



# Improving Equity and Access to Health Care: How Nontraditional Organizations Can Help Increase Clinical Trial Diversity

## An American Diabetes Association Resource

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The American Diabetes Association® (ADA) is the nation's leading voluntary health organization fighting to bend the curve on the diabetes epidemic and help people living with diabetes thrive. For more than 80 years, the ADA has driven discovery and research to treat, manage, and prevent diabetes while working relentlessly for a cure. Through advocacy, program development, and education we aim to improve the quality of life for the over 133 million Americans living with diabetes or prediabetes. Diabetes has brought us together. What we do next will make us Connected for Life®. To learn more or to get involved, visit us at [diabetes.org](https://diabetes.org) or call 1-800-DIABETES (1-800-342-2383).

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## Executive Summary

In 2020, the American Diabetes Association (ADA), the nation's leading organization for all people with diabetes, launched Health Equity Now, a national platform to ensure all people living with diabetes, and the millions of underserved Americans who are at greatest risk for diabetes, have access to health resources that are too often unavailable to them. The ADA crafted a Health Equity Bill of Rights, a set of ten principles that continue to guide ongoing efforts to tackle systemic barriers to health and health care in the United States today.

This paper will focus on the organization's efforts around the sixth principle, "The right to participate in clinical trials without fear." Too often, the communities that most need the drug or medical product are excluded from clinical trial participation, potentially hindering the ability to gauge efficacy and safety. Drugs and treatments used for diabetes and other chronic diseases must be developed in partnership with the communities that will use them, and participating individuals must be protected in the scientific process.<sup>5</sup>

In part due to the ADA's leadership, policymakers, government organizations, and the pharmaceutical industry have started to prioritize diversity in clinical trials. While broadening clinical trial diversity has been attempted in traditional settings such as academic centers, the ADA is collaborating with partners to identify new opportunities in nontraditional settings to reach historically excluded communities.

While there are multiple levers to influence health, this paper provides an in-depth look at clinical trial diversity, how it relates to health equity, and how the ADA and nontraditional partners can help advance diversity goals. Analysis includes the current state of clinical trials and the historical lack of diversity, explores the common barriers to recruitment and access to clinical trials, and shows how retail industries can play an innovative role in increasing access and diversity in clinical trials. The ADA's Health Equity Now partnership with Walmart demonstrates the impact similar nontraditional partners can have in improving diversity and representation in clinical trials and ultimately help improve health for our communities.

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## Background

Health inequity in the United States—a mixture of persistent disparities in health outcomes between well-resourced communities and minority, under-resourced and rural communities—has complex, interrelated causes. A person’s health is affected by multiple factors depending on where they live, learn, work, and play. Certain environments and entrenched biases foster deep-rooted barriers that may create and exacerbate health disparities. These barriers include limited access to healthy foods, public transportation, and green space for physical activity, all compounded by overexposure to poor air quality, stress, and violence.<sup>2</sup> While impacting individual health, these social determinants of health also contribute to the lack of clinically appropriate treatment. Systemic barriers may prevent certain communities from participating in clinical trials and advancing scientific knowledge that reflects the diversity of the U.S.<sup>3</sup>

The World Health Organization (WHO) defines a clinical trial as a “type of research that studies new tests and treatments and evaluates their effects on human health outcomes.”<sup>4</sup> Clinical trial participants contribute to medical research by volunteering for studies that could lead to new medical interventions and/or help improve medication safety. These interventions include drugs, medications, other biological products, medical procedures, devices, or care. Clinical trials include distinct phases to review adverse side effects and review additional testing before a drug or intervention is approved for public use.<sup>4</sup> Conclusions and recommendations drawn from these trials are regarded as the strongest, as clinical trials are intentionally designed to minimize biases and systematic errors. Given that clinical trials are essential to health care and help many patients live better lives through technological advances and treatments, adequate representation of various populations within these studies must be ensured to generalize the results to the entire population.

Historically, very few clinical trials included any participants from diverse backgrounds.<sup>4</sup> Clinical trials often excluded women, racial and ethnic minorities, and those with disabilities or of different genders, sexual orientations, and gender expression.<sup>5</sup> Therefore, clinical findings may not be generalizable to the population most affected by a certain disease or condition, like diabetes. Thus, proper representation of a study sample is of utmost importance as certain groups may respond differently to a drug, such as older adults, who may metabolize drugs at a slower rate than others.<sup>5</sup>

The Robert Wood Johnson Foundation defines health equity as “everyone has a fair and just opportunity to be as healthy as possible. For measurement, health equity means reducing and ultimately eliminating disparities in health and its determinants that adversely affect excluded or marginalized groups.”<sup>6</sup> One way to achieve health equity is by ensuring the inclusion of people from diverse backgrounds in clinical trials. This diversity could consist of various levels of education, age, race, ethnicity, disability status, geographic residence, sexual orientation, socioeconomic status, and other health conditions. There are intrinsic and extrinsic factors



that make a person unique. Understanding the impact of new therapeutic products on diverse populations is not only analyzing any genetic or intrinsic differences, but also understanding how therapeutic products impact populations based on their extrinsic factors. Extrinsic factors include lived experience, including the burden of racism, chronic stress, and other social drivers of health. Intrinsic factors include age, weight, and genetics.<sup>7,8</sup> Clinical trial recruitment, participation, and analysis must include populations with a wide diversity of extrinsic and intrinsic factors in order to properly evaluate the outcomes.

Barriers to recruitment can exist on the individual, personal, systemic, and policy levels. Next, the current state of clinical trial diversity is reviewed and barriers (such as mistrust, lack of awareness, and accessibility) that contribute to the lack of diversity in clinical trials are highlighted.

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## Diabetes and Clinical Trial Diversity

Diabetes is a rapidly growing health condition. Approximately 1.4 million Americans are newly diagnosed with diabetes each year, a number that has doubled over the last 20 years.<sup>9</sup> Even more staggering are the disparities in the diabetes community, as Black and Hispanic people are 50% more likely to have diabetes compared to white people.<sup>10</sup> In fact, the number of Americans diagnosed with diabetes is expected to grow to 29 million people by 2050, with Black men expected to grow 363% (from 2000 to 2050).<sup>11</sup> Despite this disparity, minorities are underrepresented in clinical trials for therapies to prevent and treat diabetes. Thus, adequate diversity in these trials is essential to properly assess the safety, efficacy, and effectiveness of a drug that will ultimately be used on this population. People with diabetes are also more likely to experience comorbidities such as high blood pressure and obesity, which explains why diabetes accounts for one in four health care dollars spent in the U.S.<sup>12</sup> However, many trials exclude individuals living with diabetes due to their comorbidities. While patient safety is the objective of most exclusions, this restrictive criterion often results in the patients most in need being ineligible for each phase of the clinical trial.<sup>16,17</sup> This exclusion of patients with diabetes is counterintuitive to the nature of clinical trials themselves—while these studies are intended to deliver the highest quality of medical evidence, they are utilizing a patient sample that doesn't truly mimic the general population and thus the results are not truly generalizable.

According to the Food and Drug Administration's (FDA) 2015–2017 Drug Trials Snapshot Summary Reports, of all participants in diabetes-related clinical trials, minorities were grossly underrepresented. On average, 23% of participants were Asian, 17% were Hispanic or Latino, and just 5% were Black. Meanwhile, 75% of clinical trial participants identified as white.<sup>15</sup> Other studies have supported this FDA data.<sup>16,17</sup> Data from 2000 to 2022 shows approximately 62.3% of diabetes clinical trials had under-enrollment for minority groups.<sup>16</sup> Indeed, trials receiving industry funding increased the odds of under enrollment by historically underrepresented

communities in biomedical research.<sup>16</sup> These inequities will be further magnified given the newer diabetes medications which have potent effects on weight loss, cardiorenal protection, and have the potential to impact disease trajectory.<sup>18</sup>

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## Other Therapeutic Areas

The lack of diversity in clinical trials isn't unique to diabetes. Other therapeutic areas, many of which affect people with diabetes such as cardiovascular disease, chronic kidney disease, infectious disease, neurology, and oncology, have underrepresentation of communities adversely impacted by these conditions.<sup>19-23</sup> More work needs to be done to ensure these populations are proportionally represented so they can equally benefit from future medications.

### ***Cardiovascular Disease***

Cardiovascular disease (CVD) is the leading cause of death in the United States<sup>24</sup> as well as the leading cause of death for people with diabetes. Approximately every 36.1 seconds, someone in the United States dies from CVD.<sup>24-26</sup> While CVD management has improved over the years, there are still glaring disparities by race/ethnicity, age, geographical location, socioeconomic status, and gender/sex.<sup>17,25,27-30</sup> Despite these disparities, these groups have historically been underrepresented in randomized clinical trials of CVD prevention. Only one drug was approved by the FDA to treat CVD in 2021.<sup>15</sup> While those over 65 years old were adequately represented (63%), women and Black and Hispanic/Latino people were disproportionately underrepresented, which leaves critical questions as to the drug's efficacy, and potentially contributing to the disparities seen among these demographic populations.<sup>15</sup>

### ***Chronic Kidney Disease***

Chronic kidney disease (CKD) impacts approximately 37 million Americans and one in three adults with diabetes live with the condition.<sup>31</sup> Unfortunately, the same disparities in disease burden found in diabetes are observed in CKD.<sup>32,33</sup> Black people, Native American people, Hispanic people and Asian American people, those over 65, those in rural areas, and women are more likely to have CKD.<sup>33,34</sup>

In 2021, only one drug was approved for adults with diabetes and kidney disease and one drug was approved to help with itching for patients with CKD.<sup>15</sup> Patients with CKD or renal insufficiency have been consistently an exclusion from clinical trials, often due to possible renal side effects.<sup>35,36</sup> Although patients with CKD have an increased risk for CVD and related complications, CKD often excludes patients from more than half of all CVD clinical trials.<sup>37,38</sup> For phase 3 clinical trials for prostate, breast, lung, and colorectal cancers, 95% of cancer clinical trials excluded patients with CKD.<sup>39</sup> Unfortunately, race and ethnic minorities and women remain consistently underrepresented in CKD clinical trials compared to the groups who have CKD.<sup>40,41</sup>

## ***Infectious Disease***

Increasingly, infectious diseases are becoming more prevalent globally. Extensive travel and changes to the climate have provided fertile ground for infectious diseases to spread rapidly worldwide. Within the United States, infectious diseases disproportionately impact people with diabetes and different facets of the population. As a whole, minority populations are overburdened by infectious diseases.<sup>42-44</sup> Despite being adversely impacted by infectious diseases like influenza, HIV, and COVID-19, minorities remain underrepresented in clinical trials.<sup>45,46</sup>

Outside of the robust COVID-19 drug development pipeline, the infectious disease pipeline is quite dry.<sup>47</sup> A new report showed only five of the top 20 companies in the pharmaceutical industry are conducting clinical research on infectious disease therapies.<sup>47</sup> In fact, in 2021, the FDA Drug Trials Snapshots Summary Report indicated only four new treatments were approved to treat infectious diseases.<sup>15</sup> For each of those studies, minorities, women, and those over 65 were underrepresented in the trials.<sup>15</sup>

## ***Neurology***

Neurological disorders affect the brain and nerves found throughout the human body and spinal cord.<sup>48</sup> Some of the most common neurological disorders are Alzheimer's disease and other dementia disorders, both of which disproportionately affect people with diabetes.<sup>49,50</sup> Alzheimer's disease is one of the top ten leading causes of death in the United States. The most significant risk factor for Alzheimer's and other dementias is age.<sup>50</sup> Those over 65 are at the most critical risk for developing a form of dementia. However, women, Black people, and those of lower income and educational status are more likely to have Alzheimer's or other dementia.<sup>48,50-52</sup> The FDA approved five new neurological therapies in 2021.<sup>15</sup> In all those clinical trials, minorities and women were significantly underrepresented.

## ***Oncology***

Cancer is currently the second leading cause of death in the United States.<sup>53</sup> It is estimated that more than 1.9 million new cancer cases will be diagnosed in 2022.<sup>53</sup> Unfortunately, cancer isn't an equal opportunity condition—Americans of different races/ethnicities and geographical locations are adversely impacted by cancer. For example, Black people are more likely to die from most cancers than all racial/ethnic groups.<sup>53</sup> Rural communities are more likely to be impacted by colorectal, lung, and cervical cancers than urban communities.<sup>54</sup>

Despite these disparities, the demographic groups mentioned above are less likely to participate in clinical trials. Oncology is one of the largest pharmaceutical markets, worth more than \$71 billion. Drugs are increasingly in the pipeline to develop novel cancer-fighting therapies.<sup>55</sup> To ensure these novel drugs work in the communities that will most likely to need them, it is essential to include them in future trials.



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## Current Demographic State

Clinical trial diversity is not a new concern, but attention to the issue has not been sufficient to achieve meaningful progress. Thirty years ago, Congress passed the National Institutes of Health (NIH) Revitalization Act, which required the NIH to include more women and minorities in NIH-funded clinical trials.<sup>56</sup> Yet, despite that effort and subsequent policy efforts, clinical trial participants are still predominantly white and male.<sup>57</sup> While strides are being made to improve clinical trial diversity, more work needs to be done to improve the collection of a diverse range of demographic data like socioeconomic status, race/ethnicity, age, geographical location (rural vs. urban), disability, education level, and comorbidity.<sup>58</sup> Below, the current state of diversity by race/ethnicity, sex/gender, disability, comorbidity, and educational attainment is discussed.

### ***Race and Ethnicity***

Although nearly 40% of Americans currently identify as a racial and ethnic minority, they are consistently underrepresented in clinical trials.<sup>57,59-61</sup> This lack of diversity unfortunately prevents the ability of therapies to be safe and efficacious in all individuals. According to the FDA 2015–2019 Drug Trials Snapshots Summary Report, while white and Asian communities were adequately represented in trials for approved drugs, Black, Hispanic or Latino, and American Indian or Alaskan Native people were underrepresented, despite a stated commitment from the FDA and industry to tackle this problem.<sup>15</sup> This lack of diversity in clinical trials is compounded by the fact that more than 50% of U.S. trials fail to report race/ethnicity enrollment data even if they do enroll minorities.<sup>57</sup>

There are many factors contributing to the lack of racial and ethnic diversity in clinical trials. Unfortunately, racial and ethnic minorities are less likely to have access to health care and a regular health care provider that could potentially inform them about the possibility of participating in a clinical trial.<sup>62</sup> Other barriers, including comorbidities, transportation, geography, mistrust, affordability and accessibility, among others are discussed below.

### ***Sexual Orientation and Gender Identity***

Until 1993, the law did not require clinical trials to include women. Before, clinical trials comprised mainly white men (white males assigned at birth) because of gender biases against including women in research, some of which included concerns about fluctuating hormones and potential pregnancies. It has been well established that there are gender differences in how an individual presents disease/condition systems as well as how one responds to drugs used to treat the disease.<sup>4,32,48,55,56</sup> Indeed, since January 1997, studies have shown that 8 out of 10 prescription drugs were removed from the market because of adverse responses in women.<sup>56,57</sup> Since 1993, the inclusion of women in clinical trials has improved. A National Academies of Sciences study indicated there has been about an 18% increase in the participation of women

in clinical trials.<sup>5</sup> However, there is still much work left to be done as women are still not equally represented in clinical trials.<sup>15</sup>

On the other hand, capturing data on sexual and gender minorities (SGM) and the LGBTQ+ community needs improvement. SGMs include, but aren't limited to, people who identify as lesbian, gay, bisexual, transgender, non-binary, and intersex.<sup>66</sup> Until recently, medical researchers didn't often ask sexual orientation, gender identity, and gender expression questions to consider the inclusion of SGM, and the federal government failed to set meaningful standards to facilitate accurate data collection. That has made it challenging to capture individuals within SGM populations in clinical trials in significant numbers to make results representative of them. This is important as a growing body of evidence suggests that SGMs are disproportionately impacted by health issues such as obesity, substance abuse, mental/behavioral concerns, and tobacco use, solidifying the importance of ensuring this community is adequately represented in clinical trials.<sup>66</sup>

### **Age**

More than 56 million adults in America are 65 and older, making them one of the most rapidly growing population segments in America.<sup>59</sup> While the elderly comprises a large segment of our country's population, they are systemically underrepresented in clinical trials. Among NIH-funded clinical trials, those over 65 made up 19% of clinical trial participants and made up 31% of participants in all FDA-approved drug trials in 2021.<sup>58,67,68</sup> Adults over 75 are more likely to be excluded from clinical trials for drugs they would most benefit from.<sup>69</sup>

There are many reasons why those over 65 are often excluded. Researchers exclude older adults because of safety concerns, comorbidities, and at times, the capacity of older adults to comprehend the requirements of clinical trial participation and give informed consent.<sup>60,69</sup> Since research shows that older patients may respond to medications differently than younger adults, given the pharmacological changes that a body undergoes as it ages, it is essential for older adults to participate in clinical trials.<sup>14,70</sup>

### **Comorbidity**

Nearly 60% of Americans have a chronic disease, and 40% have comorbidities (two or more chronic health conditions such as diabetes, obesity, heart disease, cancer, and chronic kidney disease).<sup>71</sup> Despite this high prevalence, individuals with comorbidities are often excluded, as researchers are concerned about the ability to distinguish between any potential adverse event to a clinical trial treatment and a complication from the condition not targeted by the treatment. In addition, there are well-documented barriers to chronic disease management, which may impact a person's ability to adhere to clinical trial treatment plans.<sup>72-74</sup> The issue of comorbidity as a barrier to clinical trials is inextricably linked with race, ethnicity, and socioeconomic status, as these populations are more likely to have comorbid conditions.<sup>14,75,76</sup> Though there may be barriers to overcome, people with comorbidities must be included in clinical trials to ensure there are no adverse effects when used in combination with other medications they might be taking to

manage their other conditions. It is essential to have broader inclusion criteria for clinical trials to provide valuable information about the drug's impact, especially on patients who are most likely to use it once the drug is approved.

### **Education**

Educational attainment is a critical factor that can impact a person's earning potential and health outcomes.<sup>77</sup> Those with lower levels of educational attainment have been shown to be less likely to receive primary preventative care.<sup>78</sup> Additionally, this population is more likely to have chronic diseases such as diabetes and hypertension.<sup>79,80</sup> Although those with lower educational attainment are more likely to face chronic illness, they are less likely to participate or be asked to participate in clinical trials necessary to develop treatments they would ultimately use.<sup>62</sup>

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## **Barriers to Recruitment**

The lack of diversity in clinical trials is a multifaceted issue. Below, some of the most common barriers to participation are discussed: mistrust, health literacy, language barriers, lack of diversity in the clinical trial workforce, technology, ineligibility, and accessibility. Also highlighted is the importance of overcoming these barriers and recommendations on how to tackle them.

### **Mistrust**

One of the most significant barriers to clinical trial participation is mistrust in medical research and clinicians. Centuries of medical research conducted unethically on minorities have fueled this mistrust. Enslaved people often underwent painful procedures to evaluate treatments for diseases and conditions without their consent. The most notable example often cited by many is the U.S. Public Health Service Syphilis Study at Tuskegee, where U.S. government officials withheld syphilis treatment from Black men.<sup>81,82</sup> More recently, Henrietta Lacks, a Black woman diagnosed with an aggressive form of cervical cancer, had tissue samples taken during her treatment and studied in laboratories without her or her family's consent.<sup>83</sup> The cancer cells harvested from her tissues, named HeLa cells after her first and last two initials, still exist today and are used by research scientists throughout the world without any compensation to her surviving family.<sup>83</sup> Studies have shown that knowledge of these historical unethical injustices has contributed to a mistrust of medical institutions and a hesitancy to participate in clinical trials.<sup>84,85</sup>

In addition to mistrust at the institutional level, there is also mistrust of clinicians, which may cause individuals to delay preventative care, or prevent individuals from seeking care or even being open to participating in a clinical trial. Unfortunately, cultural stereotypes and biases (gender, implicit, etc.) often impact how a clinician might treat a patient of lower socioeconomic status, different race/ethnicity, sex/gender, or geographic location.<sup>86</sup> Individuals of lower

socioeconomic status or from a racial or ethnic minority group are less likely to receive the appropriate number of disease diagnostic tests or novel treatments needed to diagnose and treat a condition.<sup>87</sup> Individuals from underrepresented or underserved groups are often thought to be non-compliant or unable to afford recommended therapy, so they are not usually offered treatment.<sup>85,88</sup> For example, a recent cancer study revealed that Black women were less likely to be referred for genetic counseling or testing for breast cancer than white women, despite Black women being disproportionately impacted by breast cancer.<sup>88</sup>

Trust is a crucial factor to encourage individuals to feel empowered to seek and maintain regular care from medical providers. It will be essential to apply measures at both the system and the clinical levels to tackle this deep-seated barrier. Mistrust can be overcome by building sustained relationships with communities and individuals before clinical trial recruitment begins. In addition, clinical trial sponsors should engage communities early in the research design process. One method to accomplish this is through patient focus groups that include patients with diverse backgrounds. This method both builds transparency and trust within the community. Clinical trial sponsors should also focus on increasing the diversity of the clinical research staff as well as the institutions conducting the trials. Lastly, clinicians and researchers must understand their inherent biases and institutions should explore policies and practices that limit the impact of implicit biases and stereotypes. Additionally, clinical trial sponsors should develop tangible metrics to understand how well interventions address mistrust. The best approach for incorporating community perspectives into clinical trials is through policies that help build trust.<sup>89</sup>

### ***Health Literacy***

According to the Centers for Disease Control and Prevention (CDC), health literacy is the “degree to which individuals can find, understand, and use information and services to inform health-related decisions and actions for themselves and others.” Education is not necessarily tied to health literacy—those with high educational attainment can have limited health literacy.<sup>90</sup>

Low health literacy can directly impact a person’s ability to understand some medical terminology used to describe clinical trials and impair the ability to provide informed consent to participate in a clinical trial.<sup>91</sup> In addition, lower health literacy could also foster anxiety and fear of participating in medical research.<sup>92</sup> To raise health literacy levels, clinical sponsors and staff must incorporate plain language and visual aids in clinical trial recruitment and educational materials. A focus on culturally competent messaging is critical. Additionally, researchers should take time to ensure the individual understands what is shared with them. Clinical trial sponsors should also consider incorporating a screening test to identify participants with low health literacy and develop tailored approaches to overcome barriers to comprehension.<sup>93</sup>

### ***Language Barriers***

Language barriers associated with limited English proficiency can lead to barriers to health care service access, lower quality of care, and reduced participation in clinical trials.<sup>94</sup> Language

barriers are often associated with reduced participation in clinical trials due to miscommunication between the clinical trial staff and participants and the ability to provide informed consent.<sup>95</sup> To tackle this barrier, sponsors should incorporate bilingual staff that speak the languages of targeted populations.<sup>96</sup> In addition, research materials should be translated into multiple non-English languages and integrate more visual rather than written educational materials.<sup>97</sup>

### ***Lack of Incorporation of Diverse Researchers or Health Professionals***

Studies show that clinical trial sites with greater racial and ethnic diversity among their staff have greater participant diversity.<sup>98,99</sup> A survey conducted by the Tufts Center found that significant racial disparities exist among clinical investigators.<sup>100</sup> They found that participation in medical research among minority physicians is below that observed among white physicians. In addition, minority investigators are less likely to be funded to conduct medical research compared to white investigators, exacerbating the lack of diversity in clinical research and lack of clinical research tailored to address specific health disparities. Because research has shown that underserved groups are more likely to trust providers with their same lived cultural experience, it is crucial to widen the pool of diverse researchers conducting clinical trials.<sup>101,102</sup> Efforts to strengthen the clinical research pipeline through improved and targeted recruitment practices, training programs, and fellowships should be considered. In addition, where a diverse workforce cannot immediately be improved, more cultural sensitivity training should be undertaken.

### ***Technology***

Over 21 million people in the United States do not have access to the internet or other digital technology like smartphones, including six million rural Americans.<sup>103</sup> Even more glaring is that of the Americans with internet access, over 163 million do not have access to high-speed internet.<sup>103</sup> These technological access disparities, also known as the digital divide, highlight the gap between those with access to technology and those who don't. The digital divide is more starkly felt among rural and low-income communities that have decreased access to digital technology, which has become essential to accessing health care through telehealth.<sup>104</sup>

Lower internet connectivity and reduced access to high-speed internet can be a barrier to health care services offered remotely through telehealth approaches and hinder the ability to engage in clinical trials that might offer virtual appointments. According to a recent United States Department of Agriculture report, only 72% of rural residents and only 63% of rural residents in persistent poverty counties had moderate or high-speed broadband available in their census blocks.<sup>105</sup>

Although there was a 63-fold increase in telehealth usage during the pandemic, Black and rural communities were less likely to use the service than white, urban, and high-income communities.<sup>106</sup> As technological use becomes more commonplace, due to decentralized trials and efforts to meet the patient where they are, removing barriers to broadband access will be necessary. Several states and organizations are working to close the digital divide.



### ***Ineligibility***

Inclusion and exclusion criteria are the blueprints of who and who is not allowed to participate in a clinical trial. Historically, women, those over 65, pregnant and lactating people, individuals with two or more chronic conditions, children, and those with organ dysfunction were typically excluded from clinical trials.<sup>56,58,70</sup> Existing inclusion and exclusion criteria are often excessively restrictive and can impact the ability to recruit the individuals most affected by the condition being addressed with the medication, which is especially true for chronic illnesses like diabetes. For example, many trials exclude people because they have comorbidities.<sup>107</sup> While patient safety is the objective of most exclusions, this restrictive criterion often results in the patients most in need being ineligible for the trial. A recent assessment of more than 300 NIH clinical trials found that almost 80% of the practices excluded patients with comorbidities.<sup>99</sup> To address this barrier, it will be essential to consider how eligibility criteria could be broadened to increase diversity but not hinder patient safety efforts. In recent guidance, the FDA recommended broadening inclusion criteria in later Phase 3 trials and designing a clinical trial that would allow one to safely expand the eligibility criteria through enrichment strategies that could better target populations traditionally excluded from medical research.<sup>108</sup>

### ***Affordability***

Within the U.S., the huge cost of health care is a massive burden on Americans and often impedes access to preventative care. Half of American adults cannot afford their health care costs, especially uninsured, Black and Hispanic adults, and those with low household income.<sup>109</sup> According to an analysis of the 2021 National Health Interview Survey, 16.5% of insulin users or 1.3 million Americans with diabetes ration their insulin to save money. These patients, especially Black people, those under 65 years old, and uninsured individuals, skip doses, take a lower amount, or delay purchasing insulin despite the dangerous and possibly life-threatening consequences.<sup>110</sup> Even when insured, many Americans face unaffordable monthly premiums. Lower socioeconomic status is directly tied to poor health outcomes. It can also affect an individual's ability to access clinical care and create an unwillingness to participate in clinical trials.<sup>111</sup>

Studies have shown that individuals with fewer financial resources or lower socioeconomic status were underrepresented in clinical trials.<sup>62,76,87</sup> This underrepresentation is the result of multiple factors. People with lower socioeconomic status are less likely to participate in clinical trials due to concerns about lost wages or penalties from having to take time off work or a lack of childcare. Even though some clinical trials utilize virtual check-ins, many people still can't afford high-speed internet service or computers at home.<sup>104,111,112</sup> Data shows that those of higher socioeconomic status are told more often about relevant clinical trials and are more likely to participate in a clinical trial than those of lower socioeconomic status.<sup>14,62</sup>

Recent studies have also demonstrated that Asian and Black individuals are less likely to be prescribed two new classes of diabetes medications, sodium-glucose cotransporter-2 inhibitors

(SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA), compared to White patients. Furthermore, commercial insurance and higher median household income were associated with higher rates of prescribing SGLT2i and GLP-1RA.<sup>113,114</sup> (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA), compared to white people. Furthermore, commercial insurance and higher median household income were associated with higher rates of prescribing SGLT2i and GLP-1RA.<sup>113,114</sup>

To tackle this barrier, it is necessary for medical researchers to consider more financially inclusive practices to ensure those from diverse socioeconomic backgrounds can equally participate in clinical trials. Studies should be designed to facilitate participation, such as having easy-to-access clinical trial sites closer to targeted communities, offering appointments outside the traditional 9:00 to 5:00 pm business hours, providing childcare services, transportation assistance, and reimbursement for lost wages.<sup>5</sup> Additionally, effective January 2022, the Clinical Treatment Act requires states to cover routine care for Medicaid clinical trial participants. This coverage is another way to increase representation in clinical trials and reduce any financial barriers to participation. However, this coverage may not be well known among researchers and participants despite the Center for Medicaid and Children's Health Insurance Program (CHIP) Services publishing a State Medicaid Director Letter that outlines guidance of the new law.<sup>115</sup>

### **Geography**

Approximately 19% of Americans live in rural areas.<sup>105</sup> People who live in rural communities often face significant health disparities, a higher increase in disease and disability due to clinician shortages, and a lack of access to medical facilities due to geography, among other reasons.<sup>28,62,116,117</sup> Geographical isolation, lower income levels, limited access to specialty clinicians, and limited opportunities for clinicians influence these rural disparities.<sup>116</sup> Rural community members are less likely to have health insurance or be covered by Medicare/Medicaid and have lower internet connectivity.<sup>112,118</sup> Even when rural residents are aware of the clinical trials available, they may not be able to access them due to transportation requirements. Unfortunately, most of the top 50 clinical research sites funded by the NIH are in urban locations, making it harder for rural communities to access clinical trials.<sup>108</sup> To remove these barriers, it will be necessary for more clinical sponsors to consider adding more clinical trial sites in locations that are more readily accessible to rural residents. Ensuring proper travel and wage reimbursement or providing travel services will also be essential.

### **Transportation Barriers**

Transportation also can be a substantial barrier to clinical trial participation. Many patients live far away from participating clinical trial sites traditionally held at large academic centers, cannot drive, and lack access to reliable public transit.<sup>118,119</sup> Lack of transportation access impedes clinical trial participation in several ways. Older Americans with decreased physical function are less likely to have access to transportation.<sup>119,120</sup> They could have trouble getting to clinical trial sites even after successfully consenting to participate in a clinical trial. Those with lower incomes

may be unable to afford transportation to a clinical trial site. The site might be far away or outside of public transportation access, or the public transportation might need reliable services to promptly get them to the clinical trial site.<sup>119-122</sup> Studies showed that people were more likely to participate in a clinical trial close to their doctor's office.<sup>123</sup>

To overcome this barrier, clinical trial sponsors should meet potential participants where they are. For example, sponsors should consider moving some clinical trial sites to more rural locations and partner with a transportation service to provide a way for those older and with reduced mobility or lower income to make their appointments. Also, minimizing the number of visits can remove this barrier.

### ***Lack of Awareness/Low Physician Referral***

A recent study found that only 9% of Americans have been invited to participate in clinical trials.<sup>124</sup> However, those that are asked are 50% more likely to participate, regardless of background.<sup>125</sup> This suggests that people, regardless of background, would be more likely to participate in clinical trials if they were asked. Clinicians are often the gatekeepers of clinical trial participation. They often are the ones that educate their patients about relevant clinical trials that might benefit them and are the ones that ultimately refer them to be considered for clinical trial participation.<sup>111,121,126-129</sup> A clinician needs to evaluate a patient for a clinical trial before referring.

Even if the patient is a suitable candidate, data shows clinicians do not recommend individuals equally. Clinicians are less likely to refer a person with comorbidities to participate in a clinical trial because the provider may believe the patient would be excluded.<sup>107</sup> It is also possible that the clinician is unaware of the clinical trial options available for their patients. The clinician could be aware of clinical trials, but time constraints and pressures to see a high volume of patients does not allow them the ability to discuss it with their patients. It is also possible that a clinician's unconscious or conscious biases may prevent them from referring patients of a particular sex/gender, race/ethnicity, socioeconomic status, geographical location, educational attainment level, or insurance status.<sup>86</sup> To tackle this barrier, it is essential to provide clinician cultural sensitivity training, education on clinical trial eligibility, and exclusion criteria education so clinicians understand who exactly is eligible to participate in clinical trials.

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## **Why Clinical Trial Diversity Matters**

### ***Benefits***

The inclusion of racially and ethnically diverse patients in clinical trials is vital for drugs and therapeutics to be proven safe and effective among the entire patient population. For example, minorities in the United States carry disproportionately higher rates of disease burden among common diseases such as diabetes and cardiovascular disease. However, these groups continue to be underrepresented in clinical trials due the barriers listed above.<sup>24,130</sup> Ensuring

diversity during the development process can not only help to ensure that treatments are clinically safe for the patients, but may uncover some differences in effectiveness across different subgroups (external validity). There was widespread recognition of this need throughout development of the vaccines for COVID-19, as several initial surveys found vaccine hesitancy within minority communities due to medical mistrust.<sup>131</sup> One survey found that Black and Hispanic respondents were considerably more likely than white respondents to feel that more COVID-19 vaccine testing on individuals of their own race or ethnicity would make them comfortable, with as many as 41% of Black respondents saying they would be more comfortable receiving the vaccine if there was “more testing on people of my race/ethnicity.”<sup>132</sup> Especially due to barriers of mistrust in certain minority communities, participants want their voices to be heard and further amplified through tangible steps in the research community. Examining drug effects among a representative population most likely to benefit from a new drug or medical product accomplishes that goal and continues to mend and build trust across partners and participants.

### ***Policy Implications***

Through better data, clinical trial diversity can increase safety in drug treatment and effectiveness and improve quality of life by improving health outcomes. Without federal support, research can remain stagnant. In 2020, Congress authorized the NIH to fund a study conducted by the National Academies of Sciences, Engineering, and Medicine to examine and quantify the long-term medical and economic impacts of the inclusion of women and minority population groups in biomedical research and subsequent translational work. The 2022 report found an “urgent” need to increase trial diversity and highlighted that underrepresentation in clinical trials not only compromises generalizability of clinical research findings to the overall population, but also costs hundreds of billions of dollars. This, the report argues, is because an increase in clinical trial diversity would decrease health disparities and reduce costs associated with disability and comorbidities.<sup>5</sup>

While there is general alignment among the federal government, stakeholders, the pharmaceutical industry, and other industry professionals to increase clinical trial diversity, discrepancies in implementation persist. Some leading organizations are giving power to communities, which in turn improves health equity on an individual and population health basis.<sup>125</sup> Below, we outline the ways some stakeholders are addressing clinical diversity.

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## **Various Efforts to Improve Clinical Trial Diversity**

### ***American Diabetes Association***

Patient advocacy groups support ways to assess medications, interventions, and drugs that can help their patient population. The American Diabetes Association (ADA) is part of several initiatives, including Glycemia Reduction Approaches in Diabetes, a nationwide clinical trial comparing common medications for type 2 diabetes, and the Accelerating Medicines Partnership

between the NIH, nonprofits, and pharmaceutical companies.<sup>126</sup> In 2020, the ADA launched the Health Equity Now platform to ensure Americans living with diabetes and prediabetes, along with those at risk for diabetes—no matter their race, income, zip code, age, education, or gender—get equal access to the most basic of human rights: their health. The Health Equity platform also includes the Health Equity Bill of Rights, a set of 10 principles guiding the ADA's ongoing efforts to confront, through policy and programmatic action, the systemic barriers to health and health care that persist in our country today. The sixth right in the Bill of Rights is to participate in clinical trials without fear.<sup>5</sup> The ADA believes all Americans living with diabetes should have equal opportunity to participate safely in clinical trials.

The ADA has begun to make its impact in the clinical trial diversity space by supporting efforts to address the social determinants of health barriers that prevent many people with diabetes from participating in clinical trials. In 2022, the ADA hosted a roundtable discussion on promoting diversity in diabetes clinical trials and convened experts in diabetes care and clinical trials to help shape policy, clinical, and educational strategies to increase participation among diverse communities in diabetes clinical trials. Two key takeaways from the discussion were that medical distrust is deeply rooted within many minority communities and that patient voices need to be heard when discussing the issues of barriers and access to clinical trials.

### ***Federal Government***

In January 2021, President Biden signed an Executive Order (EO) for Advancing Racial Equity and Support for Underserved Communities Through the Federal Government. While the EO did not specifically mention clinical trials, it was monumental in having agencies identify, recognize, and address barriers to health equity and defining underserved communities. The EO also directed each agency to conduct equity assessments to understand barriers to enrollment of benefits in federal governments. Most importantly, the EO promotes agencies to engage and collaborate with community members.<sup>135</sup> That same week, President Biden also published an EO on Ensuring an Equitable Pandemic Response and Recovery. This EO created a COVID-19 Health Equity Task Force. In October 2021, the task force recommended the federal government improve clinical trial best practices and standards including diversity enrollment targets. The task force also suggested a national research agency for health equity and COVID-19. This includes the federal government promoting public-private partnerships for clinical trials and other research studies.<sup>136</sup>

### ***Federal Agencies***

As seen from multiple clinical trial guidance updates, the FDA continues to advance diversity in research as part of its good guidance regulations. In April 2022, the FDA published draft guidance called Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials, which recommends a sponsor to submit a Race and Ethnicity Diversity Plan when applying for new drug approval. This includes measuring enrollment goals for racial and underrepresented patient populations.<sup>137</sup> The CDC and NIH also prioritize clinical trial diversity. The NIH's All of Us Research Program and Precision Medicine Initiative looks to create a health database from one million people of all backgrounds with



special interest for how social determinants of health, lifestyle, and environmental factors affect health. The program also encourages researchers from diverse backgrounds, especially to build trust in the community. As the program's slogan states, "The Future of Health Begins with You."<sup>138</sup>

### ***Promising Practices: How Nontraditional Industries Are Impacting Clinical Trial Diversity***

As health equity and clinical trial diversity become more of a priority in the United States, industries in the private sector are looking for ways to bring more inclusivity to medical research. Because geography is a barrier to research recruitment, many organizations are using decentralized clinical trials to increase access to clinical research. Decentralized methods include using mobile vans where research teams come to the community, remote monitoring, telehealth, and virtual check-ins. For example, a recent randomized clinical trial in Texas focused on low-income Latinos with type two diabetes. The research study improved participants' A1C levels, blood pressure, and adenosine deaminase by using community health worker-led telehealth platforms for patient check-ins.<sup>139</sup> Decentralized trials have become critical during the COVID-19 pandemic, allowing patients to remain at home, especially for participants already enrolled in ongoing studies.<sup>140</sup> Additionally, studies often use social media for participant recruitment. In a recent literature review, 45% (43/96) of studies only used social media for recruitment, many of which targeted underrepresented populations.<sup>141</sup> In another review that looked at 33 studies, 17 studies showed enrollment outcomes—9 of those studies met or exceeded their enrollment goal.<sup>142</sup>

Some grocery stores have partnered with universities and health systems to study food and nutritional interventions, particularly in the space of online food shopping and digital applications.<sup>135</sup> Pharmacy retailers are leveraging their affiliated digital spaces, applications, in-person health appointments, and medication pick-up to increase awareness and access to clinical trials. Pharmaceutical companies also are partnering with community members, medical schools, and patient advocacy groups to fund and increase diversity in trials.<sup>144</sup> Software and technology companies as well as private equity firms have shifted focus to clinical trial diversity through analytic development tools and data access.

Given these promising practices, the ADA has established a clinical trial diversity partnership with Walmart, which acts as a grocery store, pharmacy, and community gathering space.

### ***Case Study: Walmart's Dedication to Clinical Trial Access***

Walmart is an ADA Health Equity Now campaign partner on a number of key initiatives, including training and educating a diverse workforce and advocating for the diabetes population. Together the organizations strive to help the general public and the diabetes community live healthier lives and close gaps in health disparities.<sup>145</sup>

In particular, Walmart offers a unique opportunity to drive access to clinical trials and improve overall diversity due to its broad footprint in American communities. Approximately 90% of Americans live within 10 miles of a Walmart store, and the corporation serves 150 million people

each week. Walmart serves patients across 4,600 pharmacies in addition to its role as a retail store, vision center, health center, and often the only grocery store in some rural areas. Nearly 4,000 of its stores are in federal designated medically underserved areas. Altogether, Walmart has the reach and visibility necessary to enroll a more diverse population in medical research.

In addition, Walmart has established clinical research as an organizational priority through their Walmart Healthcare Research Institute<sup>SM</sup> (WHRI). The institute builds on their existing commitment to provide safe, high quality, and more equitable health care to those in need.<sup>146</sup> Walmart's main priority for WHRI is to enable clinical research to serve as an accessible care option by identifying and engaging patients on trials that are relevant to them and empowering them in their own care. WHRI approached diversity through the lens of health equity and looks to increase access to underserved patients, including those who live and work in rural/sparsely populated areas, older adults, women and minority populations. Walmart believes that there is a responsibility for all partners in clinical research to ensure participation in trials reflects those who bear the burden of the disease and is focused on enabling its patients and communities equitable access.

Study focus areas and opportunities for patient engagement span diabetes care, obesity care, and cardiovascular care. The company also leverages technology through their digital tool that lets patients access all of their eligible medical records in one secure place and receive reminders for care services and research opportunities to better manage their health.

To date, WHRI has effectively engaged with thousands of patients and is demonstrating strong results, with a referral rate well above the industry benchmark. This engagement greatly increases the awareness of trials, helps enroll participants in suitable research that benefits them, and allows for continued follow-up on their care. With such a large pool of patients, WHRI can help researchers for a variety of studies, including potential rare disease clinical trial participants who may be hard to find but deserve the most innovative research and techniques available.<sup>147</sup>

Walmart's partnership with the ADA helps to leverage the ADA's scientific expertise, connection to patients, and vast experience in the needs and preferences of people with diabetes. Walmart extends the ADA's reach through its expansive network and digital platform, allowing it to reach more potential trial enrollees. While the partnership continues to grow, the ADA and Walmart will work together to advance health equity, improve clinical trial diversity, and address key social determinants of health.

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## Conclusion

Although the lack of diversity in clinical trials is challenging, new models of outreach and engagement hold significant promise. The ADA is committed to improving health care and accessibility to the 133 million Americans living with diabetes and prediabetes, along with the millions more who are at high risk for diabetes—no matter their race, income, zip code, age, education, or gender—get equal access to the most basic of human rights: their health. The ADA will continue to foster new and existing partnerships with other stakeholders like Walmart who are moving the needle to increase clinical trial diversity to ensure that all Americans have equal access to safe and efficacious medical products. Clinical trial diversity will promote research that can help patients now and for future generations.

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