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Investing in Public Health: Legislation to Support Patients, Workers, and Research

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Chairwoman Eshoo, Ranking Member Guthrie, and Members of the Committee, thank you for the opportunity to testify today on this important topic. I am the Lee Goldman, MD Professor of Medicine and Professor of Epidemiology and Biostatistics at the University of California, San Francisco. I am also the incoming Editor and Chief of the Journal of the American Medical Association (JAMA) and the JAMA Network. I am here today speaking in my capacity as a physician-scientist and also as someone who has personally faced the issue of the importance of diversifying clinical trials and clinical research.

This issue has long been an important one for me, but the year this issue became urgent was 2017. I was then chair of the U.S. Preventive Services Task Force—an independent body charged with reviewing the scientific literature to generate evidence-based guidelines on the use of clinical preventive services. During my tenure, we had issued recommendations on preventing diabetes and common cancers such as breast, colorectal, lung, and prostate that are responsible for considerable morbidity and mortality in the United States, as well as being important contributors to health disparities.

In my formal talks and informal discussions with lay and professional stakeholders, I inevitably encountered a similar pattern of questions:

How confident are you that these recommendations and the evidence on which they are based apply to me and to patients like me?

You are recommending screening for diabetes in those who are overweight or obese, but my Asian patients seem to develop diabetes at lower BMI, what about them?

What about my Latino patients who are developing diabetes at younger ages or my Black patients who are developing colorectal cancer at younger ages—shouldn't we start screening earlier?

Black women get breast cancer at the same rate as others, but are more likely to die—should we screen differently?

My recurring response was, “Unfortunately, we just don’t have the studies in these populations that allow us to say with certainty whether or how to adapt our prevention guidelines.” While it is true, this answer rang hollow. As a physician caring for patients in an urban safety-net setting and wanting to provide the best evidence-based preventive care, these were my questions as well. Inevitably in these sessions, I would spend as much time on the science as I devoted to reinforcing with patients why they should still trust these guidelines and the process, despite the unrepresentative populations in the evidence base. With clinicians, we discussed how we might adapt the guidelines to the needs of our patient populations, what kind of evidence would be necessary, and how we might advocate together to ensure that coverage was preserved.

The year these issues became personal for me was also 2017. This was the year my father lost his battle with prostate cancer and another very close family member received a new diagnosis of this same disease. Prostate cancer is the most common cancer in men in the United States; its incidence in Black men (like the two in my family) is at least 75 percent higher than men of other races and ethnicities. My father was fortunate to have received care from outstanding physicians and to have had access to clinical trials as his disease advanced. He was a career Army officer, a veteran, and a strong supporter of science and medicine. He had even served as a lay reviewer for federal funding of prostate cancer research. As my father’s journey with prostate cancer ended and another family member’s began coincident with my work on the USPSTF, the stark absence of representation of Black men in prostate cancer research became acutely distressing. Black men constitute 13.4 percent of the U.S. population, have a higher prostate cancer incidence, and die at double the rate of other men in the United States. Yet the screening trials from which the US Preventive Services Task Force derived evidence for prevention included less than 5 percent Black men and the number in late-stage treatment trials was recently reported at 2.4 percent.

Much of my testimony today will pull directly from a recent National Academies report I chaired on Improving Representation in Clinical Trials and Research: Building Research Equity for Women and Underrepresented Groups¹. The main takeaways of my testimony are:

1. Failing to achieve a more diverse clinical trial and clinical research ecosystem is costly. It costs us in scientific innovation and accuracy, in timely access to innovation for the US population, in the trust we seek to build in the medical and scientific enterprise, and in U.S. dollars.
2. It is the responsibility of everyone involved in the clinical research ecosystem to diversify clinical trials, but Congress has a particular role right now to move us beyond the status quo.
3. To address this issue, we need a coordinated federal response that includes increased accountability, data collection, and incentives.

Whether you are motivated by the goal of producing the highest quality science, by pursuit of fairness and equity in how science might translate into better health for our patients, or by the

¹ For the full report, please see: <https://nap.nationalacademies.org/catalog/26479/improving-representation-in-clinical-trials-and-research-building-research-equity>

enormous economic toll of health disparities in the United States, I hope you embrace the urgency of improving representation and inclusion in clinical research.

Why Diversifying Trials is Important

The United States has long made substantial investments in clinical research with the goal of improving the health and well-being of our nation. There is no doubt that these efforts have contributed significantly to treating and preventing disease and extending human life. Nevertheless, clinical research faces a critical shortcoming. Currently, large swaths of the United States population, often those that bear the greatest health challenges, are not adequately represented in clinical trials and clinical research. The National Academies committee that I recently chaired found that while we have made great progress in including women in clinical trials and research, representation of racial and ethnic minority populations, LGBTQIA+ populations, older adults, persons with disabilities, and pregnant and lactating individuals has largely stalled.

By failing to achieve a more diverse clinical trial and clinical research enterprise, the nation suffers serious consequences, including the following:

1. Lack of representation compromises generalizability of clinical research findings to the U.S. population. Research has demonstrated that many groups underrepresented and excluded in clinical research can have distinct disease presentations or health circumstances that affect how they will respond to an investigational drug or therapy.
2. Lack of representation may hinder innovation. Diversifying study participants allows for greater exploration of variation in the overall effectiveness of a particular intervention. It is important to understand heterogeneity in treatment effects not just for safety and effectiveness of a particular intervention, but also to identify new biological processes that may lead to new discoveries important for all populations.
3. Lack of representation may compound low accrual that causes many trials to fail. Low accrual is the leading problem that causes clinical trials to fail and increasing representation not only increases enrollment, but also reduces waste caused by premature study termination.
4. Lack of representation may lead to lack of access to effective medical interventions. Approval and indications for new therapeutics are often restricted to the demographics of the populations included in the clinical studies, which limits access to therapeutics for certain populations. These decisions can impact insurance coverage of therapeutics in certain populations and reduces access to cutting-edge therapies for advanced diseases, which are often only available in clinical trials.
5. Lack of representation may undermine trust. We know that lack of trust is a barrier some investigators face when diversifying trials, but by including more diverse participants in clinical trials, we can build trust with communities and learn to become more trustworthy partners in this important work.
6. Lack of representation compounds health disparities in the populations currently underrepresented in clinical trials and clinical research. Although achieving health equity

and reducing health disparities requires far more than just equitable representation in clinical research, failure to achieve equity on this dimension leaves health disparities unaddressed and reinforces inequities.

7. And finally, lack of representation may cost the US hundreds of billions of dollars. An economic analysis carried out by the National Academies committee demonstrated high financial and social costs — measured by life expectancy, disability-free life, and years in the labor force — projected to be in the hundreds of billions of dollars range over the next three decades as a consequence of US health disparities. If better representation in clinical trials reduces health disparities by even a modest amount, the analysis found that achieving diverse representation in research would be worth billions of dollars in savings to the United States.

Addressing this problem is urgent. Too often, I hear investigators say that it is not worth recruiting a diverse population because the study may not be statistically powered to do subgroup analyses. This misses the point that exploring heterogeneity across different population subgroups is only one of the reasons to improve representation in clinical trials. The urgency to improve representation begins with the recognition that our science must generalize to the people and populations affected by the disease under study, and the best way to ensure that is the case is to include those populations in the studies from the outset. Failing to do so affects the generalizability of data collected and therefore the scientific integrity of studies. It also threatens access to scientific innovation, undermines trust in our scientific and medical enterprise, and risks exacerbating costly health disparities by failing to focus adequately on populations most burdened by particular conditions.

I also often hear that lack of willingness to participate is the cause of poor representation of some populations in research. However, the evidence on this issue is clear and quite contrary to this commonly held view: Asian, Black, Latinx Americans, and American Indian/Alaskan Native individuals are no less likely, and in some cases are more likely, to participate in research if asked.

It's Everyone's Responsibility

Inclusive clinical research will require committed and accountable action on the part of all stakeholders of the research enterprise. Funders, researchers, industry, and regulators, community leaders, patient interest groups, and journals that publish clinical research—all have an important role. Unsurprisingly, these will require investments of time, money, commitment, and effort. Building trust with local communities requires a sustained commitment and presence, with financial investment in research infrastructure and systems and technologies to reduce barriers to participation. Inclusive clinical research will require transparency and accountability. This begins with community-centered engagement and prioritization across the research life cycle, from the substance and design of questions being asked, to culturally cognizant recruitment and retention of study participants, to analysis and reporting of results, and to monitoring and reporting across the research ecosystem to ensure that the goals of inclusion are met.

An Important Role for Congress: Coordinating Federal Efforts

The federal government has a notably prominent role and responsibility in achieving the goal of more inclusive research. The federal government is the largest funder of research through the National Institutes of Health (NIH) and other federal agencies that fund research; serves as the regulator of the processes of scientific research through the Office of Human Research Protections and Institutional Review Boards; is the gatekeeper to approvals for monetizing scientific discovery through the Food and Drug Administration (FDA); and is the purchaser of new drugs and devices through the Center for Medicare and Medicaid Services (CMS). More coherence of federal policy to align investment and accountability to achieve the goals of inclusive science is warranted.

As such, Congress has a particular role to play in advancing progress on this issue. Particularly as it relates to coordinating the federal level efforts to address these issues.

There is little question that inclusion and diversity in clinical trials and research has been a major policy priority over the past three decades, advanced by federal agency offices such as the NIH Office of Research on Women's Health, the FDA Office of Women's Health, the Society for Women's Health Research, and the FDA Office of Minority Health. But while some progress has been made, there is so much work to be done, and so many in our society who still fail to benefit equitably from the clinical research enterprise.

The 2020 U.S. Census found that the number of people who identify as White has shrunk for the first time since a census started being taken in 1790, and despite the country becoming more diverse, the nation's health disparities persist. Without major advancements in the inclusion of underrepresented and excluded populations in health research, meaningful reductions in disparities in chronic diseases such as diabetes, cancer, and Alzheimer's disease remain unlikely. Purposeful and deliberate change is needed. As the United States becomes more diverse every day, failing to reach these growing communities will only prove more costly over time

The National Academies report offers a range of recommendations targeted at Congress and the federal agencies that, if implemented, I believe could have a significant positive impact on advancing progress on these issues. Among those recommendations are calls for greater transparency, accountability, cross-agency coordination of efforts, and more rigorous and coordinated data collection practices.

On the latter point, one critical area where greater coordination at the federal level could have a much needed positive impact is in increasing reporting of who is participating in clinical trials across various levels. In working on the National Academies study, I was deeply concerned to find that our current federal level data collection practices made it impossible to get a fully accurate measure of who is, and has been, participating in clinical trials. Inconsistencies in reporting in ClinicalTrials.gov makes it impossible to do a large-scale analysis of clinical trials in the US. FDA Snapshots is helpful, but only includes approved drug trials. Beginning in 2018, NIH now reports clinical trial enrollment in NIH-sponsored trials by research, condition, and

disease categories, but there is no way to examine this data longitudinally. Ultimately, the committee used FDA snapshot data and NIH institutes biennial and triennial reports from 2013-2018 to figure out who is participating in clinical trials for the purposes of the consensus report, but this took a great deal of manual effort.

If we cannot get accurate and easily accessible baseline data on who is participating in clinical trials, how can we know if we are making progress? How can we possibly build metrics to hold ourselves accountable for the commitments made across these various agencies? How can we address a problem if we cannot even properly define it?

To address this issue, the report recommends that the Department of Health and Human Services establish an intradepartmental task force on research equity charged with coordinating data collection and developing better accrual tracking systems across federal agencies. This task force should be charged with producing an annual report to Congress on the status of clinical research enrolment in the US. The report also recommends that NIH standardize demographic characteristics submitted to ClinicalTrials.gov, so that trial characteristics are labeled uniformly across the database and can be easily disaggregated, exported, and analyzed by the public.

I can appreciate that improving and coordinating data collection practices may not seem like a big and flashy idea, but I can assure you that this is vital and needed. It is an essential step in addressing the issues at hand.

I would also like to highlight that Congress can play an important role in ensuring that existing federal accountability measures are used and enforced. I think most people would agree that the federal government plays a critical role in incentivizing actors within the clinical trial enterprise to take action. As such, it is essential that government agencies make use of incentive structures and accountability measures in place to drive change. Too often, it seems this is not the case. For example, in the National Academies report we include several recommendations to the FDA, the CMS, and the NIH, which are all central to enacting federal incentives and accountability measures for diversifying research.

FDA plays a critical role in incentivizing private industry to take action, and the National Academies report recommends that Congress establish a taskforce to study new incentives for new drugs and devices for trials that achieve representative enrollment. Some ideas include tax incentives, fast-track criteria and exemption from some FDA drug application fees, extended market exclusivity, and refusing to file an application that does not appropriately reflect the target population under study.

Additionally, the report recommends that CMS expedite coverage decisions for drugs and devices that have been approved based on clinical development programs that are representative of the populations most affected by the treatable condition and that CMS should incentivize community providers to enroll and retain participants in clinical trials by reimbursing for the time and infrastructure that is required through the creation of new payment codes. Further, the committee recommends that the Government Accountability Office (GAO) should

assess the impact of reimbursing routine care costs associated with clinical trial participation for both Medicare (enacted in 2000) and Medicaid (enacted in 2020). This should include an analysis of whether there is timely and complete reimbursement and any what the challenges to implementation are.

However, the focus of the hearing today is primarily on the NIH, which is central to diversifying clinical trials and clinical research. First, NIH is the largest public funder of biomedical research in the world. With this substantial federal investment, we should ensure that the research we are funding is benefitting the full U.S. population.

Second, while private industry plays a critical role in bringing many drugs to market, NIH funds a substantial amount of research that underpins the development of new therapeutics. This partnership means that the research that NIH funds and oversees influences the research industry undertakes, the pathways they explore, and ultimately the therapeutics that are brought to market. Therefore, NIH is responsible for diversifying trials and research from an early stage in the process. Additionally the scope of research funded is broader than that linked to clinical trials. The same principles of why representation is important applies to all types of research, from genetic studies to implementation science studies – all part of the NIH portfolio.

Finally, as the major funder of biomedical research in our country, the NIH has the power to influence the actions and priorities of research institutions and individual investigators. For example, the National Academies report recommends that NIH formally incorporates considerations of representativeness in the score-driving criteria that assess the scientific integrity and overall impact of a grant proposal. This not only will influence the priorities of individual investigators, but would influence the actions of research institutions to prioritize relationships with their surrounding communities. The research infrastructure that is needed to ensure sustained progress in improving representation requires that the institutions receiving NIH funding invest in building sustained infrastructure together with the communities they serve so that participation in studies is easier and seamless across a range of studies.

The Costs Are Far Reaching

To conclude, I want to reiterate that a lack of inclusion and diversity in clinical trials and research is extremely costly to the nation and these costs are far reaching. Today, society as a whole shoulders the toll of the extraordinary disparities in the US in health outcomes. The economic analysis in the National Academies' report estimates the economic "value" of the disparate disability-adjusted life-years lost for Black and Hispanic populations (compared with White populations) for diabetes, hypertension, and heart disease alone at nearly \$20 trillion over 30 years. Even if improving studies to include communities currently under-represented were to only address 1% of these costs associated with current health disparities, the economic benefit would amount to several billions of dollars in the US.

Furthermore, the scientific integrity of our clinical research enterprise is adversely affected by lack of inclusion for a host of reasons - because diversity is critical for new discoveries, because results of these studies may not generalize to all the communities for whom they are purportedly intended, and because the lack of inclusion may be a factor hampering clinical trial accrual.

It is also important to note that the populations underrepresented and excluded from research bear the greatest cost because they may not reap the benefit from the nation's substantial investment in scientific advancement and may specifically be deprived of access to novel treatments only available in clinical trials. And finally, the gap between the stated commitment to inclusion in clinical research and the lack of progress in this area may engender or reinforce mistrust in scientific and medical establishment.

I want to thank you for this opportunity to testify today and for your attention to this critical issue. I urge you to take action to promote greater coordination across the many federal efforts to improve representation, inclusion, and equity in clinical research, which should be anchored in transparency, accountability, incentives, and rigorous data collection and monitoring.

Summary

The United States has long made substantial investments in clinical research with the goal of improving the health and well-being of our nation. There is no doubt that these investments have contributed significantly to treating and preventing disease and extending human life. Nevertheless, clinical research faces a critical shortcoming. Currently, large swaths of the U.S. population, and those that often face the greatest health challenges, are less able to benefit from these discoveries because they are not adequately represented in clinical research studies.

In the past three decades, diversity in clinical trials has become an important policy priority, advanced by federal agency offices such as the National Institutes of Health (NIH) Office of Research on Women’s Health, the Food and Drug Administration (FDA) Office of Women’s Health, the Society for Women’s Health Research, and the FDA Office of Minority Health. While progress has been made on some fronts, particularly with representation of white women in clinical trials and clinical research, progress has largely stalled on participation of racial and ethnic minority population groups. Additionally, older adults, pregnant and lactating individuals, LGBTQIA+ populations, and persons with disabilities remain underrepresented and even excluded from clinical trials and clinical research.¹ An equitable clinical research enterprise would include trials and studies that match the demographics of the disease burden under study. However, we remain far from achieving this goal.

¹ Throughout this report, LGBTQIA+ is used as an inclusive term for the various gender identities and sexual orientations, including lesbian, gay, bisexual, transgender, questioning, queer, intersex, asexual, and pansexual.

By failing to achieve a more diverse clinical trial and clinical research enterprise, the nation suffers serious costs and consequences, including the following:

- 1. Lack of representation compromises generalizability of clinical research findings to the whole US population.** Women, pregnant people, children, older adults, and racial and ethnic minority population groups can have distinct disease presentations or health circumstances that affect how they will respond to an investigational drug or therapy. These variable therapeutic responses can result in the delivery of health care that is not always evidence based.
- 2. Lack of representation costs hundreds of billions of dollars.** An economic analysis carried out by the committee, using the Future Elderly Model, demonstrates high financial and social costs, measured by life expectancy, disability-free life, and years in the labor force, in the hundreds of billions of dollars range (see Box 2-1). Given the assumption that better representation in clinical trials would reduce health disparities by even a modest amount, the analysis found that achieving diverse representation in research would be worth billions of dollars in savings to the United States.
- 3. Lack of representation may hinder innovation and new discoveries.** Diversity in study participants allows for greater exploration of variation in the overall effectiveness of a particular intervention. Exploring “heterogeneity of treatment effects” may be necessary not only to understand variation that affects safety and effectiveness of an intervention in underrepresented and excluded populations but also to identify new biological processes that may, in turn, lead to new discoveries important for all populations.
- 4. Lack of representation may compound low accrual that causes many trials to fail.** According to an analysis by GlobalData, low accrual was the cause for stopping 55 percent of all Phase I–IV clinical trials that were terminated, suspended, or discontinued during 2008–2017. Thus, increasing enrollment of underrepresented and excluded populations would help solve the leading cause of clinical trial failure.
- 5. Lack of representation may lead to lack of access to effective medical interventions.** Approval and indications for new therapeutics are often restricted to the demographics of the populations included in the clinical studies. Lack of representation may therefore impede access to a specific therapeutic agent. Guideline-making bodies must synthesize various lines of evidence when making recommendations. The generalizability of these recommendations to all populations may be limited when the evidence base for a specific population does not exist. When these recommendations are tied to insurance coverage, these gaps may affect reimbursement of, and therefore access to, health care.

6. **Lack of representation may undermine trust of the clinical research enterprise and the medical establishment.** For example, the lack of inclusion of pregnant people in the clinical trials of the SARS-CoV-2 vaccines led to lack of clarity on the use of these vaccines in pregnant people and may have contributed to vaccine hesitancy, even as subsequent observational data emerged showing the safety of vaccine use in pregnant individuals, as well as data on the importance of preventing COVID-19 infection during pregnancy. Efforts to create more representative and inclusive research environments may work to increase trust in science and medicine.
7. **Lack of representation compounds health disparities in the populations currently underrepresented and excluded in clinical trials and clinical research.** While achieving health equity and reducing health disparities requires far more than just equitable representation in clinical research, failure to achieve equity on this dimension leaves health disparities unaddressed and reinforces inequities.

STATUS OF CLINICAL TRIAL PARTICIPATION

Gaining a fully accurate status of the current participation of underrepresented populations in clinical trials and clinical research, and trends in participation over time, is very challenging due to insufficient data-reporting practices at a national level. Although reporting to ClinicalTrials.gov is required for ongoing studies, the committee found major inconsistencies in how data was reported in this national database. Further, NIH does not currently have longitudinal data available for clinical trial enrollment by disease type.

Working within these constraints, the committee commissioned an analysis to examine available data from the FDA and NIH, which found that women now represent over 50 percent of clinical trial participants in the United States, particularly for white women. However, pregnant and lactating individuals, sexual- and gender-minority populations, and racial and ethnic subgroups of women remain underrepresented in clinical trials. The analysis also revealed that the racial and ethnic diversity of clinical trials is largely stagnant, with little changes in diversity over time.

UNDERREPRESENTED AND EXCLUDED POPULATIONS ARE WILLING TO PARTICIPATE IN CLINICAL RESEARCH, IF ASKED

Due to well-documented historical and contemporary abuses against certain excluded and underrepresented populations in medical research, members of the research community often assume that a lack of willingness to participate in research is the major driver of poor representation of some populations in research. However, the evidence on this issue is clear: Asian, Black, Latinx Americans, and

American Indian/Alaska Native individuals are no less likely, and in some cases are more likely, to participate in research if they are asked. Distrust and mistrust are commonly assumed to be the reason underlying a lack of participation in clinical trials. While there is no doubt that the legacy of abuses in medical research is an important factor driving the lack of engagement of underrepresented and excluded populations with both health care and research, several studies have found that distrust and mistrust are not necessarily associated with a lack of willingness to participate in medical research. The evidence suggests that concerns of researchers about the willingness of underrepresented and excluded populations to participate in research due to distrust or mistrust in the medical establishment may misrepresent barriers to participation in research or are surmountable with effort from research teams, funders, and policy makers.

BARRIERS TO REPRESENTATION OF UNDERREPRESENTED AND EXCLUDED POPULATIONIS IN CLINICAL RESEARCH

The committee found that the existing research system has served to reduce participation by a diverse population in clinical trials and clinical research through a range of factors, operating at multiple levels. Individual research studies, the institutions that conduct research, funders of studies, institutional review boards (IRBs), medical journals, and the broader landscape of national policies and practices that govern research can all contribute to barriers to inclusion of underrepresented and excluded populations in clinical research.

- 1. Individual research studies.** At the level of an individual research study, the factors and problems that lead to the underrepresentation and exclusion of certain populations in clinical trials and research begin with and follow the life cycle of a project. Understanding and resolving underrepresentation and exclusion of these populations in research requires careful examination of almost every stage in the research process itself, including
 - the development of research questions;
 - the composition, training, and attitudes of the research team;
 - research site selection;
 - participant selection, including sampling and recruitment methods and inclusion and exclusion criteria;
 - study protocols, including informed consent processes and remuneration; and
 - development and inclusion of multilingual recruitment and consent documents.
- 2. Institutional structures.** Medical institutions of different types face a range of structural barriers to inclusion in clinical trials. For example, although academic medical centers conduct 55 percent of the extramural medical research supported by the National Institutes of Health, and

operate 98 percent of the nation's 41 comprehensive cancer centers as of 2019, sustainably and meaningfully engaging underrepresented and underrepresented and excluded populations often does not align with the traditional incentive structures for researchers at these institutions. Recruiting diverse population groups and properly engaging with community members, which is time-consuming and requires investments to build and sustain trust, are only minimally considered in promotion and tenure decisions at academic medical centers. And while community health centers serve a much more diverse community than academic medical centers, these institutions also face barriers to clinical trials and research recruitment, which, which include limited provider knowledge about available research opportunities and challenges with electronic health record (EHR) infrastructure that can limit providers' ability to query the EHR using study inclusion and exclusion criteria.

- 3. Institutional review boards.** IRBs can also present barriers to diverse participation in clinical trials by limiting the types and amount of compensation given to research participants to avoid the impression of coercion or undue influence. However, limiting incentives may ultimately compromise beneficence and justice, two of the ethical principles for research with human subjects detailed in the *Belmont Report*.
- 4. Research funders.** Research funders also have several roles and responsibilities that can influence the diversity of clinical trials. These include setting funding priorities, deciding which projects ultimately get funded, providing adequate funding to recruit and retain participants, requiring transparent reporting, and evaluating research outputs.
- 5. Industry funders.** Most clinical trials are funded by industry, and these trials present barriers, including out-of-pocket costs for participants, which are often not discussed in the informed consent process, industry pressures to gather data quickly, and the selection of easy-to-recruit samples being incentivized. It should be noted that some of these barriers are not solely unique to industry-sponsored trials.
- 6. Medical journals.** Peer-reviewed Medical journals serve as the gatekeepers to scientific advancements in clinical practice and health. Their editors yield great power for what is, and is not, published in their pages. Lack of representation on editorial boards and other journal leadership positions may contribute to biases in publication.

FACILITATORS TO SUCCESSFUL INCLUSION IN RESEARCH

There is substantial quantitative data demonstrating the size and scope of the problem of underrepresentation and exclusion of populations in research; however, there is a dearth of critical qualitative data about facilitators of successful inclusion in clinical research. This committee supplemented existing literature

with commissioned research with 20 researchers who worked on trials that met criteria for diverse trial enrollment. From this research, eight major themes emerged, which provide insights into key facilitators to inclusion:

- 1. Starting with intention and agency to achieve representativeness.** From goal setting to community partnering strategies, intentionality and planning are critical themes for overcoming the systemic barriers previously outlined to the inclusion of underrepresented and excluded populations in research. This intentionality applies to building relationships with community members, designing studies that seek to recruit these groups, considering barriers to access and the lived-realities of participants in the research design, and external factors, such as requirements from funding agencies.
- 2. Establishing a foundation of trust with participants and the community at large.** Building and maintaining trust with both study participants and their larger communities is foundational to achieving equity in research. The development of trust requires a long-term commitment by principal investigators, study teams, and local institutions involved in the research. Building trust over time takes consistent engagement in the community beyond the confines of the study itself, developing meaningful relationships with study participants, and giving to the community without the expectation of anything in return.
- 3. Anticipating and removing barriers to study participation.** Building rapport with study participants and attending to their needs is critical for making sure studies have broad accessibility. In addition, recognizing heterogeneity within cultural groups is key; a one-size-fits-all approach to developing protocols will not work.
- 4. Adopting a flexible approach to recruitment and data collection.** Flexibility in recruitment techniques, data collection, and visit windows to adapt to study needs is critical to having diverse study enrollment and retention. These changes are more helpful when made with input from community representatives and other relevant stakeholders.
- 5. Building a robust network by identifying all relevant stakeholders.** Research suggests that engaging in mapping to identify all the relevant stakeholders in a community can help study teams develop more equitable study designs and identify individuals and organizations that can help drive the recruitment and retention of diverse study participants. These stakeholders include caregivers, family members, friends, clinical providers and administrators, community advocates, peers, religious leaders, and political figures.
- 6. Navigating scientific, professional peer, and societal expectations.** Efforts to promote representativeness, and decisions made to support these efforts, are not always embraced or supported by colleagues and

organizations responsible for making funding and/or budget decisions. It is helpful if funding agencies, as well as those responsible for approving proposals and distributing budgets, understand the challenges and costs associated with nontraditional research approaches to enhance inclusion.

- 7. Optimizing the study team to ensure alignment with research goals.** Diverse study teams, including study leadership, are helpful to recruitment and to enhance congruence between research teams and potential participants. It also helps to retain staff over time for recruitment and retention success.
- 8. Attaining resources and support to achieve representativeness.** The investment of time and money are necessary to successfully engage in the long-term strategies and relationship building needed to drive inclusion in studies. This includes expanded budgets for teams recruiting and retaining diverse participants, support to expand infrastructure for community organizations, and investments in community-based partnerships to reduce power differentials between researchers and participants.

CONCLUSIONS

The committee identified five overarching conclusions, based on a comprehensive analysis of the research, presented throughout the report, which serve to frame the consensus recommendations.

- 1. Improving representation in clinical research is urgent.**

The scientific necessity to improve research equity is urgent. The 2020 U.S. Census found that the number of people who identify as white has shrunk for the first time since a census started being taken in 1790, and despite the country becoming more diverse, the nation's health disparities persist. Without major advancements in the inclusion of underrepresented and excluded populations in health research, meaningful reductions in disparities in chronic diseases such as diabetes, cancer, and Alzheimer's remain unlikely. Purposeful and deliberate change is needed. As the United States becomes more diverse every day, failing to reach these growing communities will only prove more costly over time (see Chapter 2).

- 2. Improving representation in clinical research requires investment.**

Improving the representation of underrepresented and excluded populations in clinical trials and clinical research requires a substantial investment of time, money, and effort. Investment of time and resources are needed to build and restore trust with underrepresented and excluded communities. Building trust with local communities cannot be episodic or transactional and pursued only to meet the goals of specific studies; it requires sustained presence, commitment, and investment. Investments are also needed in the systems and technologies that reduce burdens to

participation by underrepresented and excluded populations, such as by adequately compensating participants financially for their time when participating in research and by investing resources in making participation more physically accessible, and by providing research materials that are culturally informed and multilingual. Lastly, we need to invest in creating a more diverse workforce that better reflects the diversity of our country. This has implications not just for study site personnel and their direct interactions with participants, but it also influences the types of research questions that get asked, the types of research that get funded, and even the types of research that are published. To better address health disparities and ensure health equity for all, the U.S. workforce should look more like the nation (see Chapter 4).

3. Improving representation requires transparency and accountability.

Transparency and accountability throughout the entire research enterprise will be critical to driving change and must be present at all points in the research life cycle—from the questions being addressed, to ensuring the populations most affected by the health problems are engaged and considered in the design of the study, to recruitment and retention of study participants, to analysis and reporting of results. Individual investigators and research institutions on the front lines bear responsibility for transparency in reporting progress toward the goals of inclusion in research. Transparency and accountability must also be reinforced by the funding that agencies and industry sponsors have across their portfolios, that regulatory agencies have in their role governing the conduct of research as well as the approval and reimbursement of the drugs and devices that are often the final products of clinical research, and that journal editors and others that disseminate research have in communicating findings (see Chapters 3, 4, and 5).

4. Improving representation in clinical research is the responsibility of everyone involved in the clinical research enterprise.

The clinical research landscape is complex and involves multiple stakeholders—participants, communities, investigators, IRBs, industry sponsors, institutions, funders, regulators, journals, and policy makers. Each of these stakeholders has a critical role to play in achieving the goal of improving representation in clinical research, but the complex nature of the research ecosystem and research processes, combined with lack of accountability and historic underinvestment, means that an issue that should be everyone’s responsibility can become no one’s priority. In this report, the committee emphasizes that the research supports taking a systematic approach to addressing this issue, one in which all stakeholders take responsibility for the important role they can play in ensuring representation in clinical research participation.

The committee was asked, “Who bears the cost of more inclusive science?” The responsibility (and therefore the cost) will be borne to some extent by all stakeholders in the larger research ecosystem, acting in consort to achieve this larger societal and scientific goal. Those that profit from scientific discovery bear particular responsibility in shouldering the cost of inclusivity. The federal government has a notably prominent role and responsibility in achieving the goal of more inclusive research, as a primary funder of the research enterprise with taxpayer dollars, regulator of the processes of scientific research, gatekeeper to approvals for monetizing scientific discovery, and purchaser of new drugs and devices. More coherence of federal policy to align investment and accountability to achieve the goals of inclusive science is warranted.

In answering the question of who bears the cost of more inclusive science, we must also ask, “Who bears the cost of the current lack of inclusivity?” That cost is large (as evidenced by the analysis in Chapter 2) and is borne disproportionately by underrepresented and historically excluded communities, but saps the health and economic strength of the entire society.

5. Creating a more equitable future entails a paradigm shift.

The committee sees the need for both pragmatic approaches and an aspirational vision. To realize a more equitable future, the report epilogue challenges the field to embrace a paradigm shift that moves the balance of power from institutions and puts at the center the priorities, interests, and voices of the community. An ideal clinical trial and clinical research enterprise pursues justice in the science of inclusion through scalable frameworks; expects transparency and accountability; invests more in people, institutions, and communities to drive equity; and invests in the science of community engagement and empowerment. These ideals should be the foundation of the actions that stakeholders take to make sustainable change.

RECOMMENDATIONS

The committee’s recommendations focus on tangible actions that must urgently be taken within the context of the existing structures of the clinical research ecosystem in order to achieve the goals of representation and inclusion. Although individual researchers can take many actions to improve health equity in clinical trials and clinical research, as described in Chapter 5, the committee focused on system-level recommendations to drive change on a broader scale. The committee presents 17 recommendations (see Chapter 6) to improve the representation of underrepresented and excluded populations in clinical trials and clinical research and create lasting change.

The urgency of addressing the equity in research participation and the lack of substantial progress despite stated commitments led the committee to propose bold recommendations with potentially far-reaching implications. The committee is aware that the complexity of the United States health-care system poses significant challenges to transforming the clinical research system, and these systematic challenges will also influence the implementation of the committee's recommendations. While providing a complete policy assessment for each recommendation was outside of the committee's scope and charge, the committee does not deny that there will be costs—both fiscal and political—associated with the implementation of the recommendations. These costs must be carefully weighed against the potential for long-term benefit. Changing our nation's approach to clinical research may require significant upfront costs to more equitably recruit and retain a diverse group of participants and to hold investigators accountable when they do not meet these goals. In addition, it will require incentivizing sponsors of clinical research to change the status quo. However, based on the committee's expert opinion and the available evidence, the committee believes that implementation of its recommendations is necessary to truly drive significant and sustained change to the clinical research system.

Reporting and Accountability

- 1. The Department of Health and Human Services (HHS) should establish an intradepartmental task force on research equity charged with coordinating data collection and developing better accrual tracking systems across federal agencies, including the Food and Drug Administration (FDA), National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC), Agency for Healthcare Research and Quality (AHRQ), Health Resources Services Administration (HRSA), Indian Health Services (IHS), Centers for Medicare and Medicaid Services (CMS), and two departments outside of HHS, the Department of Veterans Affairs and Department of Defense. This task force should be charged with the following:**
 - a. Producing an annual report to Congress on the status of clinical trial and clinical research enrollment in the United States, including the number of patients recruited into clinical studies by phase and condition; their age, sex, gender, race, ethnicity, and trial location (i.e., where participants are recruited); their representativeness of the conditions under investigation; and the research sponsors.**
 - b. Making data more accessible and transparent throughout the year, such as through a data dashboard that is updated in real time.**
 - c. Determining what “representativeness” means for protocols and product development plans.**

- d. Developing explicit guidance on equitable compensation to research participants and their caregivers, including differential compensation for those who will bear a financial burden to participate.
2. The Food and Drug Administration should require study sponsors to submit a detailed recruitment plan no later than at the time of Investigational New Drug and Investigational Device Exemption application submission that explains how they will ensure that the trial population appropriately reflects the demographics of the disease or condition under study and that provides a justification if these enrollment targets do not match the demographics of the intended patient population in the United States.
3. The NIH should standardize the submission of demographic characteristics for trials to ClinicalTrials.gov beyond existing guidelines so that trial characteristics are labeled uniformly across the database and can be easily disaggregated, exported, and analyzed by the public. The data reported should include the number of patients; their age, sex, gender, race, ethnicity, and trial location (i.e., where participants are recruited); who sponsors them; and language accessibility.
4. In grant proposal review, the NIH should formally incorporate considerations of participant representativeness in the score-driving criteria that assess the scientific integrity and overall impact of a grant proposal. These criteria should be part of the assessment of the scientific approach, including whether it is appropriate for generating insights for the populations to whom the results are intended to generalize. The criteria should also be incorporated in the assessment of whether investigative teams and environment have detailed and feasible plans to meet the goals of representative study enrollment. Additionally, the NIH should assess in its annual review of progress reports of funded studies whether a given study has met the proposed enrollment goals of representativeness by race/ethnicity, sex, and gender, and should establish a plan for remediation for the investigator and/or organization that includes criteria for putting funding on hold that has not met predefined recruitment goals.
5. Journal editors, publishers, and the International Committee on Medical Journal Editors should require information on the representativeness of trials and studies for submissions to their journals, particularly relative to the affected population; should consider this information in accepting submissions; and should publish this information for accepted manuscripts. The information required should include the following:
 - a. The disease, problem, or condition under investigation.
 - b. Special considerations related to sex and gender, age, race or ethnic group, and geography.

- c. The overall representativeness of the trial, including how well the study population aligns with the target population in which the results are intended to generalize. If the study population does not align with the population affected by the disease, authors should provide scientific justification for why this is the case.
6. The Office of Human Research Protections (OHRP) and the FDA should direct local institutional review boards (IRBs) to assess and report the representativeness of clinical trials as one measure of sound research design that it requires for the protection of human subjects. Representativeness should be measured by comparing planned trial enrollment to disease prevalence by sex, age, race, ethnicity and trial location (i.e., where participants are recruited). Protocols in which the planned enrollment diverges substantially from disease prevalence should require justification. The OHRP and FDA should establish a plan for remediation for local IRBs that frequently approve protocols that are not representative.
7. The CMS should amend its guidance for coverage with evidence development (CED) to require that study protocols include the following:
 - a. A plan for recruiting and retaining participants who are representative of the affected beneficiary population in age, race, ethnicity, sex, and gender
 - b. A plan for monitoring achievement of representativeness as described above, and a process for remediation if CED studies are not meeting goals for representativeness

Federal Incentives

1. In order to determine how to take action on the most effective accountability and incentive structures, Congress should direct the FDA to enforce existing accountability measures, as well as establish a taskforce to study new incentives for new drug and device for trials that achieve representative enrollment. Incentive programs should be designed to improve representativeness in clinical research, improve clinical outcomes, and ensure they do not reduce access to new therapies. Some ideas include:
 - a. Tax incentives, such as tax credits for research and development.
 - b. Fast-Track criteria and exemption from some FDA drug application fees.
 - c. Extended market exclusivity to sponsors who meet predefined criteria of representativeness.
 - d. Refusing to file an application that does not appropriately represent the target population under study.

2. The CMS should expedite coverage decisions for drugs and devices that have been approved based on clinical development programs that are representative of the populations most affected by the treatable condition.
3. The CMS should incentivize community providers to enroll and retain participants in clinical trials by reimbursing for the time and infrastructure that is required. Through the creation of new payment codes, CMS should reimburse activities associated with clinical trial participation, including but not limited to data collection and personnel (e.g., community health workers, patient navigators) to support research education and recruitment.
4. The Government Accountability Office (GAO) should assess the impact of reimbursing routine care costs associated with clinical trial participation for both Medicare (enacted in 2000) and Medicaid (enacted in 2020). The assessment should include an analysis of whether there is timely and complete reimbursement, any implications for innovation and care delivery to underrepresented populations, and any challenges to implementation.

Remuneration

1. Federal regulatory agencies, including OHRP, NIH, and FDA, should develop explicit guidance to direct local IRBs on equitable compensation to research participants and their caregivers. In recognition that research participation may pose greater hardship or burdens for historically underrepresented groups, the new guidance should encourage and allow for differential compensation to research participants and their caregivers according to the time and financial burdens of their participation. Differential compensation may include additional reimbursement for expenses including but not limited to lost wages for those with lower socioeconomic status (SES), transportation costs, per diem, dependent care, and housing/lodging where applicable.
2. All sponsors of clinical trials and clinical research (e.g., federal, foundation, private and/or industry) should ensure that trials provide adequate compensation for research participants. This compensation may include additional reimbursement for expenses including but not limited to lost wages for lower SES participants and family caregivers, transportation costs, per diem, dependent care, and housing/lodging where applicable.

Education, Workforce, and Partnerships

1. All entities involved in the conduct of clinical trials and clinical research (academic centers, health-care systems, sponsors, regulatory

- agencies, and industry) should ensure a diverse and inclusive workforce, especially in leadership positions.
2. Leaders and faculty of academic medical centers and large health systems should recognize research and professional efforts to advance community-engaged scholarship and other research to enhance the representativeness of clinical trials as areas of excellence for promotion or tenure.
 3. Leaders of academic medical centers and large health systems should provide training in community engagement and in principles of diversity, equity, and inclusion for all study investigators, research grants administration, and IRB staff as a part of the required training for any persons engaging in research involving human subjects. This training should incorporate strategies to enhance diverse recruitment and retention in clinical research, as well as planning of and budgeting for these efforts and timely reimbursement of partnering agencies and organizations.
 3. HHS should substantially invest in community research infrastructure that will improve representation in clinical trials and clinical research. This funding should go to agencies such as the HRSA, NIH, AHRQ, CDC, and IHS to expand the capacity of community health centers and safety-net hospitals to participate in and initiate clinical research focused on conditions that disproportionately affect the patient populations they serve.