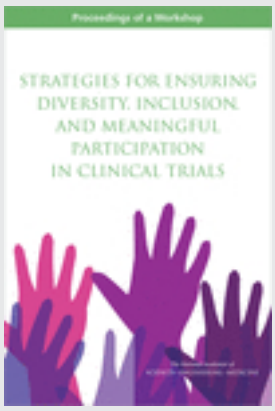

Strategies for Ensuring Diversity, Inclusion, and Meaningful Participation in Clinical Trials: Proceedings of a Workshop

DETAILS

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STRATEGIES FOR ENSURING DIVERSITY, INCLUSION, AND MEANINGFUL PARTICIPATION IN CLINICAL TRIALS

Proceedings of a Workshop

Karen M. Anderson and Steve Olson, *Rapporteurs*

Roundtable on the Promotion of Health Equity
and the Elimination of Health Disparities

Board on Population Health and Public Health Practice

Health and Medicine Division

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Reviewers

This Proceedings of a Workshop has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published Proceedings of a Workshop as sound as possible and to ensure that the Proceedings of a Workshop 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 Proceedings of a Workshop:

Kathleen A. Curran, Catholic Health Association of the United States
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Leshawndra N. Price, National Institute on Mental Health
Yolanda Savage-Narva, Association of State and Territorial Health Officials

Although the reviewers listed above have provided many constructive comments and suggestions, they did not see the final draft of the Proceedings of a Workshop before its release. The review of this Proceedings of a Workshop was overseen by **David R. Challoner,** University of Florida. He was responsible for making certain that an independent examination of this Proceedings of a Workshop was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this Proceedings of a Workshop rests entirely with the rapporteurs and the institution.

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Acronyms and Abbreviations

ATN	Adolescent Medicine Trials Network for HIV/AIDS Interventions
AZT	azidothymidine
FDA	U.S. Food and Drug Administration
IOM	Institute of Medicine
IRB	institutional review board
NCI	National Cancer Institute
NIH	National Institutes of Health
NRC	National Research Council
PCORI	Patient-Centered Outcomes Research Institute
PhRMA	Pharmaceutical Research and Manufacturers of America
STD	sexually transmitted disease

1

Introduction and Highlights of the Workshop[1]

Even as the U.S. population becomes steadily more diverse, minorities and women remain underrepresented in clinical trials to develop new drugs and medical devices. Although progress in increasing minority participation in clinical trials has occurred, "Participation rates do not fully represent the overall population of minorities in the United States" (Fisher and Kalbaugh, 2011, p. 2217). This underrepresentation threatens the health of both these populations and the general population, since greater minority representation could reveal factors that affect health in all populations. Federal legislation has sought to increase the representation of minorities and women in clinical trials,[2] but legislation by itself has not been sufficient to overcome the many barriers to greater participation. Only much broader changes will bring about the meaningful participation of all population groups in the clinical research needed to improve health. For example, careful attention to the U.S. Food and Drug Administration's (FDA's) Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data (2014) can be used as a guide to these efforts.

To examine the barriers to participation in clinical trials and ways of overcoming those barriers, the Roundtable on the Promotion of Health

[1] The planning committee's role was limited to planning the workshop, and this Proceedings of a Workshop has been prepared by the rapporteurs as a factual account of what occurred at the workshop. Statements, recommendations, and opinions expressed are those of the individual presenters and participants and are not necessarily endorsed or verified by the National Academies of Sciences, Engineering, and Medicine. They should not be construed as reflecting any group consensus.

[2] Specifically, the NIH Revitalization Act of 1993.

BOX 1-1
Roundtable on the Promotion of Health Equity and the Elimination of Health Disparities

The Roundtable on the Promotion of Health Equity and the Elimination of Health Disparities was created to encourage dialogue and discussion of issues related to the visibility of racial and ethnic disparities in health and health care, the development of programs and strategies to reduce disparities, and the emergence of new leadership. Members of the roundtable include representatives of its sponsors and additional experts from the health and social sciences, industry, and local communities.

Equity and the Elimination of Health Disparities (see Box 1-1) held a workshop in Washington, DC, on April 9, 2015, titled "Strategies for Ensuring Diversity, Inclusion, and Meaningful Participation in Clinical Trials." As Toni Villarruel, Margaret Bond Simon Dean of Nursing at the University of Pennsylvania School of Nursing, said in her introductory remarks at the workshop, the underrepresentation of minorities in clinical trials has been a persistent problem, but the dialogue to prepare for the workshop left the planning committee "energized." She pointed out that the workshop was to look at how the clinical trial process can better address subgroup differences. However, there is a balance between separating out groups and achieving numbers that are meaningful. One question is whether more race-specific trials are needed. A broader question is whether sufficient numbers of patients participate in a trial and how to put all the pieces together to drive better clinical outcomes. Answering these questions and increasing representation require a multistakeholder engagement, she said, which accounted for the breadth of institutional expertise represented at the workshop.

HEALTH DISPARITIES AND CLINICAL TRIALS

In his introductory remarks at the workshop, National Academy of Medicine President Victor Dzau said, "The issue of eliminating health disparities is essential to our society, to all of us, and certainly to me." Dzau was born in postwar China, where he observed poverty and disparities firsthand, and he has worked extensively on disparities issues as a researcher and administrator at Duke University. "The health field is not just about health care," he said. "It is about strengthening everything about health, which means, of course, addressing many social issues." In that context,

"Understanding and addressing the root cause of health disparities is what we must all do."

Despite the great advances of science and technology in medicine in recent years, inequities are still prominent in the United States and globally. The National Academy of Medicine has a responsibility, said Dzau, to discuss how to change this. As such, the work of the roundtable is a thread that runs through all the work being done by the Academies.

Barriers to meaningful participation in clinical trials include language differences, cultural differences, and a history of discrimination and exploitation, Dzau said, adding that "We all need to do better." The scientific community does not have all the tools it needs, but that is why the Academies bring the best minds together to discuss the problems and arrive at innovative ways to address those problems. "I know that you will showcase some of those innovative approaches today at this meeting," he concluded.

ORIGINS OF THE WORKSHOP

The workshop was the continuation of a historical process, said Jonca Bull, director of the Office of Minority Health at FDA, in her introductory presentation at the workshop. Thirty years ago, the *Heckler Report* documented the existence of health disparities among racial and ethnic minorities in the United States and called such disparities "an affront both to our ideals and to the ongoing genius of American medicine" (Task Force on Black and Minority Health, 1985). In 2003 the Institute of Medicine (IOM) report *Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care* began with the words, "Racial and ethnic minorities tend to receive a lower quality of health care than nonminorities, even when access-related factors, such as patients' insurance status and income, are controlled" (IOM, 2003, p. 1).

In 2012, legislation that reauthorized FDA user fees,[3] which are essential for agency operations, included provisions under Section 907 requiring that FDA publicly report data on the inclusion and analysis of women in FDA applications, with additional provisions in legislation requiring the same for race and ethnicity. This legislation mandated that, within 1 year of enactment, FDA would provide to Congress and post on the FDA website a report on the extent of clinical trial participation and on the quality of analyses to determine safety and effectiveness for demographic subgroups included in applications submitted to FDA, while taking into account FDA

[3] The FDA Safety and Innovation Act of 2012, although primarily focused on the reauthorization of user fees for pharmaceutical companies, also contained a provision, Section 907, that directs these companies to improve demographic subgroup data's completeness, quality, and availability.

regulations and requirements for protecting the confidential commercial information of sponsors.

This legislation led to an action plan designed to address deficiencies that also reflected several concerns expressed in an April 30, 2014, letter to FDA from Senator Debbie Stabenow. This letter asked FDA to require representative proportions of women and minorities in industry-sponsored clinical trials comparable to that of the National Institutes of Health (NIH). It asked about the specific actions that FDA would take, in cooperation with industry, to achieve meaningful subgroup analyses for safety and efficacy, clear timelines for enforcement that do not necessarily disrupt trials, and the provision of transparent and publicly available results. The letter also asked FDA to publicly and regularly report progress implementing the action plan and to identify when further action is needed.[4]

The action plan has three overarching priorities (FDA, 2014):

- Improve the completeness and quality of demographic subgroup data collection, reporting, and analysis.
- Identify barriers to subgroup enrollment in clinical trials, and employ strategies to encourage greater participation.
- Make demographic subgroup data more available and transparent.

As an example of the work being done under the plan, Bull cited changes to the MedWatch Form, which collects spontaneous adverse event reports after a product goes to market. The next update of the form will include demographic data beyond just male and female, which will mark "a major step forward for us and for the postmarketing environment," said Bull. She also mentioned the Drug Trials Snapshot, which provides information about the sex, age, race, and ethnicity of clinical trial participants for recently approved drugs. With one drug in the snapshot, women represented only 24 percent of participants, and more than 87 percent of the participants were white. With another drug used to treat multiple myeloma, a disease that differs among population groups, only 3 percent of participants were African Americans.

FDA's policies have been evolving since the development of the action plan and will take time to be implemented, said Bull. But FDA policy now explicitly states "The database submitted in a marketing application should reflect usage in a diverse racial population, one reflective of the likely patient mix postmarketing, for potential differences in response to become apparent." The challenge, said Bull, is to implement this policy and execute it well.

[4] An FDA website provides updates of the agency's activities related to Section 907 of the legislation: http://www.fda.gov/RegulatoryInformation/Legislation/SignificantAmendmentstotheFDCAct/FDASIA/ucm389100.htm (accessed July 1, 2015).

In a 2014 speech, FDA Commissioner Margaret Hamburg said:

> One of the core tenets of rigorous biomedical research, as well as a guiding principle of the FDA's goal to meet the health needs of patients across the demographic spectrum, is the importance of encouraging diversity in clinical trials. When a more diverse population participates in clinical trials, we increase the potential to know more about the extent to which different subgroups—males and females, young and old, people of various racial and ethnic backgrounds, and patients with differing comorbid diseases and conditions—might respond to a medical product. And when subgroup data are analyzed, we have available more information about the product that can be communicated to the public. The result is greater assurance in the safety and effectiveness of the medical products used by a diverse population.

Bull concluded with several questions to be kept in mind during the workshop:

- How can health disparities be measured, and what should be measured? Classifications of participants often are not consistent with the definitions of race and ethnicity established elsewhere in the federal government and also must take into account that data are often being generated globally. The constructs of race, ethnicity, and gender continue to generate questions and controversy.
- What is meaningful participation in the context of clinical trial design? Estimating the treatment effect within a group or the heterogeneity of treatment effect across groups is critical, which raises the question of which drugs or other medical products need to be identified early for special consideration for subgroups.
- What steps can FDA and NIH take in working together with academia and industry to ensure the meaningful participation of diverse groups in clinical trials?

HIGHLIGHTS OF THE WORKSHOP

During the concluding session and at several other points during the workshop, the workshop speakers and participants pointed to important messages that emerged from the presentations and discussions. These messages are summarized here as an introduction to the main ideas of the workshop. They should not be seen as a consensus of workshop participants or as the conclusions of the workshop as a whole.

- Progress in science and medicine requires that patients participate in clinical trials (Brooks, Buch).

- The motivations to participate in clinical trials have as much or more to do with context, including family and community, as with potential benefits to the participant (Horowitz, Solomon, C. Ulrich).
- Barriers to participation in clinical trials include mistrust, costs, language and cultural differences, lack of awareness of trials, and trial designs that tend to exclude minorities (Hickam, J. Ulrich).
- Despite these barriers, when given the opportunity, minorities are just as likely to participate in clinical trials as the majority population (Brawley, Ramirez).
- Perceptions and messaging are critical factors in decisions about whether to participate in a clinical trial (Buch, Horowitz, Solomon, C. Ulrich).
- The foundation of participation in a clinical trial is trust, whether in a health care provider, a research, a funder, or a government (Chen, Dzau, Ellen, Horowitz, Kim, Ramirez, Solomon, C. Ulrich).
- Minorities underrepresented in clinical research are heterogeneous, which requires creative and intellectually rigorous ways of collecting information from groups that may be hard to reach (Ellen, Horowitz).
- The categories used to collect information about race and ethnicity, which were developed by government for administrative purposes, create difficulties when applied to clinical research (Brawley, Rotimi, J. Ulrich).
- Federal agencies are both mandated and committed to increasing the representation of minorities in clinical trials (Buch, Bull, J. Ulrich).
- The recruitment and retention of participants in clinical trials are multifaceted problems that involve funders, researchers, health care providers, patients, advocacy groups, and the public interest (C. Ulrich).
- Incentives can influence the decisions of researchers and health care providers, as with incentives encouraging physicians to practice in particular places (Brooks).
- However, social change is slow, and incentives can take a long time to have an effect (Brooks, Buch).
- Engaging communities not as subjects but as partners in research can not only increase participation but change the nature of clinical trials (Brooks, Ellen, Hickam, Horowitz, Kim, Ramirez, Solomon, C. Ulrich).
- Greater minority representation among research leaders and research teams can boost the participation of underrepresented minorities in clinical trials (Brooks).

- New technologies such as apps on smartphones could both explain clinical trials more simply and clearly and improve recruitment into trials (Ellen, Kim, J. Ulrich).
- Basic questions such as how much information is required to ensure safety and efficacy in subgroups still have not been completely answered (Buch, Bull, Dzau).
- The emerging era of personalized medicine, in which people are treated on the basis of their individual genetic sequences and experiences, will raise fundamental questions about how to ensure diversity in clinical trials (Buch).

ORGANIZATION OF THE PROCEEDINGS OF A WORKSHOP

Following this introductory chapter, Chapter 2 provides a historical perspective on both racial and ethnic differences in human population and on the representation of minorities and women in clinical trials.

Chapter 3 examines some of the scientific issues that arise in efforts to achieve clinically meaningful inclusion, such as the size of the subgroups needed to produce useful results and how best to involve communities in scientific research.

Chapter 4 looks at some of the barriers to participation posed by health care providers, institutions, and systems, such as the difficulties in achieving informed consent and the mistrust created by historical abuses.

Finally, Chapter 5 considers potential best practices and policy options to increase the recruitment and retention of minorities and women in clinical trials, with a final list of potential best practices drawn from the presentations summarized in that chapter.

2

Historical Perspectives and Context

Diversity in clinical trials typically refers to population groups characterized by race and ethnicity, though other groupings, such as those associated with gender, age, geography, and socioeconomic status, also are components of diversity. Yet race and ethnicity are inexact concepts, and the associations among race, ethnicity, and health depend on a wide array of factors.

At the workshop, three speakers examined the role of race and ethnicity in both health disparities and in clinical trials. Race and ethnicity have both biological and social origins and consequences, which creates a rich and complex arena for policy.

THE HISTORICAL AND SOCIAL ORIGINS OF RACE

Historically, the concept of race in the United States has had two main components, said Charles Rotimi, chief of the Genomics of Metabolic, Cardiovascular, and Inflammatory Disease Branch and director of the Center for Research on Genomics and Global Health at the National Human Genome Research Institute of NIH. One component has been based on biogenetic variation determined in part by a person's biogeographic ancestry. The other component has blended social, cultural, and genetic factors into a poorly understood construct used to sort people into a few predetermined categories (Smedley and Smedley, 2005). These categories were always problematic. For example, in the United States, having just a single black ancestor was enough for a person to be considered black. Yet in

South Africa, people with different degrees of African ancestry were sorted into distinct categories.

Many aspects of racial categories are arbitrary at best, yet race "is the fundamental basis for inequality" in the United States, said Rotimi. The concept of race has been used to drive differences that disadvantage some people and advantage others. As the National Research Council (NRC, 2001) has observed, "The idea of race and its persistence as a social category is only given meaning in a social order structured by forms of inequality—economic, political, and cultural—that are organized, to a significant degree, by race." According to Rotimi, "That is really why it is so critical that we understand a historical perspective when we are talking about inequity and health disparities."

The advent of genomics has provided an opportunity to look anew at the socially derived categories associated with ideas of race. The genetic variation among humans provides an unbiased history of the human species while also providing previously unknown information about human health, Rotimi said. This variation reveals that all humans are descended predominantly from a relatively small group of anatomically modern humans who lived in Africa within the past 200,000 years. The descendants of this group have dispersed across the globe over the past 100,000 years. As modern humans encountered more archaic populations of humans outside Africa, they sometimes mated with members of these groups and added fragments of their DNA to the DNA they carried out of Africa. As Rotimi said, "One of the things that humans do very well is, whenever we travel, we are very generous in sharing our DNA."

Because of this history, most of the oldest genetic differences among people are found in all human populations. At the same time, the development of agriculture in the past 10,000 years and of urbanization in the past 700 years has led to rapid population growth and to the origin of new variants that are rare and specific to one population or even to one family. As a result, most genetic variation occurs in all populations, though some is local.

Some people have used the portion of genetic variation that is structured geographically to justify traditional racial groupings. But that interpretation is a "misunderstanding of the concept of human genetic variation," Rotimi said. For example, Rotimi and his colleagues recently published a study of 3,500 individuals from 163 ethnolinguistic groups around the world (Shriner et al., 2014). A computer program analyzed the genetic differences among these individuals and distinguished 19 major ancestral components—more than the traditional number of racial groups, and a number that varies depending on the size of the sample. Furthermore, most of the individuals—94.4 percent—showed mixed ancestry among these components. Said Rotimi, "Trying to use genetics to define race is like slicing soup. You can cut all you want—the soup stays mixed."

These results have implications for individuals who identify with particular racial groups. For example, a study of disease-associated genetic variants in self-identified African Americans found percentages of African ancestry ranging from 0.6 percent to 99.7 percent, with an average of about 80 percent (Shriner et al., 2011). Similarly, people who might self-identify as Mexican American or Puerto Rican can have very different combinations of ancestry. Thus, if the action of a drug being tested in such individuals is influenced by a specific genetic variant, their race or biogeographic ancestry is likely to say little about whether they have that variant. "You cannot use group data to say something about [an] individual," Rotimi said.

Genetic diversity needs to be studied, Rotimi concluded. It can help shed light on ancient human population migrations, the biological relationships among human populations, and why some disease-causing variants occur in higher frequencies among some populations, such as variants that protect against diseases common in particular parts of the world. But genetic diversity "does not coincide or overlap in any kind of systematic way in terms of the way we try to define ourselves," he said. "Individuals who look alike cannot be used as representing their genetics." Similarly, if people want their genetic variants to be probed in clinical trials, they need to participate in those trials, said Rotimi, not assume that the participation of other members of their social groups will suffice (Rotimi, 2012; Rotimi and Jorde, 2010). "My genetics cannot work for you," he concluded.

THE DRAWBACKS OF MANDATED INCLUSION

Otis Brawley, chief medical officer for the American Cancer Society and professor of hematology, oncology, medicine, and epidemiology at Emory University, took what he described as a somewhat contrarian view of race and ethnicity in clinical trials, while agreeing with the overall need to broaden participation. He said that he worries when legislators require analyses of subgroups in clinical trials. The advocates of representation mean well, but they need to be more scientific, he added. Subgroup analyses are often wrong because they include small numbers of people. For example, there are not currently enough women with stage-three ovarian cancer in the United States to get a statistically significant answer about the possible differences in drug action between white women and black women.

Race, as was pointed out by Rotimi, is a sociopolitical characterization, not a biological characterization, and these characterizations have changed over time. For example, someone born in India who came to the United States would have been characterized in three different ways by U.S. censuses since the passage of the NIH Revitalization Act legislation in 1993.

Populations can differ in their susceptibility to disease, yet simplified racial thinking can be misleading. Sickle cell anemia is found among people

throughout the Mediterranean region, not just among those with ancestors from sub-Saharan Africa. A mistaken finding that azidothymidine (AZT) was more effective in white populations than black populations took a decade to overcome; whereas, the actual difference was in adherence to the drug regimen. The problem with requirements for inclusion, said Brawley, is that they can send the message that human population groups are biologically different.

Legislation mandating the inclusion of racial groups has "moved the emphasis off the real problem," said Brawley. Disparities in outcomes are generally due to social issues, not biological issues. "For most diseases, equal treatment yields equal outcome among equal patients," he said. Race may help determine the quality of care, but it does not necessarily determine whether a person has a genetic variant that will influence a drug response. "There is not enough concern or emphasis on the fact that there is not equal treatment," he said.

Studies have revealed many of the reasons behind disparities in outcomes, including cultural differences in acceptance of a therapy (for example, beliefs about the causes of an illness), disparities in comorbid diseases that make aggressive therapy inappropriate (such as differences in obesity rates among groups), lack of convenient access to therapy, racism, and socioeconomic discrimination. For example, Haggstrom et al. (2005) found that 33 percent of blacks and 23 percent of Hispanics got less than minimum expected care compared with whites. Lund et al. (2008) showed that 7.5 percent of black women in metropolitan Atlanta in the year 2000 who were diagnosed with a localized, curable breast cancer did not get surgical treatment within the first year of diagnosis, compared with about 2 percent of whites. Disadvantaged African Americans who have colon cancer tend to get treated in hospitals that are overcrowded and stressed, where pathologists will look at just 3 to 5 lymph nodes for signs of cancer rather than 18 to 24, Brawley said. As a result, the belief took shape that black cancer patients had more aggressive colon cancer. "It was actually a problem with the staging because of economics," he explained. In military health systems, in contrast, where the members of different groups are treated the same way, diseases in blacks progress the same as in whites.

Using data from the early 1990s, Tejeda et al. (1996) showed that only 2.4 percent of non-Hispanic whites, 2.6 percent of non-Hispanic blacks, and 4.2 percent of Hispanics who had cancer were participating in clinical trials. "There is a shortage of people going into clinical trials of all races," Brawley said. More recent data similarly show that participation in clinical trials depends more on the nature of the study (for example, treatment versus prevention trials), the study population (for example, pediatric versus adult), and the reputation in the community of the enrolling center than on race or ethnicity. In addition, many minorities get their care from institu-

tions that cannot afford to offer clinical trials. He further noted that "In a situation where clinical trials are offered and available, if offered and available, minorities are just as likely to say yes as majorities. There is no racial difference if you are from an institution that that person trusts."

As health care enters an era of precision medicine, the genetic markers a person has will be much more important than a person's race or ethnicity, said Brawley, concluding that "It is not the width of one's nose or the color of one's skin. It is what genes are active."

HISTORICAL PERSPECTIVES ON MEANINGFUL INCLUSION

Amelie Ramirez, professor of epidemiology and biostatistics, founding director of the Institute for Health Promotion Research, and associate director of cancer prevention and health disparities at the Cancer Therapy and Research Center, all at the University of Texas Health Science Center at San Antonio, briefly reviewed the history of clinical trials and efforts to broaden participation in trials.

The origins of clinical trials date back to early ideas on experimentation in the classical era, but the first generally recognized clinical trial was conducted in the middle of the 18th century by the Scottish physician James Lind, who compared three therapies to treat scurvy—a major health problem for the British navy. Over the next 200 years, clinical trials continued to evolve as the concepts of blinded studies, placebo controls, and informed consent were developed.

Following the human experimentation conducted by the Nazis in World War II, the Nuremberg Code was developed in 1947 to protect human subjects through informed consent and the concept of minimizing harm. Nevertheless, abuses continued to occur, such as the Tuskegee syphilis experiments that were initiated in the early 1930s and continued until 1972. The Declaration of Helsinki[1] in 1964 and the establishment of institutional review boards[2] (IRBs) in 1974 marked major shifts in the consideration of how to balance the risks and benefits of participating in clinical trials.

In 1979 the *Belmont Report* identified minority populations as vulnerable research participants and recognized that many vulnerable groups may be excluded from research.[3] Since that time, improving minority and female

[1] The 18th World Medical Assembly adopted a series of guidelines to guide physicians and medical researchers to protect human subjects involved in research.

[2] IRBs are organized standing committees of researchers, administrators, physicians, and so on that review all proposed research projects to ensure the protection of human subjects.

[3] The *Belmont Report* was a set of ethical principles and guidelines to ensure protection of human subjects in research. The report was created in 1979 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research for the Secretary of Health, Education, and Welfare.

representation in clinical trials has been a focus of attention, as highlighted by the 1993 NIH Revitalization Act. However, said Ramirez, "While we have continued to make it a priority to include women and minorities in clinical trials, we still struggle to figure out the best way to accomplish this."

As an example of the progress that has been made and how much remains to be done, Ramirez cited a report by the Public Health Service Task Force on Women's Health Issues (1985), which raised concerns about the lack of research on women's health, the poor quality of health information available to women, and the poorer quality of health care that results. A 2010 report from the IOM (2010) documented major strides that have been made in the areas of breast cancer, cervical cancer, and heart disease. But that report also identified conditions where progress is still needed, including unintended pregnancy, maternal morbidity and mortality, autoimmune diseases, alcohol and drug addiction, lung cancer, gynecologic cancers (noncervical), nonmalignant gynecologic disorders, and Alzheimer's disease.

In the past, minority underrepresentation in clinical trials has been attributed to many factors, including unwillingness to participate, lack of opportunity, medical ineligibility, lack of flexibility in child care or employment, and distrust. However, a meta-analysis conducted by Wendler et al. (2006) of 20 health research studies involving more than 70,000 individuals found that individuals from minority groups were *more* willing to participate in health research than the majority population. However, individuals from minority groups were less likely to be offered enrollment. "This is something that we need to continue to look at," said Ramirez. "We must continue to understand why minority groups are underrepresented and examine our biases around this issue."

LATINOS IN CLINICAL TRIALS

At the time of the workshop, noted Ramirez, the National Cancer Institute (NCI) had more than 8,000 clinical trials that were accepting participants. However, though Latinos represent 17 percent of the U.S. population and are the largest minority group in the United States, they represent only 5 percent of the participants in NCI treatment trials.

Less is known about effective strategies to recruit Latinos into clinical trials than for other groups, said Ramirez. Differences in eligibility criteria, expected clinical outcomes, and geographic availability all raise questions. Furthermore, the issues can be different with early-phase clinical trials than with later phases.

With funding from NCI, Ramirez and her colleagues have studied early-phase clinical trials to identify cultural, economic, and environmental barriers to participation in these trials and to identify key components of an intervention to reduce these barriers and increase participation. Among

health care providers, the barriers for recommending participation in trials include logistical factors, such as the time and effort involved in explaining protocols to patients, and personal factors, such as worries about the loss of control over patient care (Ramirez et al., 2012). Among patients, prominent barriers were the lack of knowledge about the disease and treatment; cultural, language, and literacy issues; a lack of discussion with their doctors about the option; and the costs, travel, and insurance issues involved in participation (Chalela et al., 2014). For example, many trials are offered at centralized cancer centers, and people living in rural areas do not necessarily have access to these trials. For this reason, local providers need the education and training to provide quality treatments, Ramirez said. Also, people without the insurance to cover basic screening costs usually cannot participate.

Yet when patients are told about the option of participating in a clinical trial, many are eager to do so. Ramirez quoted one patient who said, "I did not know cancer clinical trials were an option for me until my doctor told me about them. . . . I thought they were for very ill people. But now I know there are clinical trials for all stages of breast cancer."

Ramirez explained that when patients were asked about what would enable them to participate in a clinical trial, several factors were prominently cited, including

- Trusting the doctor
- Trusting the trial center
- Feeling that joining a trial will give hope and help future cancer patients
- Having clear information
- Encouragement from family members

For example, one patient said, "To know that every new medicine goes through a clinical trial puts me and my family more at ease and gives us more options if we get sick."

In a test of three registry recruitment methods among South Texas Hispanics into the Cancer Genetics Network, one randomized group received a letter from their doctors asking them to participate, another received the letter plus a culturally tailored bilingual brochure, and the third received the letter, brochure, and interpersonal contact to urge them to participate. The result was that extra information and interpersonal contact increased accrual, reported Ramirez.

In another experiment, an in-clinic patient navigator/clinical research associate sought to increase accrual to pediatric cancer trials in south Texas (Wittenburg et al., 2010). The result was that accrual rose from 38 in 2007 to 118 in 2010, which is the highest local total ever.

Finally, in a study ongoing at the time of the workshop, Latinas were empowered to make informed decisions regarding breast cancer clinical trials through enhancement of knowledge, attitudes, and skills; increases in self-efficacy; and encouragement to discuss clinical trials as a potential treatment option with doctors and family members. Preliminary results showed that the proportion of Latina breast cancer patients taking steps toward participating in a clinical trial—through asking their doctors about clinical trials, talking with family and friends about participating, and considering the pros and cons of participating—was significantly higher in the intervention group than in the control group. Particularly important, said Ramirez, was informing patients about clinical trials before they talked with their doctors, because providers have limited time to discuss the possibility of clinical trials. Empowering interventions that enhance patients' awareness and self-efficacy foster a sense of control and provide patients with the knowledge and skills they need to make informed decisions regarding treatment options.

Ramirez made two additional suggestions to increase Latino participation in clinical trials, based on her experiences and observations. Computer-based videos, if specifically tailored to Latina breast cancer patients, are a particularly effective strategy to increase patients' knowledge and understanding of clinical trials and to promote their participation in clinical research. Also, other populations are underrepresented in clinical trials and need to be considered for inclusion, including individuals with disabilities, the aging population, and gender difference groups.

THE EFFECTS OF PRECISION MEDICINE

During the discussion, workshop participants and the presenters continued to talk about what will happen as precision medicine continues to advance. Brawley noted that, today, someone who is dark skinned or of Mediterranean ancestry is more likely to have a genetic variant that would suggest how best to treat a urinary tract infection. "That is what I would call benign racial profiling," he said. However, as genomic testing spreads, more people will receive tailored therapy depending on exactly what genetic variants they have. Treatments will then be based not on skin color but on an individual's genomics. One drawback to a genomic approach is that it will be more expensive, Brawley said, than making judgments based on a person's appearance.

As Rotimi noted, appearance is a proxy that can be useful, but it gives only a vague idea of what genetic variants a person might have. "It would definitely have been better if you had the genetic variant and you made a decision and you do not have to use the phenotypic characterization to do that. We are not there yet. That is where we are moving," he said.

According to Ramirez, increasing minority accrual in clinical trials is critical to the development of novel therapeutics, including personalized therapies. Without adequate representation of minorities, researchers cannot assess the differential effects among groups, nor ensure the generalizability of trial results.

Rotimi also pointed out that the optimal population to enroll in a clinical trial depends on the questions being asked. For some questions, a genomically uniform population might be better, while for others a heterogeneous population would be better. But representation needs to be done carefully. Having just a few members of a population group in a trial does not provide sufficient statistical power to say anything meaningful about that population. The trial organizers may satisfy a political ideal but not produce scientific results. At the same time, diversity is not an illusion. "If we want to represent [diversity] from a genetic point of view, a social point of view, a cultural point of view, we need to broaden the representation of the people who are at the table," he concluded.

3

Scientific Issues: Clinically Meaningful Inclusion

As presented in the previous chapter, a host of scientific issues arise when considering the inclusion of subgroups within clinical trials. Subgroup analyses can broaden the findings from a trial, but subgroups also can be too small or unrepresentative to provide useful results. Community involvement requires real partnerships, not just occasional meetings with community leaders. Involving minorities in clinical trials requires changes among many of the stakeholders in the clinical trials system, not just among researchers, government officials, or advocacy groups.

Three speakers examined many of these issues from the perspectives of academia, industry, and government. All three sectors face challenges in overcoming the barriers to clinically meaningful inclusion of minorities in clinical trials, which requires that they work together to overcome these barriers.

OVERCOMING THE BIASES OF THE RESEARCH COMMUNITY

One way to overcome the biases evident in the underrepresentation of minorities and women in clinical trials is to make sure that every research project partners with people who are disproportionately and unjustly affected by the conditions being studied, said Carol Horowitz, associate professor of health policy and medicine at the Icahn School of Medicine at Mount Sinai. As a community partner once told Horowitz, "If you change the way you look at things, the things you are looking at change."

Researchers and research partners can have very different perceptions of a clinical trial, Horowitz pointed out. Researchers may think that the

purpose of a project is clear and important, that the research needs to be done quickly, that the benefits are obvious and the risks minimal, and that patients should of course agree to participate. Potential research participants may have earned skepticism from past experiences, may not see the need for haste, may perceive the benefits as unclear, and may view the risks as unacceptable if the benefits are minimal. "We have to tell people honestly that we are doing the research because we do not know whether it is going to have a benefit," said Horowitz. "That, for people, might right away be a game stopper. 'If you do not know if it is going to work, try it out on somebody else and let me know.' People know about historical abuses."

Many people who are asked to participate in research know why they are sick. In a series of focus groups that Horowitz did with people with hypertension, they said that their blood pressure was high because of poverty, pollution, racism, and stress. "You are medicating a social condition," they said, according to Horowitz. "Fix our communities, and our blood pressure will go down."

For researchers, the research system is designed to get the patients it gets. Participants tend to be easy to contact, easy to enroll, easy to follow up, and compliant. These are usually not the patients who are underrepresented in research, Horowitz pointed out. In addition, stated and unstated design and inclusion criteria have a tendency to exclude people. For example, Horowitz cited a diabetes prevention program that required patients to keep a multiple-day food diary. In a heart failure study, a self-efficacy questionnaire asked potential patients how confident they were that they could take all their medicines as prescribed and follow a low-salt diet, and respondents with low self-efficacy were excluded.

Horowitz asked the workshop participants who had been involved with clinical trials whether they would take part in their own studies. Would they take a phone call at home? Did they have enough time to participate? Would they be available at night or on weekends? Did they have easily accessible child care? She also asked how much time researchers spend crafting their strategies and messages. Do they craft these messages within the social networks they hope to reach? Can potential participants understand the messages? Are they likely to trust a researcher? "People do not separate a hospital from a researcher," she said. "If you do not have a good experience with the asthma clinic or the asthma practice at your hospital, you are not going to be in a study."

She described two case studies, starting with a diabetes prevention trial in East Harlem, which is a mostly black and Latino low-income community in northeastern Manhattan. Increased physical activity and weight loss can reduce the progression to diabetes by two-thirds and eliminate the disparity between blacks, Latinos, and whites in the development of diabetes. The study looked at whether a peer-led intervention in Harlem

could prevent diabetes through lifestyle change, with not just the methods but the subject of the study being chosen by the community. Recruitment occurred, according to Horowitz, "anywhere in East Harlem where we thought people were": churches, food pantries, senior centers, schools, health centers, and other community gathering places. Participants did not need regular health care providers in order to enroll in the trial, and half of the patients were uninsured. "We are fierce," she added. "We have an agreement with the clinical sites that partner with us that they will accept patients. We have a list . . . of all the places that can accept people for care, places that take uninsured patients. We always try to connect people to care," she explained. After giving their consent, participants did glucose tolerance and other blood tests, filled out a survey, participated in eight sessions, and did follow-up sessions at 3, 6, and 12 months.

The study faced several challenges, Horowitz said. The population represented by those living in East Harlem has been underrepresented in these kinds of studies and historically has been seen as difficult to engage in research. Trying to get people to change how they move and eat is difficult. Efforts to reach out to the community sometimes were misguided. Early in the study, a poster showing an obese black man with an amputated leg and the words "Portions Have Grown: So Has Type 2 Diabetes, Which Can Lead to Amputations" was criticized for showing just one ethnic group—especially when it was revealed that the photograph had been digitally altered to remove the model's leg.

The study sought to overcome these challenges by working in partnership with a community action board. Through this board, the community chose the topic, methods, strategies, incentives, domains for surveys, and analytic questions for the study. The community did not want a control group and opted for a delayed intervention. "We do not want to tell people they are going to get nothing, but if they can have it now or in a year, that is fine," said Horowitz. The community called attention to such factors as residential segregation, sleep apnea, and food insufficiency, which made the study more complex but more accurately reflected the community context. Social marketing, street art campaigns, and other forms of outreach sought participants. The study provided community benefits such as employment and capacity building, and team members did not need a primary care provider, literacy, or a Social Security card in order to enroll in the research.

The study enrolled about 500 diverse patients, mostly through their community partners. The result was significant weight loss that was maintained at 1 year. "People lost weight," said Horowitz, and "they kept it off."

The second case study involved disparities in kidney disease. A genetic variant that is more common in African Americans than in other populations can increase the risk for kidney failure in people with high blood pressure. This variant was favored in Africa because it protects against sleeping

sickness, but in today's world it can have harmful effects. The object of the study was to incorporate risk information into clinical care in an attempt to motivate people to improve management of their blood pressure. The study was still ongoing at the time of the workshop, but Horowitz described some of the challenges this study has faced. She was warned that studying a genetic variant that affects the health of a particular population group could contribute to racism, but that has not been her experience. Horowitz explained that "the first person I talked to was one of my colleagues, who is a pastor, who said, 'Now maybe white doctors who see black people on dialysis won't think it is because we didn't try hard enough. They will recognize there is more to disease than bad behavior.'"

Recruitment was also a challenge in a patient population that is difficult to reach and schedule. An inclusive approach was again the answer, said Horowitz, with formative research to develop outreach, a stakeholder board that included patients and community leaders, and stakeholder engagement throughout. For example, the board changed aspects of the study design and worked with the IRB at Mount Sinai to gain approval of study modifications. The study also developed apps with QR-type barcodes for enrollment and verbal consent procedures to overcome low literacy levels. The study has been designed to produce actionable information, so that participants know what to do with the results of a test. In the event of a positive genetic test, for example, patients talk not only with a genetic counselor but with another patient who has had a positive test.

Horowitz concluded with several lessons drawn from these experiences. First, look through participants' lenses, she said. Studied need to be designed with inclusiveness in mind at every step; she added that "You should have studies that people want to join." Teams should be committed to research and include people from the target community, she said, with both proven and novel strategies being used. Evaluation of these strategies, with publication of data so other people can learn from the experiences, can lead to modifications that improve the strategies. Finally, she urged study leaders to share results with participants and communities and democratize data. Every patient who was in a study should receive a note thanking them and telling them what was learned, she said, and the data should be freely available for anyone to examine.

INCLUSION IN INDUSTRY TRIALS

The number one priority for the biopharmaceutical industry is improving timely access to innovative new medicines, said Jocelyn Ulrich, senior director of scientific and regulatory affairs at Pharmaceutical Research and Manufacturers of America (PhRMA), which represents biopharmaceutical research and discovery companies in the United States. The cost of devel-

oping a new medicine currently exceeds $2 billion and takes more than a decade, she explained. Advancements in science and technology are changing the understanding of disease and the development of drugs. But the regulatory framework and acceptance of drug development tools and methodologies must evolve to keep pace with these advances and encourage the inclusion of participants in ways that are both science based and meaningful, she said.

Patient engagement at appropriate times throughout the drug development process has a number of benefits, Ulrich observed. During the design phase, the inclusion of patient perspectives allows for designs that encourage participation and reduce burdens on patients and caregivers, which creates the potential to improve recruitment and retention. Patient-focused drug development tools, if accepted by patients and regulators, can improve efficiency and provide data that are meaningful to patients, including novel clinical endpoints, clinical outcome assessments (including patient-reported outcomes), and benefit–risk assessments.

Scientific factors should be the primary drivers when considering the need for specific racial, ethnic, or geographic groups to be represented in a trial, said Ulrich. This decision needs to be informed by nonclinical, preclinical, and early clinical data and by biological and medical knowledge about the disease prevalence and mechanism of action of the compound, she added. In addition, when significant differences in drug metabolism are expected, specific subpopulations need to be included in early-phase development to better understand pharmacokinetics, safety, and dose–response data.

The overarching principle for considering the need for specific racial, ethnic, or geographic groups to be represented in a trial is that sample sizes for trials should be driven by the primary objectives and hypotheses of a study, Ulrich noted. From a scientific perspective, it should not be necessary for studies to be powered to be significant in any specific subgroup unless there is a biologically plausible reason to do so, she said, and sponsors must balance the need to make treatment options available in a timely manner with the need to enroll a defined subpopulation.

Another overarching principle is that prespecification and documentation of the plan for subgroup assessment in the protocol are essential for interpreting the results, Ulrich explained. Remaining questions about subgroup differences then need to be monitored and answered, she said. In some cases, these differences may be most effectively studied through the use of real-world evidence after approval, as when there are cases of low incidence rates or where it may not be practical to enroll a particular population. The context can drive the balance between pre- and postapproval information collection. For example, better understanding of patient tolerance for risk may create more willingness to accept uncertainty in return for earlier access to the medicine in a broader population.

Innovative tools and approaches are being developed and used in the drug development space, Ulrich pointed out. For example, adaptive designs may use accumulating data to modify aspects of a study as it continues without undermining the validity and integrity of the trial. Such designs could be designed to drop a study arm if prespecified safety or efficacy measures are not met, so that more patients can be enrolled in an arm that would be beneficial to them. "From an ethical perspective, that is a great advancement in drug development, rather than being given the choice between placebo or standard of care versus the active treatment," said Ulrich.

Inclusion and exclusion criteria generally are developed based on the intended patient population for the investigational treatment and the questions that the study seeks to answer. These criteria need to allow for the identification of a well-defined population and minimize patient risks without being unnecessarily restrictive, Ulrich said. Arbitrary limits, such as 65 years as an upper limit for age, may generally be inappropriate, and the exclusion of patients with common concomitant illnesses should be done only if this is expected to affect treatment effect or safety, she added.

As pointed out in the previous chapter, standard categories of race and ethnicity are widely acknowledged to be inadequate for understanding meaningful genetic differences. Self-identified race and ethnicity generally correlate with population groups but not necessarily with an individual's distinct genetic background, which can lead to confusion and debate about the relationship between the risk of disease, treatment options, and self-identified race. Adding country of origin in addition to race may be one way to disaggregate the data and get more meaningful data for patients. Also, drug development is a global enterprise, Ulrich reminded the workshop participants. Multiregional clinical trials with non-U.S. data constitute more than 70 percent of applications to FDA.

Drug development tools, such as biomarkers and surrogate endpoints, are indicators of biological processes that may be used to identify patients who are more likely to benefit from investigational treatments, Ulrich explained. Use of such tools may increase the efficiency of the drug development process and provide meaningful results back to patients.

Achieving greater diversity in clinical trial participation faces significant practical barriers that add to the scientific complexities mentioned earlier, Ulrich said. According to one survey that she cited, 57 percent of patients would prefer to receive information about trials from their primary physician, but only 20 percent do. The study design or process may be too complex, with lengthy informed consent and too many visits and procedures. Staff may not be adequately trained to deliver linguistically and literacy-appropriate information, and patients may fear or mistrust researchers. Participation may involve lost time or wages and create child

care or transportation problems, and patients may lack awareness or have misperceptions about the clinical trial process. The lack of proximity to research sites and trial processes that may only be conducted at an individual site may also cause difficulties.

The biopharmaceutical industry has been engaged in improving awareness and knowledge about clinical trials. For example, PhRMA partnered with the National Minority Quality Forum in 2014 to launch "I'm In," which is an advocacy, social media, and educational campaign.[1] PhRMA is a member of the Coalition for Clinical Trials Awareness, and it sponsored the first Center for Information and Study on Clinical Research Participation AWARE for All event in Washington, DC, in 2015. In addition, PhRMA also has created a website to provide educational resources and information about clinical trials.[2]

Some of the scientific challenges mentioned could be addressed by innovative designs and methodologies in combination with advanced drug development tools. These collectively have the potential to accelerate drug development while obtaining evidence-based information about subgroups in an efficient manner. However, to realize this potential, a multistakeholder approach is needed to address the practical barriers to participation that affect people from historically underrepresented populations, Ulrich concluded.

CLINICAL TRIALS AT THE PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE

The Patient-Centered Outcomes Research Institute (PCORI) is very interested in strategies for ensuring broad participation in clinical trials, said David Hickam, program director of the clinical effectiveness research program for PCORI. The institute funds comparative clinical effectiveness research that engages patients and other stakeholders throughout the research process. Hickam described PCORI's research interest as studies of the real-world effectiveness of clinical interventions that have made their way into clinical practice. PCORI strives to produce research results that are applicable to broad population groups, even if treatment effects are heterogeneous, and it disseminates information about the results of this research.

Comparative effectiveness research compares alternative approaches to the management of a clinical condition. The starting point for such research, said Hickam, is looking at the choices that patients and clinicians make in deciding among management options. Those choices provide

[1] More information is available at https://www.joinimin.org.

[2] The website is http://www.phrma.org/innovation/clinical-trials (accessed July 1, 2015).

insights into what information is needed by decision makers and where there are important gaps in the available clinical evidence. The research defines important patient subgroups up front, recognizing disparities in their health and health care and the origins of those disparities. It then seeks to define the outcomes that are important to patients, including benefits and harms.

Comparative effectiveness research also is characterized by patient and stakeholder engagement. Studies are designed to integrate with routine clinical or office operations and minimize disruption to participants' daily routines. It seeks to refine recruitment strategies and deal proactively with recruitment issues.

PCORI believes that comparative effectiveness research should be carried out by interdisciplinary teams, Hickam said. Once a study starts, the team works together, so that when problems arise, multiple perspectives can be brought to bear on those problems, including the perspectives of patients. The stakeholder and patient partners also can participate in the monitoring of data and safety issues, and they can help to think about how to make the studies more efficient by capitalizing on existing resources, such as electronic health records, claims databases, or data networks.

PCORI has initiated more than 200 studies based on this model, which has revealed certain barriers that can arise in the course of such research, said Hickam. First, researchers can be inexperienced in building and managing interdisciplinary teams. Also, partners sometimes are kept at arm's length, with overly formal meetings and a reluctance by investigators to acknowledge problems. Meetings may be monthly or even quarterly instead of the regular interactions that are important for engagement. When problems do come up, researchers may be reluctant to share bad news with partners. As a result, "The people who could actually help you troubleshoot some of your problems are not in the loop with the problems they are encountering," said Hickam, adding that "Researchers have a tendency to want to reassure the stakeholder partners that everything is going well." This is human nature, he said, but it emphasizes the need to think about how multidisciplinary teams are put together.

Another problem arises when partners do not have sufficient access to clinical sites or enough time or resources to participate sufficiently. Partners may be asked to volunteer their time to the project in an otherwise busy workday, and even the best-intentioned plans sometimes can have trouble getting carried out. These barriers can be overcome, but the community needs to consider these problems so it can move forward together, said Hickam.

Hickam also noted that PCORI requires reports on the demographics of the people participating in the studies it supports. In some cases, the racial and ethnic composition of participants turned out to be different

than planned in the original applications, which may result from investigators concentrating their recruitment activities in narrow settings, such as university clinics. "One of the things that we have tried to do with projects is to push for more broad-based recruitment strategies," he noted.

Hickam also talked about the movement for pragmatic clinical trials. Developed as an alternative to conventional, tightly controlled clinical trials, pragmatic clinical trials have been seen as a way to evaluate the effectiveness of clinical interventions in real-world settings (Thorpe et al., 2009). They typically are designed to minimize exclusion criteria that act as a barrier to participation by some patients. Thus, all patients with a condition are invited to enroll, with few if any exclusion criteria. These studies are conducted in real-world settings, such as during regular clinical visits, rather than in specially designed clinical research units.

Pragmatic clinical trials look at the effectiveness (whether a treatment works under typical circumstances) rather than the efficacy (whether a treatment works under optimal conditions) of interventions, typically investigating treatments that are in common use, even if those interventions are complex. Pragmatic clinical trials provide a way to make head-to-head comparisons, whether between drugs, surgical procedures, or other interventions. Hickam added that PCORI has been insisting that comparisons to "usual care" be approached with caution. If a usual care condition is used, it should be carefully defined and measured. He added, "Generally, we try to steer people to more active comparators rather than usual care comparators." Placebos can be used in pragmatic clinical trials, though the pharmacy has to be brought in as a partner.

Pragmatic clinical trials have limitations, Hickam noted. They often do not provide sufficient outreach to patients who are uninsured or have other problems with access to care. Methods used to measure outcomes also often have lower precision with regard to such factors as time courses, resulting in a loss of power.

PCORI also is funding initiatives that focus on learning about best practices for trial recruitment. Its comparative effectiveness research methods program is looking at novel approaches to engagement and to informed consent. Its disparities research program is examining patient navigation and literacy and numeracy barriers.

Hickam briefly touched on statistical approaches for analyzing the heterogeneity of treatment effects. Stratified analyses separate important subgroups but increase the risk of spurious findings. Multivariate analysis with interaction terms reduces the risk of spurious findings but lacks power, requiring substantially larger sample sizes. Post-hoc analyses of subgroups should be considered exploratory, he observed.

"Patient and stakeholder engagement in clinical trials is an important emerging strategy," said Hickam. "It can prevent and correct problems with

recruitment. [But] it requires the commitment of investigators and skills in how to manage interdisciplinary teams and approaches."

INCREASING DIVERSITY AMONG RESEARCHERS

One topic that arose during this discussion session and several other times during the workshop involved the diversity of the researchers and research leaders conducting clinical trials. Ulrich said that broadening the representation of underrepresented minorities in research has been "a constant topic of conversation" within industry. For example, PhRMA has been working with minority physician groups such as the National Hispanic Medical Association and the National Minority Quality Forum to support policies that can diversify the research community. This is particularly important, she said, to increase the referral rate from physicians and participation rates from underrepresented populations.

A related issue is how to support investigators as they are engaging communities, which often takes longer than the usual schedule of research grants. Horowitz pointed out that pilot grants can help generate stakeholder engagement while pilot data are being gathered, whereas other kinds of grants are designed for research teams that are already in place. Hickam added that PCORI has started a program called Pipeline to Proposals, which is a tiered system that offers a limited amount of funding for front-end work to pull together community partnerships.

Ulrich also pointed out, in response to a comment, that recruitment can be a challenge in industry, which has budgetary and time constraints. But the use of more patient-focused drug development tools can increase inclusion and enable industry to go beyond working with the same sites over and over. It will take time for such changes to permeate the entire system of sites, investigators, and procedures, but the pendulum is starting to swing toward more inclusive studies.

4

Recruitment and Retention Issues: Patient, Provider, Institutional, and System Barriers

Factors spread throughout the clinical trials ecosystem affect minority recruitment and retention. Many of these factors directly involve the patients who ultimately agree or decline to participate in a trial. But many factors also involve health care providers and systems, communities, businesses, and governments.

Three speakers described some of the ways that components of the clinical trials ecosystem can work together to influence these factors. The community is often the locus of these efforts, since it can look both out to broader societal institutions and in toward families and individuals.

THE INTEGRITY OF RESEARCH AND CLINICAL TRIALS

Cancer clinical trials are meant to improve the health and well-being of future patients, said Connie Ulrich, associate professor of bioethics and nursing at the University of Pennsylvania School of Nursing. Such trials potentially reduce disparities and promote the generalizability of information. They test new treatments and improve models of care, and they help move science from the bench to bedside.

But low recruitment and retention rates in clinical trials are problematic, she continued. Only 3 percent to 5 percent of all eligible adults participate in clinical trials, which reduces the ability to develop effective and efficacious treatments for all relevant population groups.

One reason more people do not participate in clinical trials involves the integrity of research, Ulrich explained. Media stories about misconduct in research can create fear among members of the public, and examples

of past abuses of human participants can compound those fears. Patients fear that they will be used as human guinea pigs, Ulrich said, adding that "There is a perception of untrustworthy science and scientists, which I think hurts the integrity of science and ultimately the public trust in the research enterprise."

Ulrich cited several representative quotations from patients: "Before I decided 'yes' for the clinical trial, both my husband and I were very confused with the events leading up to my trial study. I believe more information in layman's terms [needs to] be explained to the patient." Another patient stated that "I think the big problem is word of mouth. Too many people are told by too many other people who are not knowledgeable and who have a negative attitude or who have developed a mindset maybe through a relative who died of cancer or some other disease. . . . I think people are just turned off by what they hear."

Information is generally available for patients about clinical trials, Ulrich observed, but there can be a disconnection between what people understand and the knowledge they need to be able to give informed consent and participate.

Ulrich and her colleagues have been studying the benefits and burdens of research participation in cancer clinical trials. They have developed a model of the many factors that shape the benefits and burdens of participation and thus recruitment and retention (see Figure 4-1).

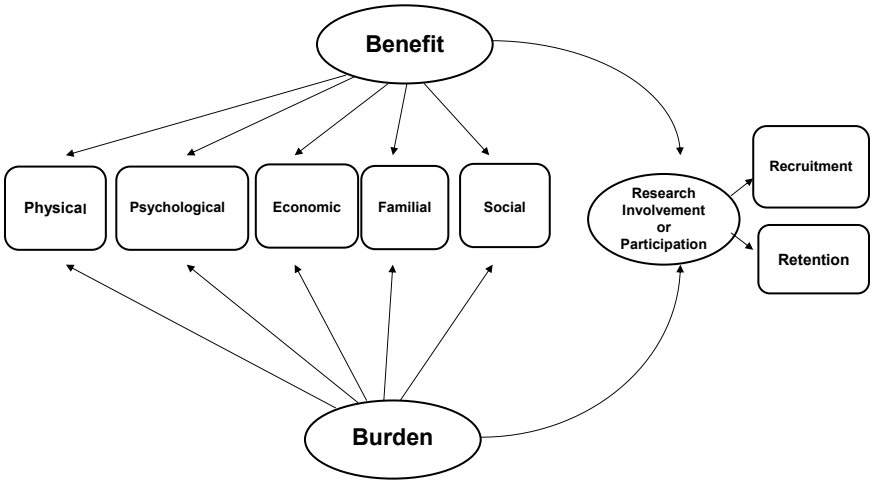

FIGURE 4-1 A variety of factors affect decisions involving participation in clinical trials.
SOURCE: Ulrich et al., 2012.

The variety and salience of these factors make decisions extremely challenging. Ulrich quoted one patient as saying, "Fear of the unknown has got to come into a lot of people's heads. Why would I put myself through something that I do not know what the effects are going to be, if I'm even going through that added stress? Why bother, why do that to me, when I'm already dealing with enough on my plate?" People can be fearful of the experimental treatment itself and what side effects it might have. They may be concerned that they will receive the placebo rather than the treatment. They may worry about whether they will continue to receive good care after the trial ends.

Ulrich and her colleagues compiled a list of issues that increase the burden of research participation, in order of increasing frequency among patients:

- It is costing me money out of pocket.
- It might not benefit me.
- There are unknown side effects that are potentially life threatening.
- I have had to rearrange my life to participate.
- I have experienced bothersome side effects.
- It makes me worry about other family members.
- It has made me recognize the seriousness of my disease.
- I would be disappointed if I received a placebo.

Other burdensome issues were the uncertainty of whether a treatment is helping or hurting, the failure of insurance to cover all expenses, the need to rely on others, managing the disease, fatigue, quality-of-life issues, balancing family needs, and an overwhelming amount of information to understand. The higher the burden of concerns, the more people thought about dropping out of a trial.

Ulrich and her colleagues also developed a list of issues about the benefits of research participation, again in order of increasing frequency among patients:

- It might help my children or other family members in the future.
- I am able to extend my life.
- I am hoping for a cure.
- It is a way for me to actively treat my disease.
- It gives me a sense of hope about my disease.
- I am treated like a person and not a number.
- I am providing a valuable contribution to society.
- I might help future patients with my disease (although it might not help me).

Other benefits listed by patients included trusting the researchers, access to drugs and other medicines or tests that are not available otherwise, feeling more informed, having control over a disease, lessening stress, helping to pay costs of drugs and other medicines, insurance coverage, and reducing risks in the future. The higher the perception of benefits among patients, the less likely they were to think about dropping out of a trial.

INFORMED CONSENT AND OTHER FACTORS

Ulrich has also studied the issue of informed consent. When clinical trial participants were asked whether they assessed the risks and benefits directly associated with participating in the trial, 52 percent said no and 48 percent said yes. "My colleagues and I have been talking about whether this is really informed consent as we think about informed consent," she said. Individuals who did not assess the risk delegated their autonomy to their physician to make the decision. They tended to be older, more trusting, have less education, perceive that they had limited treatment options, rated their spirituality as important, indicated that the trials helped to pay the cost of care, were retired or not employed, and reported being unsure or that they do not feel informed when they enrolled or were informed about study changes (Ulrich et al., 2015).

As a pediatric nurse by training, Ulrich also was interested in the role of nurses associated with clinical trials to help people better understand the issues they face. When patients were asked about the importance of communicating with the research nurse, 85 percent said it was very important to them. Nurse communication also was significantly associated with patients remaining in the trial. "Nurses should be part of [interdisciplinary] teams," said Ulrich. "They clearly are important and can provide information to patients."

Relational communication also was significantly associated with patients remaining in a trial. Such communication involves being compassionate and honest toward a patient, providing a friendly and relaxing environment, speaking in a way that the patient understands, encouraging patients to ask questions, reviewing study information, and helping them feel good about a particular situation. Doctor communication and nurse communication were both positively correlated with the patient being informed, which "speaks to the importance of interdisciplinarity and the role of teams with research," said Ulrich.

Finally, Ulrich defined interdisciplinary integrity as a commitment on the part of the clinical and research teams to provide honest and clear information about the benefits and burdens of clinical trials in an atmosphere that respects the rights of human participants as active partners in decision making. Such integrity is essential to research participation, she said.

In closing, Ulrich said that more work is needed on the benefits and burdens of research participation. For example, she is involved in a study on the weight that patient participants give to informed consent compared to other factors in recruitment and retention. More data are also needed on the attitudes, beliefs, and practices of health care providers and the link between clinicians and researchers, she said. "We need to bridge the gap between the researcher and primary care, especially those primary care providers whose patients are seen within our communities," Ulrich concluded.

PATIENT PERSPECTIVES ON CLINICAL TRIALS

As was pointed out by all three members of the panel, the term *clinical trial* generates many questions in the minds of patients. In his remarks, Moon Chen, professor in the Division of Hematology and Oncology, Department of Internal Medicine, at the University of California, Davis, School of Medicine, noted that the word *trial* has multiple meanings in English, some of which have negative connotations. When a clinical trial is described as an experiment, people can be fearful of having experiments conducted on them. "What would be a better translation or English terminology for clinical trials?" he asked, "because that is the major obstacle in moving forward." Additionally, *trial* in lay terms could also refer to legal proceedings, and thus, that reference could also invoke negative reactions.

Every major population group is going to experience an increased number of cases of invasive cancers in the United States in coming years, Chen noted. Yet of approximately 10,000 clinical trials funded by NCI and listed on ClinicalTrials.gov, fewer than 150 were substantively focused on racial or ethnic minorities, including 83 on African Americans, 32 on Latinos, 5 on Asian Americans, 8 on Native Americans and Alaska Natives, and 1 on Pacific Islanders (Chen et al., 2014). Despite the 1993 NIH Reauthorization Act, investigators are prioritizing disease over adequate racial or ethnic representation, said Chen.

Stakeholders have many different perspectives on clinical trials, Chen observed, including patients, researchers, health care providers, IRBs, and families. But research shows that providers are the most influential factor in patient enrollment in clinical trials. Chen recalled being asked to recruit a patient into a trial because he was the only one available who spoke Cantonese. "I'm so glad that I was called to meet with this patient to recruit her to clinical trials because she would not have volunteered," he added.

Chen's research has demonstrated that the factor mentioned most often as a barrier to participation in clinical trials is distrust and discomfort with uncertainty in a trial. "We are going to have to deal with how to overcome that through authenticity and willingness to invest time," he said.

People have many other questions about clinical trials: How am I going to get there? How do I handle my family responsibilities? Do I ask for time off from work? Who is going to take care of my children? Some of the relevant factors are demographic, involving gender, age, education, insurance coverage, and income. Others are social, including considerations of altruism, stigma, and communicability. Some factors are cultural, including values, beliefs, historical experiences, and fear and mistrust.

Echoing other presenters, Chen said that the foundation of participation is trust. The question is how to engender and earn trust. Chen said that trust is built on a record of believability, credibility, fulfillment of prior commitments, and shared interests. He also said, in response to a question, that respect is a critical factor in the relationship between a patient and a health care provider. For example, many Asian patients view their physicians as respected figures, which means that their eyes look down in the presence of a physician. This creates even greater responsibility on the part of the provider to honor that respect.

As with restaurants, word of mouth is a powerful way to build trust, and Chen urged that a similar approach be taken with clinical trials. This approach typically takes time to understand community concerns, build relationships, and conduct outreach and education. It also requires involving the community in every step of the process. And it requires transparency in the form of culturally appropriate and ethnically specific outreach and education, continuous community input and feedback, and community ownership.

As an example, Chen cited the Thousand Asian American Study, which is "all based on trust because it was based on a track record of earned respect." Educational sessions are available using a brochure and video. Patients work through a computerized menu in which they can chose from five languages or receive spoken information. Patients receive follow-up on possible enrollment in a trial. The experience has shown that minorities are willing to participate in health research, said Chen (Dang et al., 2014).

One dramatic way to promote greater participation, said Chen, would be for journals not to accept research articles unless the research has meaningful representation and analysis of data by racial or ethnic groups, with several of the higher-impact journals trending in this direction. This suggestion reveals the extent to which journal editors and reviewers have an opportunity to affect minority participation in clinical trials.

Another possibility would be to convene the leaders of journals to discuss requiring or recommending that any time minority groups participate in a trial, their participation yields meaningful data. "This is where the NIH and FDA can really exercise their influence, because we will follow," he said. "If they change the format for the instruction to authors, we will make our changes."

Chen said that the authors and reviewers of scientific papers have an opportunity to practice what they preach, adding that "when we write up our results, we want to make sure that the minority populations or the populations that we deal with are adequately represented and the data is analyzed sufficiently so that it is meaningful to advance the science."

Chen also made the point, in response to a question, that "All adults are underrepresented in clinical trials." Pediatricians have been better about enlisting children into clinical trials, which raises the question of whether lessons can be learned from their approaches to increase the numbers and diversity of adults in trials.

ENGAGING COMMUNITIES IN HIV RESEARCH

Community engagement can improve the feasibility, acceptability, and effectiveness of research, said Jonathan Ellen, president at Johns Hopkins All Children's Hospital. These goals are all more complicated when working with vulnerable populations at risk of HIV infection.

Youth aged 13 to 24 accounted for an estimated 26 percent of all new HIV infections in the United States in 2010. Most new HIV infections among youth occur among gay and bisexual males. Among 15- to 19-year-olds, the highest percentages of new infections in minority youth are among African Americans (56 percent), Latinos (21 percent), and Pacific Islanders (15 percent). Recognizing the vulnerability of these populations, leaders at NIH stepped up, said Ellen, and issued a call to action to build a community infrastructure of prevention and partnerships.

Communities are not always accepting of this attention, Ellen observed. As was pointed out by Ulrich, some communities mistrust researchers because of a history of experimentation that has involved those communities. For example, Ellen worked for many years on syphilis elimination in Baltimore, Maryland, which required continually addressing concerns about the Tuskegee syphilis experiments. Clinical trials also have the potential to stigmatize communities by identifying and associating them with particular problems.

With HIV infections, a critical step in the "cascade of care," said Ellen, is diagnosis. Once an infection has been identified, patients can be linked with care, retained in care, and treated. However, only about 40 percent of infected adolescents are being diagnosed, compared with 82 percent of adults, Ellen noted. Furthermore, only about 6 percent of HIV-infected youth are having their infections suppressed. "That is a problem both from a public health standpoint and from an individual standpoint in terms of the progression of infection," he said.

To address the problem, NIH supported a community consultation in 2001 to talk with stakeholders about the potential involvement of com-

munities in adolescent HIV trials. This consultation uncovered a clear interest among communities in having their youth participate in trials. But the communities also expressed a desire to have the trials be part of larger prevention activities that involve the entire communities. The stakeholders also asked to be educated about vaccines, that the impact of the trials on the community be measured, and that community participation precedes the vaccine trials.

The Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) has engaged in three important strategies to carry out these requests. The Connect to Protect project sought to determine whether community mobilization can lead to structural changes, in the form of new or modified policies, practices, and procedures, and whether these changes can lead to decreased risk for HIV transmission. The structural changes had to be logically linked to HIV acquisition and transmission and sustained over time, so that the changes would persist even when key actors were no longer involved. The changes also had to have a direct or indirect effect on individuals so that communities and the members of those communities would be safer.

The critical component of the program, said Ellen, was community mobilization, which he defined as collaborative problem solving that leads to fewer health or other social problems. Sustained efforts over time were essential to the effectiveness of the mobilization, and leadership, ongoing feedback, and continued growth in capacity were key elements of the sustained effort.

Ellen listed some of the structural changes made as part of this program:

- The Louisiana Juvenile Justice System will implement HIV/sexually transmitted disease (STD) screening of youth upon intake into New Orleans juvenile justice facilities.
- The Shelby County Health Department (Memphis) will change its policy to allow alternate forms of identification from individuals seeking HIV test results.
- All Montefiore Community Health Centers (Bronx) will modify policies to offer routine HIV testing to patients over 13 years old.
- The Washington, DC, Department of Health will require all grantees that are HIV testing/treatment sites to adhere to youth competency protocol.
- The Florida Department of Health will register Our Kids of Miami-Dade and Monroe as HIV testing sites for youth in foster care.
- The Hillsborough County Health and Human Services Ryan White Administration will amend guidelines to exempt minors with HIV from providing income eligibility documentation.

- The Detroit Receiving Hospital emergency room will have a new policy to refer youth into care when they test preliminary positive.
- The New Orleans Regional Transit Authority will provide free bus tokens to HIV-positive youth referred for medical care.
- The Fenway Medical Division (Boston) will modify its existing appointment policy for HIV-positive youth to ensure that all youth receive a scheduled follow-up appointment at the end of all medical visits.
- Denver's school-based health centers will adopt a long-term care policy for students identified as HIV-positive.

Since the program started in 2002, Ellen reported, "There has been an amazing amount of transformation that has gone on in these communities."

The second project was known as the ATN Community Education Plan. People have many questions about clinical trials, starting with what a trial is. Many do not know what a placebo is, the distinction between treatment trials and prevention trials, or the meaning of clinical research. Informed consent may not be the most important factor for an individual to be enrolled in a trial, Ellen said. Such factors as the characteristics of the provider, trust, respect, or even logistics may be more important. Furthermore, "a whole host of cultural and social factors" come into play in a clinical trial beyond the pharmacokinetic properties of a drug in the body, he explained. For example, adherence to a treatment can affect the outcome a clinical trial, and adherence can vary by population group.

In each community, the protocol chair and team made a determination of the need for an education plan. This education took place in a wide range of places—churches, schools, Boys & Girls Clubs—and reached out to a wide range of populations, including youth, adults, and parents. The content of the education ranged from basic information to quite sophisticated concepts. For example, the definition of clinical research presented in the educational modules was:

- Research is an investigation to find an answer to a problem.
- Research tries to find better ways to prevent, diagnose, treat, and understand illness.
- Clinical trials can test new medications and vaccines.
- Clinical trials depend on the people who volunteer to participate in the research.

The educational program also described major types of clinical research (see Table 4-1). The program also described why clinical research is important for everyone:

TABLE 4-1 Types of Clinical Trials

Type of Trial	Goal
Treatment	To test new medications or procedures that could help to treat an illness
Prevention	To look for better ways to prevent an illness in people who have never had the illness. Better ways to prevent an illness may include medicines, vaccines, and/or lifestyle changes
Diagnosis	To find better tests or procedures for identifying a particular illness or condition
Screening	To test the best way to detect certain illnesses or health conditions
Quality of Life	To explore ways to improve the comfort and quality of life of people with a long-term illness

SOURCE: Ellen presentation, April 9, 2015.

- Illnesses do not affect everyone in the same way.
- Medicine does not always work the same in everyone.
- Clinical research helps us understand what these differences are and why they happen.

The third project was known as the Community Impact Monitoring Plan, which had the goal of combining ongoing assessments from the community, particularly from those members most affected by the research, with assessments from the research group and established community advisors to provide a comprehensive view of the effect the research is having on the community. Phase I of the plan determined the need and, if required, identified community-related consequences. Phase II developed a plan for information collection necessary to monitor the effect on the community. Phase III consisted of annual reporting to the Community Impact Monitoring Plan Oversight and Ethics Advisory Committees. In essence, said Ellen, the goal of the plan was to apply the ethical concepts usually applied to individuals, in such areas as privacy and autonomy, to communities.

Ellen concluded by briefly mentioning two important trials that have gone on within the ATN. The first was working with youth less than 18 years old on preexposure prophylaxis, which required working with the IRB to gain consent from people younger than 18 without their parents' consent. The second involved surveys with youth ages 13 and up, which required the awareness and participation of community leaders. Both required the infrastructure established by the ATN, he said, to be successful.

As Ellen pointed out in response to a question, building a coalition of stakeholders and keeping them engaged are critical in efforts to work with communities. Paying people, however, to participate can create problems. Instead, providing technical assistance and other forms of support to com-

munity coalitions can catalyze their work and keep them active. "You can get a broad coalition maintaining itself in a community that then can work, when the time comes, for these trials," he added.

He also pointed out, in response to another question, that partnerships mean giving up some authority and power. "Otherwise, you are not really entering into a partnership." A true partnership is built on trust, and building this trust requires time, he said. "It is not something you can do on the cheap, and it is not something you can do afterwards with the analysis. That kind of investment . . . has to happen intentionally, and it is going to cost some resources," Ellen concluded.

IMMIGRANT POPULATIONS

One of the topics discussed during the question-and-answer session involved the particular challenges of enrolling immigrant populations in clinical trials. Asian populations are diverse in terms of language, Chen said, which requires working with translators for those languages. These translators should understand and have "a paragraph-long explanation of what a clinical trial is," he added, since two words are not enough to explain the concept.

Ulrich said that few data are available on how immigrant populations view clinical trials and the accompanying benefits and burdens. Furthermore, terms like *placebo*, *randomization*, or *equipoise* mean little to most people.

Ellen responded that immigrant populations are very different, whether Russian, Ethiopian, or Chinese immigrants. He also pointed out that language to some extent acts as a proxy for acculturation, in that populations that have mastered English tend to be more acculturated. With populations still speaking largely in some other language, cultural issues can increase the difficulty of explaining what a clinical trial is and what a particular trial entails.

5

Potential Best Practices and Policy Options

In the final panel of the workshop, three presenters discussed their ideas about best practices and policy options for including minorities in clinical trials. They did so largely by drawing on their experiences with Asian Americans, Pacific Islanders, Native Americans, and Native Alaskans, but the lessons they drew apply much more broadly. In particular, all speakers emphasized the critical role of community involvement throughout the research process for meaningful inclusion of minorities in clinical trials.

POTENTIAL BEST PRACTICES AND POLICIES FOR INCLUSION OF ASIAN AMERICANS INTO CLINICAL TRIALS

Urban Asian Americans and Pacific Islanders in the Midwest—which are the populations at the center of the work done by Karen Kim, dean for faculty affairs and head of the Office of Community Engagement and Cancer Disparities at the University of Chicago—have several characteristics that increase the difficulty of involving them in clinical trials. First, the populations are relatively small compared with other populations and the populations of Asian Americans on the East and West Coasts. The populations also are heterogeneous, with many cultural and linguistic subgroups. About 70 percent of all Asian Americans in the United States are foreign born, and about 30 percent are limited English proficient, Kim noted. The health care system is not well equipped to handle the cultural and language needs of these populations. Asian Americans' reputation as a "model minority," marked by generally good health and educational achievement, is belied by the structural barriers and adversity facing the members of these groups.

"Unfortunately, this model minority status often creates hostility from other minority groups. 'You do not have problems; look at us.' This sense of hierarchy and competitiveness [is] really challenging," she explained.

In addition, data on Asian Americans tend to be statistically unreliable, not analyzed, or not collected in the first place, Kim explained. Subgroups tend to be aggregated, or data from one subgroup are extrapolated to others, even when such methods are inappropriate. As a result, Asian Americans are in many ways "a nonrecognized minority in the health care system," said Kim.

Kim described several policies that can increase the representation of Asian Americans and could be applied with other populations. One is to make study designs adaptable to include diverse but relatively small populations. This can be complicated by the need to involve people with limited English proficiency in the design and implementation of studies, which can create budget pressures for translations. But involving the community as an equal partner needs to start at the beginning rather than being an afterthought, Kim said. One approach is to form community advisory boards, she said. Another is to flip the structure and have studies done in the community with academic advisory boards. Several initiatives have demonstrated how communities can be involved in the planning and implementation of studies, including research sponsored by PCORI, community clinical oncology programs, and practice-based research networks. "We are starting to shift the process and the place where research is done," said Kim. "The successful recruitment models often are happening in the communities themselves," she added.

As an example of how these policies can be instituted, Kim described an ongoing study called the Partnership for Healthier Asians, which has been funded by the Agency for Healthcare Research and Quality. The partnership uses a market-oriented dissemination framework to take evidence-based information into limited English proficient populations in Chicago, Illinois. It has sought to make changes in the health care system and in the community through collaboration, including capacity building at the community level and joint priority setting.

As an example of a specific issue, Kim mentioned that the Asian American community has a low rate of colorectal cancer screening compared with other racial and ethnic groups. Surveys revealed that many Asian Americans thought that screening was something they would do only when they exhibited symptoms of a problem. The Screen for Life campaign of the Centers for Disease Control and Prevention (CDC) had only one campaign picture featuring an Asian American, and the campaign was not resonating with the population. Meetings created an infrastructure for the dissemination of information, which was time consuming and costly, said Kim, but also effective. New posters featuring members of Asian American communities

were used to change attitudes. In essence, said Kim, the project created its own infrastructure and tools to support the needs of the community.

The community partnership also took the lead in authoring papers. The initial publication of the research went to the community first in the form of a community-generated white paper, which helped the community build capacity and infrastructure around the disease.

Kim cited several other factors that can increase participation. One is a new paradigm for peer review to be more diverse and to recognize diverse participation. Who is on a review panel and who makes decisions about funding are both critically important issues, said Kim.

Another important policy issue involves the academic reward structure. Academics traditionally are rewarded for writing papers that appear in journals, but could rewards also be based on the outcomes of the work a researcher does, such as a community brief?

IRBs need to be trained to understand the value of diverse participation and inclusion, said Kim. For example, excluding non-English speakers from a clinical trial is understandable because of the cost of translation, but it can generate problems for the trial. "How are we going to move the bar forward and close this disparity gap if we can't even study these individuals?" she asked. One study found that less than 22 percent of IRBs report clinical research with limited-English proficient populations (Glickman et al., 2011). The need for human protections remains as important as ever, Kim acknowledged, but IRBs also need to understand the value of diverse participation, which may result in study designs that are somewhat different than for larger populations. In addition, cultural competency training for the members of IRBs can help them understand the issues involved.

As an example of what is possible, Kim cited the language capacity of students at the Pritzker School of Medicine at the University of Chicago, where nearly half the incoming medical school class is able to speak Spanish. Yet of this group, only one person who was not Asian spoke an Asian language, and Asian Americans tend not to work with Asian American populations because of the difficulty of the work. "We need to shift that thinking," she urged.

Kim urged applying new methodologies to allow oversampling that can ensure representation. Sampling can be done in different ways, depending on the community and the context. She also urged that data be disaggregated, even if doing so raises issues about the power of findings. "There has to be a better way to think about how data on Asian Americans can be reported," she said.

Health information technology can be used to increase access to diverse populations; for example, PCORnet[1] is doing this well, according to Kim.

[1] The National Patient-Centered Clinical Research Network.

Technology can reach not just a population in one geographic region but across the nation, which can increase the statistical reliability of data on minority populations.

She urged greater cultural competency among researchers. Also, global does not equal local, in that what happens in another country does not necessarily reflect what happens in the United States.

Surveys conducted as part of the Partnership for Healthier Asians study found that more than half of respondents said they would participate if they knew more about clinical trials. As pointed out earlier, though it is widely claimed that minority groups are less willing than non-Hispanic whites to participate in health research, there are only small differences by race and ethnicity in willingness to participate. As Kim said, "We should not be making assumptions; we should just ask."

Kim also pointed toward the difficulties with paying high indirect costs on a grant when the research is done outside of an institution. When the institution receives more funding than the communities in which a study is being conducted, priorities may be skewed. This is "something to start thinking about," she said.

POTENTIAL BEST PRACTICES AND POLICIES FOR INCLUSION OF NATIVE AMERICANS INTO CLINICAL TRIALS

Many of the observations made about Asian Americans and Pacific Islanders apply as well to Native Americans and Alaska Natives, said Teshia Solomon, associate professor of family medicine and head of the Native American Research and Training Center at the University of Arizona. But American Indians and Alaska Natives are distinct in some ways. They suffer some of the highest rates of health disparities among minority populations. They also exhibit greater differences between tribal and urban populations, with between 50 and 70 percent of the population identified in the U.S. Census living in urban communities but migrating to other communities for health care or other reasons. The health system is complex, and even when American Indians receive free health care, "Not all free health care is good health care," said Solomon. Members of the group live in poverty, are located in remote regions, face discrimination, and are vulnerable in other ways. Many American Indians and Alaska Natives are members of sovereign nations within the United States, which have unique relationships with the federal government. The federal government has a responsibility to Indian tribal communities to provide health care, but each tribe has distinct laws and institutional structures, and researchers need to be aware of these differences to work effectively with these populations, said Solomon. In addition, IRB processes with tribes can be lengthy and complicated.

Accurate and complete data are critical, said Solomon. Partial, incomplete, or missing data are not useful and can contribute to stereotypes and misinformation.

Solomon became interested in this issue when the original sampling design for the National Children's Study focused on Native American women from three counties in Arizona, who do not necessarily represent women from other areas, Alaska Natives, or urban Indians. To broaden recruitment, she and her colleagues developed a tool kit that could be used by the study centers in urban communities. As part of this process, they did six focus groups with women aged 18 to 40 and one focus group with men aged 18 to 50.

The process yielded several policy recommendations that Solomon described at the workshop. One is to allot time to build trust between researchers and communities. Solomon said that it generally takes about a year, and maybe longer, to work with a specific community, and processes involving IRBs can take longer than that.

She recommended selecting the right community leader with whom to work and partnering with community organizations. Validation from communities can transfer to other communities. "If I did good work in Oklahoma, it may . . . transfer to my work in Arizona. I can guarantee you that if you did bad work in Oklahoma, it will definitely be heard of in Arizona," she said.

She insisted that communities need to get something in return for collaborating in a project. Important findings about diabetes have come from projects involving Native American communities, Solomon observed, yet these communities still have the highest rates of diabetes in the nation.

She also urged researchers to acknowledge the private and uncomfortable nature of the discussions they may be having with people, adding that "If you are talking about biological samples or you are talking about a disease, to some researchers it is a study, to other people it is their lives."

Building trust means collaborating. Communities can prefer to work with individuals from local agencies and organizations that are trusted. "Having role models who look like the community that you are working with is incredibly important," said Solomon. In this way, local community members can be trained and community capacity built.

Having Native American staff and consistent staff is important. Physicians tend to turn over in Indian country, but the nursing staff is generally more consistent over time. Having familiar faces who are advocating for or collaborating on a project also can build respect and trust. One example is having an elder or respected community member talking on a video about the importance of a study.

Messages need to be culturally appealing, with respect for traditional meanings, Solomon observed. For example, women are considered sacred,

and the relationship between a mother and child or a father and child is as important as showing just a picture of a baby.

In addition, support for community champions, both in terms of fiscal support and capacity building, can develop relationships and trust. "They are giving you a gift," said Solomon. "They are giving the field of science a gift. They are giving . . . health research a gift. You have to have respect for that," she explained.

Researchers need to be visible at community events, Solomon continued. These might be county fairs, rodeos, or dinners at people's homes. She noted that "You are going to do everything required, as if you were going to see your family, because that is what you are trying to do—build a family."

Knowing your audience allows ideas and messages to be presented through a Native American lens. The daily lives of participants take precedence over the concerns of a study. How are people going to get to a study? Do they need housing? How are they going to make arrangements with employers?

A systematic tracking system can counter the unreliability of phone service and mobility challenges. When participants can be seen at multiple facilities over numerous years, keeping track of individuals can be difficult.

Outreach can create links with many different agencies, activities, and groups, such as local health care clinics, community colleges, vocational and job training programs, American Indian and Alaska Native church groups, language programs, food banks, child care, parenting programs, and adult education programs. At the same time, word of mouth remains the best way to communicate with American Indian and Alaska Native populations, said Solomon. But word of mouth does not necessarily mean face to face, so it could be something heard on the radio or from a friend or relative.

Native Americans and Alaska Natives in urban communities said that they rely heavily on social media, Solomon reported. Some cities may have Chinatowns, but they do not have American Indian towns. Native American people may have gathering places, but they also communicate in other ways, including tribal newsletters and radio stations. They also still go to powwows, which Solomon called "a universal language for urban American Indians."

People need detailed information about a study, including its purpose, how samples will be gathered, how those samples will be used, who is collecting the data, and whether the study has involved other American Indian communities. People also want to know about the benefits not only to individuals but to families and the community as a whole, Solomon observed.

A COOPERATIVE GROUP PERSPECTIVE ON POTENTIAL BEST PRACTICES AND POLICY OPTIONS

More than 60 percent of the patients enrolled in cancer clinical trials have come through NCI Cooperative Groups.[2] These groups have a central core, usually at an academic center, with affiliated organizations. The trials they conduct undergo peer review and auditing, and they adhere to NIH policies for the inclusion of women and minorities. However, said Sandra Brooks, chief medical officer of CompleteCare Health Network, "Specific strategies are needed to further realize the intent of those policies."

Though more minorities have been enrolled in cancer clinical trials in recent years, they remain underrepresented compared with their representation in the population (see Figure 5-1). Furthermore, the representation of minority groups in the population will continue to grow, demanding even greater efforts to increase their representation in clinical trials.

Several meetings, trials, and other activities in recent years have generated lists of best practices and policy recommendations for increasing minority representation in clinical trials, Brooks noted. One is to emphasize peer mentors and to recruit minority investigators. Another is to provide incentives for a wider range of physicians to participate, such as protected time or funding. Another is to adopt a quality improvement approach to the clinical trial enterprise at each site and to take into account that developing new sites with new populations takes time.

Brooks cited several factors associated with deciding to participate in a trial, drawing from a prospective study of 781 patients and 150 physicians at 60 sites (Brooks et al., 2015). Of the 781 patients, a trial was available for about 37 percent. In these trials, the number of eligible nonwhite patients who chose to enroll was 78 to 83 percent, so "quite high," according to Brooks; in contrast, enrollment was only about 45 percent among white patients.

Among the factors that made patients decide to enroll were:

- Enrolling in a trial might help me.
- I would consider a future trial.
- My doctor wanted me to go on a trial.
- I am concerned about my care if I do not go on a trial.

[2] NCI Cooperative Groups, which were first begun in the 1950s, were transformed into the National Clinical Trials Network about 5 years ago.

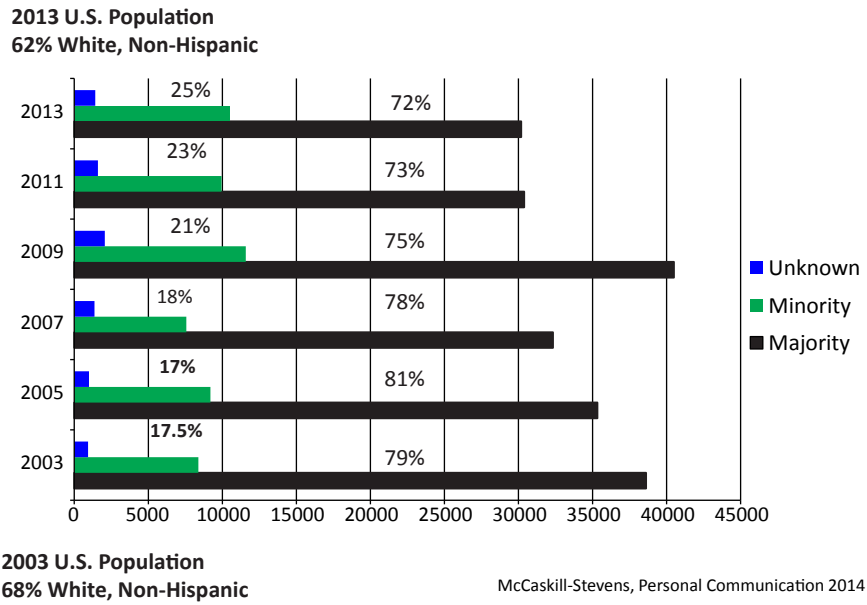

FIGURE 5-1 Minorities are underrepresented in the clinical trials supported by NCI Cooperative Groups.
SOURCE: Brooks presentation, April 9, 2015.

Brooks also listed several factors that worked against decisions to participate:

- I felt pressure to enter a trial.
- It is time consuming to participate.
- I provide care to someone without being paid.
- Transportation would be difficult for me.

In this study, African American physicians enrolled patients at a very high rate. In addition, physicians were more likely to enroll a patient if they thought that the patient would not respond well to standard therapy or if they thought that the trial would not take a lot of a patient's time. African American physicians enrolled at high rates irrespective of the race or ethnicity of the patient, which while not directly answered by the study, may point to the approach of these physicians and their research team, said Brooks, especially in explaining the trial and its associated consents to patients.

Brooks also derived several best practices from a breast cancer preven-

tion trial that sought to improve the enrollment of underserved minorities compared with previous trials. The interventions featured centralized support, outreach workers, patient materials and a website, physician training, partnerships with nontraditional partners such as corporations and foundations, and a working group that focused specifically on novel ways to promote accrual. Minority enrollment nearly doubled compared with a previous prevention trial without a targeted enrollment initiative (McCaskill-Stevens et al., 2013).

Another set of insights came from a survey of physicians accompanied by cultural competency training (Ulrich et al., 2010). According to the survey, only about one-third of respondents had formal mechanisms for screening for eligibility. Also, only about 13 percent of respondents had access to large percentages of minority populations. Some of the resulting actions from that survey included the development of an education and recruitment working group that was charged with looking at how to develop strategies, took kits, and best practices for dissemination, while another working group reviewed the feasibility of protocols. Cultural competency training for physicians and research assistants produced significant differences in cultural attitudes (Ulrich et al., 2010). Additional strategies to address enrollment that Brooks mentioned were the use of community advisory boards that take an active role in projects, input from patient advocates into protocols and materials, and centralized committees focused on disparities.

Brooks concluded by listing several of the most important factors that she derived from her review of best practices and policies:

- Population-specific recruitment strategies and sites
- Funding and institutional support for targeted infrastructure
- Feedback mechanisms for recruitment goals
- Sensitivity to socioeconomic factors
- Centralized disparities committees
- Workforce and research team diversity
- Cultural competency training for research teams

ACHIEVING DIVERSITY AMONG RESEARCHERS

In the question-and-answer session, the panelists again turned to the topic of how to increase the diversity of the researcher population, which in turn could facilitate more minorities to participate in clinical research.

Kim said that the need for diversity extends to the leadership of the research enterprise and to the people who are driving research. Minority researchers can act as role models for students and inspire them to become researchers themselves. They also can enable students to have experiences that allow them to see the value in research, and specifically

in research on diverse populations. At the same time, involving a diverse set of patients and advocates can demonstrate to young people the effects of research on a community and on individuals.

Solomon noted that she does a lot of student and junior faculty training, and a critically important step in this training is reaching out across a campus and involving the people who are doing work that involves diversity. They can act as role models and mentors in a variety of occupations, fields, and roles. In addition, scholarships and internships can be ways of getting diverse researchers involved in this kind of work, along with filling gaps in the funding of junior faculty.

Brooks cited the importance of early exposure to research, mentoring opportunities, and funding mechanisms to support students and faculty members. These strategies can be both formal and informal, she added.

The moderator of the panel, Francisco García, director and chief medical officer of the Pima County Health Department in Arizona, provided a concrete example of the advantages minority researchers can bring to the recruitment and retention of minorities in clinical trials. In his work at the University of Arizona, he was able to speak Spanish, allowing him to talk directly with patients and Spanish-speaking staff members. He worked not just at the cancer center but at other locations in the community. Everything in the environment was bilingual, and he had a team that "looked like the population that we were trying to recruit." When he left the university, 48 percent of the more than 4,300 women who had been recruited for trials were Hispanic. "I feel very proud of that accomplishment," he said.

Yet even this accomplishment was far from perfect, he added, noting that the rates of recruitment for American Indians and African Americans were "not where I wanted." The techniques used with women of Mexican American background did not necessarily generalize to other settings or populations.

POTENTIAL POLICY CHANGES

A final topic of discussion during the panel was the policy changes needed to bring about changes in practices. Brooks again called attention to funding and to the development of infrastructure. If the goal is to recruit populations that are typically not represented, investigators who have access to those populations need a ramp-up period to develop an infrastructure to support that recruitment, she said. Sometimes the funding mechanism does not bridge from one time period to the next. Institutional support, either for the investigator or for the research enterprise, can bridge these gaps and create an environment in which the value of the enterprise is acknowledged.

Brooks also recommended looking at the exclusion criteria in recruitment strategies as well as involving communities in the development of

recruitment strategies. In addition, she said the monetary and human costs of disparities can demonstrate the potential return on investment to insurance companies, employers, and funders.

Solomon noted that it can take 10 years to build a relationship with a community that will enable research to move forward, so "a 4-year grant is not going to do the job." Policies that can create more time to build that relationship would be useful. She also emphasized the importance of researchers being able to reach the populations they say, in grant applications, that they plan to reach. Finally, she mentioned making resources available to work directly with communities in culturally appropriate ways, including support for cultural competency training so that researchers know how a clinical trial could affect a community.

García pointed out that the need to have measures of the return on investment to more diverse participation is "probably the greatest need in this arena." Industry understands on a marketing level the value of diversity, which could offer lessons for other groups. "The diversity of the individuals that are represented in their commercials very much acknowledges the fact that their marketplace is a global one that is far reaching," he said.

Finally, Kim said that policies are only as good as their implementation, adding that "I do not think we need another laundry list of things. . . . How you enforce the policies that are already existent would be a really great start."

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Appendix A

Workshop Agenda

APRIL 9, 2015

Strategies for Ensuring Diversity, Inclusion, and Meaningful Participation in Clinical Trials

8:30–8:45 a.m. **Welcome and Overview**
Victor Dzau, M.D.
President, National Academy of Medicine

Antonia M. Villarruel, Ph.D.
Roundtable Chair
Dean, College of Nursing, University of Pennsylvania

Jonca Bull, M.D.
Director, Office of Minority Health, U.S. Food and Drug Administration (FDA)

8:45–10:15 a.m. **Panel 1: Historical Perspectives and Context**
Moderator: Chazeman Jackson, Ph.D., Office of Minority Health, U.S. Department of Health and Human Services

Amelie Ramirez, Dr.P.H.
University of Texas Health Sciences Center

Otis Brawley, M.D., F.A.C.P.
American Cancer Society

Charles Rotimi, Ph.D.
National Institutes of Health (NIH)

10:15–10:30 a.m. **BREAK**

10:30 a.m.–12:00 p.m. **Panel 2: Scientific Issues: Clinically Meaningful Inclusion**
Moderator: Allan Goldberg, M.D., Merck & Co., Inc.

Objectives:
- Study design adequacy for subpopulation analyses and outcomes
- Inclusion/exclusion criteria that results in unintentional bias against some populations
- Research designs that are relevant to diverse populations and subpopulation analyses

Dave Hickam, M.D., M.P.H.
Patient-Centered Outcomes Research Institute

Jocelyn Ulrich, M.P.H., R.A.C.
Pharmaceutical Research and Manufacturers of America

Carol Horowitz, M.D., M.P.H.
Mount Sinai

12:00–1:00 p.m. **LUNCH**

1:00–2:30 p.m. **Panel 3: Recruitment and Retention Issues: Patient, Provider, Institutional, and System Barriers**
Moderator: Deidra Crews, M.D., S.C.M., Gilbert S. Omenn Anniversary Fellow of the Institute of Medicine, Johns Hopkins University

Objectives:
- Describe barriers to research, including culturally incongruent research designs, inaccessibility of clinical trials locations to diverse communities, inadequate outreach, and legal status
- Community engagement in clinical trials research

Connie Ulrich, Ph.D., R.N., F.A.A.N.
University of Pennsylvania

Jonathan Ellen, M.D.
Johns Hopkins All Children's Hospital

Moon Chen, Ph.D., M.P.H.
University of California, Davis

2:30–2:45 p.m. **BREAK**

2:45–4:15 p.m. **Panel 4: Best Practices and Policy Recommendations**
Moderator: Francisco García, Pima County Health Department

Karen Kim, M.D.
University of Chicago

Teshia Solomon, Ph.D.
University of Arizona

Sandra E. Brooks, M.D., M.B.A.
University of Louisville

4:15–4:45 p.m. **Concluding Reflections**

Toni Villarruel, Ph.D., R.N., F.A.A.N.
Roundtable Chair

Barbara Buch, M.D.
FDA

4:45 p.m. **ADJOURN**

Appendix B

Speaker Biographical Sketches

Otis W. Brawley, M.D., F.A.C.P., is the chief medical officer for the American Cancer Society, where he is responsible for promoting the goals of cancer prevention, early detection, and quality treatment through cancer research and education. He champions efforts to decrease smoking, improve diet, detect cancer at the earliest stage, and provide the critical support cancer patients need. Dr. Brawley currently serves as professor of hematology, oncology, medicine, and epidemiology at Emory University. From April 2001 to November 2007, he was medical director of the Georgia Cancer Center for Excellence at Grady Memorial Hospital in Atlanta, and deputy director for cancer control at Winship Cancer Institute at Emory University. He has also served as a member of the Society's Prostate Cancer Committee, cochaired the U.S. Surgeon General's Task Force on Cancer Health Disparities, and filled a variety of capacities at the National Cancer Institute, most recently serving as assistant director. Dr. Brawley is a member of the CDC Advisory Committee on Breast Cancer in Young Women. He was formerly a member of the CDC Breast and Cervical Cancer Early Detection and Control Advisory Committee. He served as a member of the Food and Drug Administration Oncologic Drug Advisory Committee and chaired the NIH Consensus Panel on the Treatment of Sickle Cell Disease. He is listed by Castle Connelly as one of America's top doctors for cancer. Among numerous other awards, he was a Georgia Cancer Coalition Scholar and received the Key to St. Bernard Parish for his work in the U.S. Public Health Service in the aftermath of Hurricane Katrina. Dr. Brawley is a graduate of University of Chicago, Pritzker School of Medicine. He completed his internship

at University Hospitals of Cleveland, Case Western Reserve University, his residency at University Hospital of Cleveland, and his fellowship at NCI.

Sandra E. Brooks, M.D., M.B.A., is a Phi Beta Kappa and Alpha Omega Alpha (AOA) Medical Honor Society graduate, completed her B.S. and M.D. at Howard University, in Washington, DC; residency in obstetrics and gynecology at the University of Pennsylvania; and Fellowship in Gynecologic Oncology at Brigham and Women's Hospital, Harvard Medical School. Dr. Brooks completed an M.B.A. at Johns Hopkins University. Dr. Brooks rose to the rank of professor, and has served as Director of the Division of Gynecologic Oncology at the University of Maryland. Dr. Brooks served most recently as an executive with a major health system in Louisville, Kentucky, developing and leading health disparities research, and population health efforts. She currently serves on the volunteer faculty, Public Health–Health Behavior, University of Kentucky. Nationally, she chairs the Clinical Trial Enrollment working group of NRG Oncology, and serves on the Joint Policy Committee and Education Board of the American Public Health Association. In 2011, she was the recipient of the Jewish Hospital and St. Mary's Foundation Excellence in Community Service award, being one of six Louisville health leaders honored for excellence in leadership, innovation, or service. Dr. Brooks has published extensively, with a current focus on health disparities and health services delivery. She has served as the principal investigator on an NCI National Community Cancer Centers Program award, and on a Gynecologic Oncology Group Clinical Trial focused on clinical trial enrollment.

Barbara Buch, M.D., is a fellowship-trained orthopedic surgeon who came to FDA in 2001. Following residency, Dr. Buch completed an M.B.A. certificate at the Johns Hopkins School of Professional Studies in the Business of Medicine. During her time at FDA, she has worked at all three product centers (Center for Devices and Radiological Health, Center for Drug Evaluation and Research [CDER], and Center for Biologics Evaluation and Research [CBER]), the Office of Policy and the Office of Special Medical Programs in the Office of the Commissioner, with review, research, management, and leadership functions. Her current title is Associate Director for Medicine in the Center Director's office of FDA's CBER and she is CBER's liaison to the FDA's IRB and International Conference on Harmonization expert working group on clinical investigation of medicinal products in pediatric populations. Most recently she has also been involved with the activities surrounding Food and Drug Administration Safety and Innovation Act (FDASIA) Section 907, which deals with the participation, analysis, and communication of outcomes of demographic subgroups in clinical

trials. She currently chairs FDA's steering committee for FDASIA section 907 as described in FDA's 2014 FDASIA section 907 Action Plan.

Jonca Bull, M.D., returned to FDA in August 2012 as the Director of the Office of Minority Health. She serves as a member of the senior staff and advisor to the commissioner, interfacing with all human product centers. Dr. Bull brings extensive public- and private-sector experience in dealing with a range of medical product development and diversity issues to this important position. Dr. Bull previously served in FDA in a variety of positions in both CDER and the Office of the Commissioner spanning 12 years. Dr. Bull returned to FDA after most recently serving as Vice President for U.S. Drug Regulatory Policy at Novartis and, prior to that, as Director of Clinical Regulatory Policy at Genentech. Dr. Bull also previously spent 11 years providing clinical care in a multispecialty group practice, and she currently serves as an Assistant Clinical Professor at George Washington University Medical Center. Dr. Bull is a graduate of Princeton University and received her medical degree from Duke University School of Medicine. She did her postgraduate training at George Washington University, is board certified in ophthalmology, and is a fellow of the American Academy of Ophthalmology.

Moon S. Chen, Jr., Ph.D., M.P.H., is a Professor in the Division of Hematology and Oncology, Department of Internal Medicine, University of California (UC), Davis, School of Medicine; Associate Director for Cancer Control at the UC Davis Comprehensive Cancer Center; and the lead principal investigator of the NCI-funded National Center for Reducing Asian American Cancer Health Disparities, headquartered in Sacramento, California. He previously served on IOM committees that resulted in *The Unequal Burden of Cancer: An Assessment of NIH Research and Programs for Ethnic Minorities and the Medically Underserved* (1999) and *Examining the Health Disparities Research Plan of the National Institutes of Health: Unfinished Business* (2006). The American Society of Clinical Oncology highlighted research he led (Chen et al. 2014. *Cancer* 120:1091-1096), which was selected as one of 2014's major achievements in clinical cancer research and care and included it in *Clinical Cancer Advances 2015: ASCO's Annual Report on Progress Against Cancer.* His presentation to the Academies' Roundtable on the Promotion of Health Equity and the Elimination of Health Disparities is based in part on this research funded jointly by the National Institute on Minority Health and Health Disparities and NCI.

Jonathan M. Ellen, M.D., is a pediatrician and adolescent medicine specialist who currently is president and vice dean of Johns Hopkins All Children's Hospital. Dr. Ellen joined the Johns Hopkins University (JHU) School of Medicine in 1999. He was named vice dean for All Children's Hospital in

2011 and president of All Children's Hospital in 2012. Dr. Ellen is a professor of pediatrics at the JHU School of Medicine and a professor of epidemiology and population, family, and reproductive health in the Bloomberg School of Public Health. He has trained more than 40 pre- and postdoctoral fellows in adolescent medicine and public health and authored more than 200 peer-reviewed scientific articles, reviews, editorials, and book chapters. After graduating from the University of Pennsylvania, he received his medical degree from Temple University and completed a pediatric residency at Children's Hospital of Philadelphia. Dr. Ellen completed a fellowship in adolescent medicine at the University of California, San Francisco (UCSF), followed by fellowships in sexually transmitted diseases at UCSF, the San Francisco Department of Public Health, and CDC. He pioneered community-led approach to public health problems as a leader of the Adolescent Medicine Trials Network for HIV/AIDS Intervention, serving as principal investigator for Connect to Protect, a community coalition-based program. He is recognized internationally as an expert on preventing HIV and other infections in adolescents through structural change and has received more than $25 million in research awards from CDC, NIH, and other agencies.

Francisco A. R. García, M.D., M.P.H., is the Director and Chief Medical Officer of the Pima County Health Department in Tucson, Arizona. Pima County is a large government jurisdiction the size of New Hampshire and has a population of nearly a million inhabitants. Dr. García is a member of the U.S. Preventive Services Task Force, which produces national evidence-based clinical guidelines, as well as the Academies' Roundtable on the Promotion of Health Equity and the Elimination of Health Disparities. Prior to joining Pima County Department of Health, he was a Distinguished Outreach Professor of Public Health and Obstetrics & Gynecology, and served in a variety of roles at the University of Arizona including director of the Center of Excellence in Women's Health, the Arizona Hispanic Center of Excellence, and the Cancer Disparities Institute of the Arizona Cancer Center.

David Hickam, M.D., M.P.H., is the Program Director of the Clinical Effectiveness Research program at PCORI. He is responsible for developing PCORI's research program that evaluates comparisons among alternative clinical strategies in a broad range of clinical domains, and he also provides staff support to the PCORI Methodology Committee. Hickam is a specialist in internal medicine and has 30 years of experience as a health services researcher. His past research has focused on strategies for improving health care outcomes among adults with chronic diseases. Hickam previously held the rank of professor in the Department of Medicine at Oregon Health & Science University (OHSU). He also held a joint faculty appointment in

OHSU's Department of Medical Informatics and Epidemiology. He was a senior investigator in the Oregon Evidence-based Practice Center at OHSU and also served as codirector of the health services research and development program at the Portland Veterans Affairs Medical Center. He has expertise in a broad range of both quantitative and qualitative research methodologies. In 2005, he became the founding director of the John M. Eisenberg Clinical Decisions and Communications Science Center, funded by the Agency for Healthcare Research and Quality. The Eisenberg Center has developed innovative approaches for helping people use evidence-based information to participate in decision making about their health care. Hickam received his B.A. from Stanford University, an M.D. from the University of California, San Francisco, and an M.P.H. from the University of California, Berkeley.

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. With a focus on using community-based participatory research to address health disparities, she is the principal investigator of several NIH-funded, community-based interventions. She co-founded the Center for Health Equity and Community-Engaged Research, and directs the East Harlem Partnership for Diabetes Prevention, as well as the Community Engagement and Research Core for Mount Sinai's Institutes for Clinical and Translational Sciences. She has implemented numerous community-based health improvement interventions, and mentors students, residents, and faculty interested in addressing disparities and partnering with communities on research to improve local health and influence policy. She leads the community engagement and diversity activities for the National Human Genome Research Institute-funded U01 grant Biorepositories for Genomic Medicine in Diverse Communities. She is also principal investigator of the NIH/CDC-funded grants and centers on diabetes, obesity, and stroke prevention. Dr. Horowitz is the recipient of numerous awards including the National Leadership Award from the Academy for the Public's Health; Excellence for Contributions, the U.S. Department of Health and Human Services (HHS); and the Community Service Award, Mount Sinai Medicine. She has an M.D. from Cornell University, and received an M.P.H. from the University of Washington as a Robert Wood Johnson Foundation Clinical Scholar.

Karen E. Kim, M.D., is a professor of medicine at the University of Chicago Medicine. She specializes in the prevention, screening, and early detection of colorectal cancer, hepatitis B, and women's health issues—particularly functional bowel diseases. She is skilled in the assessment of hereditary colon cancer syndromes and colon cancer risk in families. Dr. Kim's research

explores chemoprevention for colon cancer and screening methods for populations with average and high risk. Her research interests include underserved and minority populations, understanding health disparities, cultural competency, and cancer prevention. She has also studied the education and awareness of hepatitis B in Asian Americans through screening, advocacy, treatment, and immunization for liver cancer prevention. Dr. Kim received her medical degree from Loyola University Stritch School of Medicine.

Amelie G. Ramirez, Dr.P.H., is an internationally recognized researcher and spokesperson on Latino cancer health disparities, and is a professor of epidemiology and biostatistics at the University of Texas Health Science Center at San Antonio, where she also is founding director of the Institute for Health Promotion Research. She also is associate director of cancer health disparities at the Cancer Therapy and Research Center, a National Cancer Institute Cancer Center. Over the past 30 years, Dr. Ramirez has directed many research programs focused on human and organizational communication to reduce disparities—differences in cancer rates and survival among Latina women compared to white women. Dr. Ramirez directs *Redes En Acción*, an NCI-funded national Latino cancer research network. Redes and her other projects have led to unique health communication models and interventions that have contributed to reducing Latino cancer rates and increasing Latino screening, clinical trial participation, and healthy lifestyles. She also has helped pioneer the use of bilingual, bicultural patient navigators and *promotoras* to erase Latinas' lag times between an abnormal cancer screening and confirmatory diagnosis and treatment initiation, while also increasing Latina survivors' access to support services. Dr. Ramirez also mentors Latino students and fellows, contributes to the scientific literature, and serves on several journal editorial boards. Dr. Ramirez has received many awards for her work to reduce cancer disparities, including 2007 election to the National Academy of Medicine. She is a member of the Scientific Advisory Board, Susan G. Komen for the Cure; Scientific Advisory Board, Avon Foundation Breast Cancer Crusade; and Board of Directors, Lance Armstrong Foundation. She also is the former chairperson of CDC's Breast and Cervical Cancer Early Detection and Control Advisory Committee. Dr. Ramirez received M.P.H. and Dr.P.H. degrees from the University of Texas Health Science Center at Houston School of Public Health.

Charles Rotimi, Ph.D., is a genetic epidemiologist with substantial training in genomics, biochemistry, statistics, and health disparities research. He is the Chief of the Metabolic, Cardiovascular, and Inflammatory Disease Genomics Branch and the Director of the Center for Research on Genomics and Global Health in the National Human Genome Research Institute, NIH. His lab conducts genomic and epidemiologic studies that explore the

patterns and determinants of metabolic disorders with particular emphasis on disease etiology and health disparities in African ancestry populations. His team published the first genomewide scan for hypertension and blood pressure in African Americans and for type 2 diabetes in West Africans. His lab contributes to the development of global genomic resources including the International Haplotype Mapping project, the 1000 Genome, and the African Genome Variation Project. He is a member of the Executive and Scientific Committee for the International Federation of Human Genetics Societies and the Human Genome Organization (HUGO) Council. He is the founding president of the African Society of Human Genetics (AfSHG). He successfully led the establishment of the Human Heredity and Health in Africa (H3Africa) initiative with more than $76 million commitment from NIH and Wellcome Trust. H3Africa is creating a pan-African network of labs that is conducting leading-edge research into the determinants of diseases in Africans. He is on the editorial board of several professional journals including *Clinical Genetics* and *Genome Medicine*. He was recently awarded an Honorary Professorship in the Division of Human Genetics, University of Cape Town, South Africa, and received the Gold Scientific Achievement Award from the South African Medical Research Council Scientific Merit Awards in recognition of excellence in research.

Teshia G. Arambula Solomon, Ph.D., is Associate Professor in the Department of Family and Community Medicine in the College of Medicine at the University of Arizona. She was appointed Codirector of the Native American Research and Training Center (NARTC) in June 2007. She has more than 18 years of experience in health-related research and training involving Native American students in public health. She is principal investigator and Director of the Faculty and Student Research Development program of the American Indian Research Centers for Health (AIRCH5) as well as Director of the Research Core. She serves as coinvestigator and Codirector of the Native American Cancer Program research training initiative and as a coinvestigator on the community outreach component with the Arizona Cancer Center. As coinvestigator for the Arizona Study Center of the National Children's Study (HHS *Eunice Kennedy Shriver* National Institute of Child Health and Human Development), she is responsible for the tribal community engagement component. She is a founding member and past cochair of the Native Research Network, Inc. She previously served as the Director of the Southern Plains Inter-Tribal Epidemiology Center at the Oklahoma City Area Inter-Tribal Health Board. She has been a fellow at Northwest Portland Indian Health Board, Native American Research Centers for Health, and a National Center for Minority Health and Health Disparities Scholar. She has published research in cervical cancer prevention and control and is a co-author of two papers in the 2008 supplement

to *Cancer* on American Indian and Alaska Native cancer. She is currently editing a book on the ethical conduct of research in Native American communities. Dr. Solomon has mentored students as a faculty member for more than 10 years and has promoted research development by pursuing and providing funds for students to attend the annual American Public Health Association meeting and the annual Native Health Research conference. She has mentored more than 20 graduate public health students.

Connie M. Ulrich, Ph.D., R.N., F.A.A.N., is an Associate Professor of Bioethics and Nursing in the Department of Biobehavioral Health Sciences, University of Pennsylvania School of Nursing. Dr. Ulrich also holds a secondary appointment in the Department of Medical Ethics and Health Policy in the Perelman School of Medicine and is the Associate Director of the New Courtland Center for Transitions and Health at the University of Pennsylvania School of Nursing. Currently, she also serves as the Graduate Group Director of Ph.D. Studies at the School of Nursing (2014–2016). Dr. Ulrich received her undergraduate and graduate degrees from the Catholic University of America and her Ph.D. with a concentration in nursing ethics from the University of Maryland, Baltimore. She was the first nurse to be awarded a 2-year postdoctoral fellowship in bioethics at NIH where she received training in both clinical and research ethics. Her publications in clinical ethics focus on clinician moral distress, ethics education, and patient–provider communication. Her research ethics publications include work on the risks and benefits in cancer clinical trials and how cancer patients view their research participation, respondent burden in research, informed consent, international ethical issues, and scientific integrity. She is the recipient of funding from various organizations, including NIH (National Institutes of Nursing Research), the Pennsylvania Health Research Formula Funds Research Grant/Oncology Nursing Society, the Robert Wood Johnson Foundation Future of Nurse Scholars program, and others. Dr. Ulrich is currently the lead cochair of the Bioethics Expert Panel, American Academy of Nursing, of which she reestablished in 2013. She also currently serves on several data and safety monitoring boards appointed by NIH. Dr. Ulrich is the editor of *Nursing Ethics in Everyday Practice*. Dr. Ulrich is an elected fellow of the American Academy of Nursing and a Salzburg Global Fellow.

Jocelyn B. Ulrich, M.P.H., R.A.C., is Senior Director of Scientific and Regulatory Affairs at PhRMA, where she supports PhRMA's policy advocacy strategies on clinical trials and innovative biologics and biosimilars. Prior to joining PhRMA, Ms. Ulrich held positions of increasing responsibility at Pfizer and Human Genome Sciences in clinical research management and medical affairs. From 2011 to 2013 Ms. Ulrich led the Investigator-Initiated

and Sponsored Research Association's (IISRA's) Collaboration Forum, a cross-functional group that aims to establish best practices for research conducted in partnership with industry and the NCI-funded Cooperative Groups. Ms. Ulrich also served as chair of the Membership and Outreach subcommittee of the Mid-Atlantic Women in Science Committee in the Healthcare Businesswomen's Association (HBA) Mid-Atlantic Chapter from 2012 to 2014. She received her M.P.H. in Global Health Policy and Management from New York University.

Antonia M. Villarruel, Ph.D., R.N., F.A.A.N., is Professor and the Margaret Bond Simon Dean of Nursing at the University of Pennsylvania School of Nursing. Internationally renowned for her leadership in policy, practice, and research, Dr. Villarruel is a former board member of the American Academy of Nursing, was elected to the National Academy of Medicine in 2007, and currently serves as chair on the Institute of Medicine Roundtable on the Promotion of Health Equity and the Elimination of Health Disparities. Prior to becoming dean, Dr. Villarruel was a professor, the Nola J. Pender Collegiate Chair, and the associate dean for research and global affairs at the University of Michigan School of Nursing. She also held a joint faculty appointment in the School of Public Health and was director of the school's World Health Organization Collaborating Center for Research and Clinical Training in Health Promotion Nursing. Her current research projects include sexual risk reduction interventions for Latino and Mexican youth, parent–adolescent communication interventions to prevent teen pregnancy and sexually transmitted diseases, the use of virtual environments to train community participants to implement evidence-based interventions, and language learning to promote global health competency in undergraduate nurses. Dr. Villarruel earned her M.S.N. at Penn's School of Nursing and served as an assistant professor at the School from 1995 to 2000 and as an adjunct professor from 2005 to 2011. She has co-authored a number of papers with Penn faculty, led the 2012 Office of Nursing Science Colloquium on Health Promotion and Risk Reduction Practices in Latina Populations at the school, and created and led the school's study abroad program in Oaxaca, Mexico. Dr. Villarruel is the recipient of numerous awards and honors, and was also inducted in the Michigan Nurses Hall of Fame in 2004.

Appendix C

Statement of Task

The Roundtable on the Promotion of Health Equity and the Elimination of Health Disparities will form an ad hoc committee to plan and conduct a 1-day workshop that will include invited speakers and discussions. The committee will define the specific topics to be addressed, develop the agenda, select and invite speakers, and moderate discussions. This workshop will explore the reasons behind the underrepresentation of racial and ethnic minorities in clinical trials and outline potential strategies to address this underrepresentation. An individually authored summary of the presentations and discussions at the workshop will be prepared by a designated rapporteur in accordance with institutional guidelines.