a daily memo, which evaluates studies and news releases. It is distributed throughout ABC News and to over 50 medical producers and reporters at ABC-affiliated stations. Sergel also created OnCall, a video Internet resource on ABCNews.com, where leading experts provide video answers in dozens of specialty areas. Sergel joined ABC News in 1984 with Dr. Timothy Johnson, formerly ABC News' Medical Editor. As Dr. Johnson's primary producer, Sergel has produced medical segments for all ABC News broadcasts. Sergel currently works with Rich Besser, ABC News' current Health and Medical Editor. In 1982, prior to joining the network, he teamed with Dr. Johnson as executive producer of a syndicated health program. Previously, Sergel was a general assignment reporter in Charlotte, North Carolina; a writer for WCPO-TV, the ABC affiliate, in Cincinnati; a show producer for WDIV-TV, the NBC affiliate, in Detroit; and a medical producer for five years with the NBC-owned station WMAQ-TV in Chicago. Sergel has won the AHA's Blakeslee Award three times, and was part of the ABC News teams that won the duPont-Columbia Award on two occasions.

Greg C. Simon is Senior Vice President for Patient Engagement at Pfizer, Inc. In that role he engages with people worldwide to help Pfizer develop policies, practices, and medical solutions to improve health, happiness and productivity. Specifically he is focused on how to engage patients more productively in the research and clinical trial process. From June 2009 to February 2010, Simon was head of Pfizer's Worldwide Policy group. In that capacity he led a global team of professionals in (1) worldwide government policy, (2) science policy, (3) economic policy and research, and (4) international policy. He served as an advisor to the CEO in coordinating the company's efforts in Healthcare Reform. Prior to joining Pfizer, Simon was the founding president of FasterCures/The Center for Accelerating Medical Solutions, an independent, nonpartisan organization that is a center of the California-based Milken Institute. There he led efforts to reform policies governing biopharmaceutical discovery and development, with the goal of bringing a greater number of lifesav-

ing medicines more quickly to doctors and patients. The journal *Nature Medicine* named Simon one of "Ten People to Watch" in health care policy, noting that he was among "a handful of influential people who quietly keep the wheels of biomedical science turning." In 2010 he received the Genetic Alliance's "Art of Advocacy" award. Simon was Chief Domestic Policy Advisor to Vice President Al Gore from 1993 to 1997. He oversaw a number of key initiatives, including programs at NIH, the National Cancer Institute, FDA, and the Human Genome Project. He was also instrumental in crafting the regulatory framework that is now the foundation for the biotechnology industry. From 1985 to 1991, Simon was Staff Director of the Investigations and Oversight Subcommittee of the U.S. House of Representatives Committee on Science, Space and Technology. He served as Senator Gore's Legislative Director from 1991 to 1993. Immediately prior to joining FasterCures, Simon was CEO of Simon Strategies, a consulting firm focusing on science and technology issues. He received his law degree from the University of Washington in 1983. He has a B.A. in history from the University of Arkansas.

Nancy Sung, Ph.D., is a Senior Program Officer with the Burroughs Wellcome Fund (BWF; www.bwfund.org), an independent foundation whose mission is to support the advance of biomedical research and education. BWF's major strategy is to invest in the career development of young scientists. Dr. Sung directs BWF's grantmaking in the areas of Interfaces in Science and Translational Research. This portfolio has included individual bridging awards for postdoctoral fellows, midcareer awards for clinical investigators conducting translational research, and institutional awards for interdisciplinary training programs that bridge the physical/mathematical and biological sciences. She also represents BWF's interests in consideration of national science policy issues related to BWF's grantmaking, and is a leader in the community of biomedical research funders. Dr. Sung is founding board chair of the Health Research Alliance (www.healthra.org), a growing consortium of private foundations and voluntary health agencies. Dr. Sung has served as a member of several IOM panels, most recently the Forum on Drug Discovery, Development, and Translation, and Committee on Accelerating Rare Diseases Research. She serves on the Board of Directors of the Samaritan Health Center (Durham, NC) and of Justice Ventures, Intl. (Washington, DC). Dr. Sung earned a B.A. from the University of Pennsylvania and a Ph.D. in microbiology from the University of North Carolina at Chapel Hill (UNC-CH), where she was named a Lineberger Fellow for excellence in research. She conducted postdoctoral research in tumor virology at the Lineberger Comprehensive Cancer Center at UNC-CH. Prior to joining the Fund's staff, Dr. Sung was a visiting fellow at the Chinese Academy of Preventive Medicine's Insti-

tute of Virology in Beijing, with the support of the WHO and the NIH-NCI. Beginning in August 2011, she is on a 1-year sabbatical leave from BWF, while serving as a Program Director in the Office of International Science and Engineering of the National Science Foundation.

Douglas C. Throckmorton, M.D., is the Deputy Director for Regulatory Programs CDER, FDA. In this role, he shares responsibility for overseeing the regulation of research, development, manufacture, and marketing of prescription, over-the-counter, and generic drugs in the United States. From aspirin to cancer treatments, CDER works to ensure that the benefits of approved drug products outweigh their known risks. Dr. Throckmorton is board-certified in internal medicine and nephrology, having received his training at the University of Nebraska Medical School, Case Western Reserve University, and Yale University. Prior to coming to FDA he practiced medicine at the Medical College of Georgia in Augusta, Georgia.

Janet Tobias has two careers: the first in health care, the second in television and film. At Ikana Health and as an adjunct assistant professor at Mount Sinai's School of Medicine, Tobias works at the intersection of technology, information, media, and design to create better health care experiences for patients and their caregivers. Past and present clients include Babycenter.com, AARP, Johnson & Johnson, Bristol-Meyers Squibb, St. Luke's Roosevelt Hospital, Genentech, and Cisco Systems. As CEO of Sierra/Tango Productions, Tobias produces, directs, and writes content for theatrical release, television, and the web. An Emmy and Peabody award winner, Tobias has worked for all three American networks, PBS, MSNBC, Discovery, and the History Channel. She is currently directing a film for worldwide theatrical/broadcast release based on the longest-ever-recorded uninterrupted underground survival.

Bruce C. Vladeck, Ph.D., is Senior Advisor to Nexera Inc., a wholly owned consulting subsidiary of the Greater New York Hospital Association, which he joined in June 2009. His long and varied career has included senior leadership roles in the public, nonprofit, academic, and business communities. He is a widely recognized expert in health care policy and finance, Medicare, Medicaid, long-term care, and health care for the homeless, and a much-sought-after speaker and writer in all of those areas. In the health care community, Dr. Vladeck is perhaps most widely known for his tenure as Administrator of the Health Care Financing Administration (HCFA) from 1993 through 1997, a period that encompassed Health Reform, the Contract with America Congress and budget stalemates, and the Balanced Budget Act. Dr. Vladeck's time at HCFA was marked by significant innovation in statewide Medicaid programs

through demonstration waivers; the development of Medicare prospective payment systems for hospital outpatient services, skilled nursing facilities, and home care agencies; implementation of the first quantitative quality measures for managed care plans; major initiatives to combat fraud and abuse; and significant improvements in beneficiary services. His work at HCFA was recognized in 1995 by a National Public Service Award. He remained closely involved in Medicare policy in 1998-1999 as a Presidential Appointee to the National Bipartisan Commission on the Future of Medicare. After leaving HCFA, Dr. Vladeck spent 6 years at Mount Sinai Medical Center, as Professor of Health Policy and Geriatrics and Senior Vice President for Policy of the Medical Center. In that latter role, he successfully undertook a wide variety of administrative assignments, from managing the medical school's affiliation with New York's public hospital system to acting as interim chair of the Department of Geriatrics. Dr. Vladeck joined Ernst & Young's Health Sciences Advisory Services in 2004. He left that position for 16 months in 2006-2007 to serve, at the request of Governor Jon Corzine, as Interim President of the University of Medicine and Dentistry of New Jersey (UMDNJ) after it had entered into a Deferred Prosecution Agreement with the U.S. Attorney. While at UMDNJ, Dr. Vladeck restored fiscal stability to the system, rebuilt its governance, compliance, and internal control processes, and laid the groundwork for restoration of full academic accreditation. A graduate of Harvard College and the University of Michigan, Dr. Vladeck has held full-time faculty positions at Columbia University and Mount Sinai, and has served as adjunct faculty at Rutgers, Princeton, New York University, and the Aquinas Institute of Theology. He is a member of the IOM and the New York Academy of Medicine, and serves on the boards of the Medicare Rights Center and Ascension Health, and on the New York City Board of Health.

Heather Won Tesoriero is a medical producer for the CBS Evening News with Scott Pelley. She covers a wide range of health care and medical stories, producing both breaking news and features. Prior to joining CBS in 2008, she was a staff reporter at *The Wall Street Journal*, where she covered health care and medical-legal issues. She broke several stories on the Vioxx litigation and health care fraud investigations. She's also been a reporter at *Time* and *Newsweek*. In 2010, Won Tesoriero attended the Salzburg Global Seminar on informed medical decision making as a Knight Fellow.

Christina Zarcadoolas, Ph.D., Associate Professor, City University of New York (CUNY) School of Public Health at Hunter, is a sociolinguist and internationally recognized expert in health literacy and public under-

standing of health and science. Her research focuses on analyzing and closing the gaps between expert knowledge and public understanding. Her critically acclaimed book, *Advancing Health Literacy: A Framework for Understanding and Action* (co-authored with Dr. Andrew Pleasant and Dr. David S. Greer, Jossey-Bass/Wiley, 2006), was reviewed by the *New England Journal of Medicine*, which called it "required reading" for public health professionals responsible for developing new tools for communicating with patients and the general public. Dr. Zarcadoolas recently joined the CUNY School of Public Health at Hunter to launch a Health Literacy initiative. Prior to this, she was an Associate Professor in the Preventive Medicine Department at Mount Sinai School of Medicine, and had a long tenure as a faculty member of Brown University's Center for Environmental Studies. Dr. Zarcadoolas' work is presently focused in three areas of research and teaching: chronic disease management, health informatics, and communicating complex emergencies. She is currently working on a new book entitled *The Simplicity Complex*, which explores the limits of simplification in a complex world.

Bram Zuckerman, M.D., is a graduate of the Boston University Medical School. He completed postgraduate training in internal medicine at Baltimore City Hospital and cardiology at the Johns Hopkins program. Prior to joining FDA in 1992, he was involved in basic research in hemodynamics at the University of Colorado Medical School and practiced noninvasive and invasive cardiology in Denver, Colorado, and Northern Virginia. He joined the FDA Division of Cardiovascular Devices (DCD) as a Medical Officer in 1992 and has been actively involved in development and review of clinical trials for many new cardiovascular devices. In May 2001 he was appointed a Deputy Director in DCD. He was appointed to his current position as Director of the FDA Division of Cardiovascular Devices in September 2002.