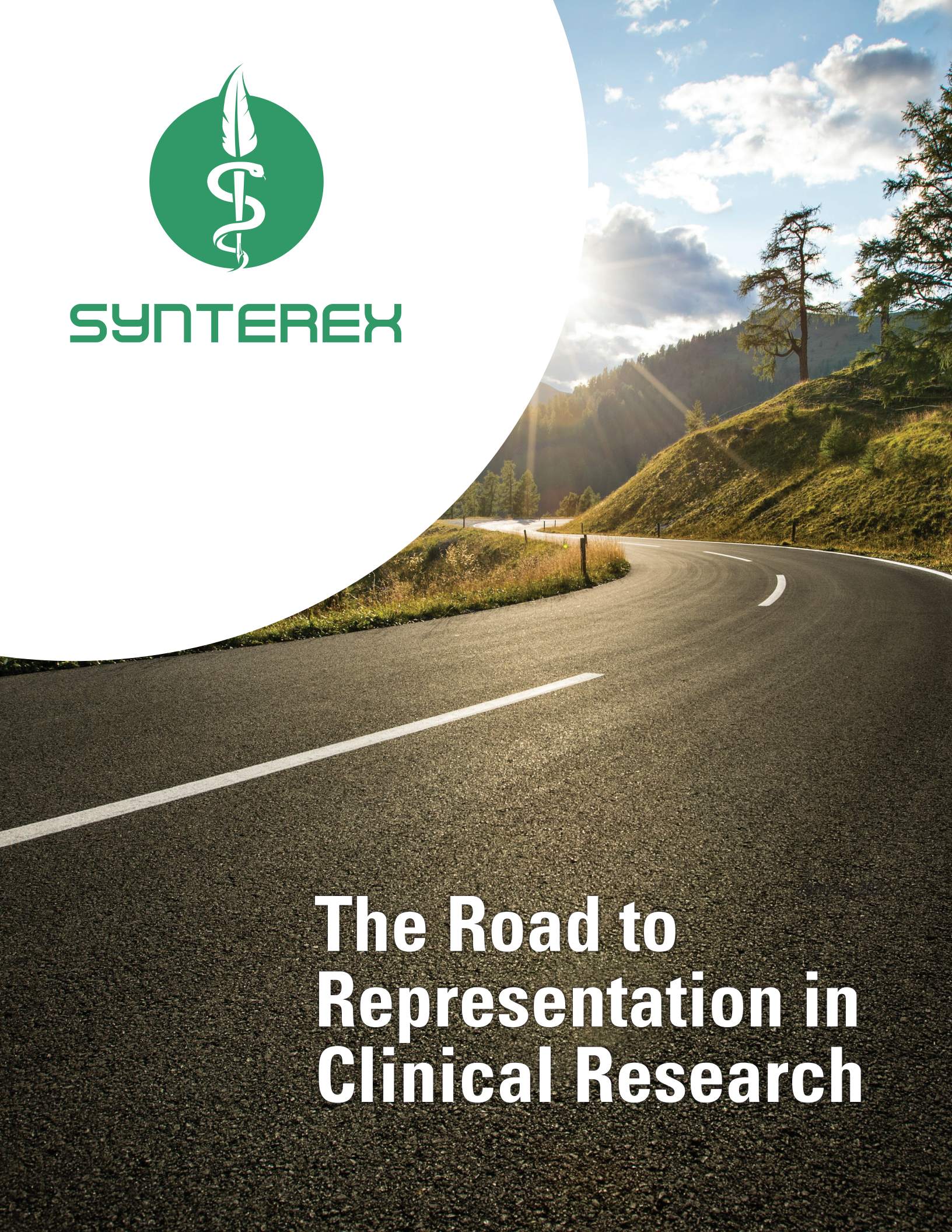
SYNTEREX



# The Road to Representation in Clinical Research

# THE ROAD TO REPRESENTATION IN CLINICAL RESEARCH

*Updated United States Food and Drug Administration Guidance on Diversity and Inclusion*

SYNTEREX

**Innovative development of human drugs, biologics, and medical devices (medical products) and their quick advancement through the United States Food and Drug Administration (FDA) approval pipeline is necessary to improve the lives of patients. It is also imperative for sponsors to consider diversity when enrolling study participants throughout the clinical development pipeline to adequately represent the population of patients who have a disease or condition.**

Historically, health equity has not been a primary consideration of clinical research. Groups affected by underrepresentation include, but are not limited to, individuals who identify as Asian, Black or African American, Hispanic/Latino, Indigenous and Native American, Alaska Native, Native Hawaiian and Other Pacific Islanders.[1] In recent years, however, physicians and scientists have come to understand that individuals from diverse racial and ethnic populations may have divergent experiences with medical products. Although these groups can have a disproportionately higher disease burden compared with the general population, they are often inadequately represented in clinical research studies. One example of this is the high incidence and mortality rate of African American women with triple-negative breast cancer.[2] It is unclear whether differences in treatment response are due to intrinsic factors, such as genetic mutations or molecular differences in tumor type, or extrinsic factors, such as income status or access to healthcare.[2,3] As a result, the FDA encourages sponsors to further diversify clinical trial enrollment with consideration to sex, gender identity, age, socioeconomic status, disability, pregnancy status, lactation status, and other comorbidities.[1] With increasing diversity in clinical trial enrollment, sponsors will need to be even more prepared to identify any group-specific safety and efficacy concerns.

Barriers to clinical trial participation are not necessarily due to a lack of willingness to participate. A 2022 consensus study report by the U.S. National Academies of Sciences, Engineering, and Medicine that analyzed clinical trial data, qualitative and quantitative review studies, and data from the FDA and NIH from 2003 to 2021 concluded that individuals from these underrepresented groups may be more likely to participate in clinical trials.[4] An analysis by Adeyemi et al. in 2009 from over 400 HIV-infected patients showed the strongest predictor of participation was being approached for enrollment recruitment, and 65% of patients would participate in a study if their primary care physician recommended it.[5] In many cases, altruism has been cited as a strong facilitator of research participation[6]; in general, members of these underrepresented groups have cultural customs or traditions that are community-based.

One systematic review shows that there are both shared and distinct barriers to research participation among African Americans, Latino/Hispanic, Asian Americans, and Pacific Islanders.[7] As stated in the review, "the continuing effects of slavery and colonization at a systemic institutionalized level have manifested in ongoing health inequalities through differential access to health care and poor health outcomes for racial/ethnic minorities in the United States."[7]

Barriers can be summarized by 4 main issues:

- **Mistrust of medical research or healthcare**: From the Tuskegee Study[8] (African Americans) to the sterilization of Native American Women by the Indian Health Service,[9] both historically underrepresented minorities.
- **Limited health and research literacy**: There is a lack of information regarding clinical trial opportunities for many underrepresented minorities. Many have also reported that informed consent forms can be culturally insensitive and hard to understand (e.g., language barriers).[6,7,10]
- **Logistics and competing demands**: Participation in clinical trials is a time commitment that some may not be able to adhere to for a myriad of reasons including childcare, lack of transportation, work schedule conflicts, and cost.[4,6,7]
- **Researcher bias and lack of diversity**: At the recruitment level, some practitioners are not intentionally targeting underrepresented populations due to inherent bias, whether conscious or subconscious. There could be notions that certain populations would not adhere to guidelines, would take more work or effort to recruit, or would not be interested in the study.[4,7,10]

**Recent legislative efforts through H.R. 2617 (Subtitle F, Section 3601), passed in December 2022, and the Diverse and Equitable Participation in Clinical Trials (DEPICT) Act, introduced in February 2023, could enable changes in the regulatory space by requiring a defined plan for integrating enrollment strategies.**

## Devising a Plan

Recent legislative efforts through H.R. 2617 (Subtitle F, Section 3601), passed in December 2022, and the Diverse and Equitable Participation in Clinical Trials (DEPICT) Act, introduced in February 2023, could enable changes in the regulatory space by requiring a defined plan for integrating enrollment strategies for underrepresented populations and demographic reporting activities. As of April 2022, The FDA has provided draft industry guidance to improve enrollment of participants from underrepresented racial and ethnic populations in clinical trials. Discussion of implementation strategies by the sponsor may occur at any stage of development for the medical product, and it is recommended for a Race and Ethnicity Diversity Plan ("Plan") to be established under the following circumstances:

### Drugs

- That require an Investigational New Drug (IND)
- Clinical studies intended to support marketing submissions:
  - As a standalone Biologics License Application (BLA) under section 351(a) of the Public Health Service Act
  - For a New Drug Application (NDA) under 505(b)(1) or 505(b)(2)19 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act)

### Medical Devices

- That require an Investigational Device Exemption (IDE)
- Clinical studies intended to support device marketing submissions:
  - Premarket notification (510(k))
  - Premarket approval (PMA) application
  - De Novo classification request
  - Humanitarian device exemption (HDE) application

**There is a lack of information regarding clinical trial opportunities for many underrepresented minorities.**

## What are the Proposed Timelines and Submission Processes?

### Drugs:

- During drug development, the Plan should be submitted to the associated IND application expeditiously, but prior to when feedback is solicited for the pivotal trial(s) supporting the IND, which is often at the end-of-phase 2 (EOP2) meeting.
- The Plan may be submitted independently or together with a milestone meeting package.
- Request a formal milestone meeting and include specific questions in the Meeting Package when requesting FDA feedback on the Plan.

### Medical Devices:

- The Plan should accompany the investigational plan as part of the IDE application.
- Sponsors should follow Q-submission processes to request an FDA meeting or feedback if:
    - Discussion of the enrollment strategy is needed prior to submitting the Plan.
    - The study is not conducted under an IDE.

### IND, IDE, or Q submissions containing a Plan:

- The submission cover letter should be clearly labeled "RACE AND ETHNICITY DIVERSITY PLAN" in large, bold print.
    - Periodic updates to the Plan may be requested by the FDA throughout the development of the medical product.

### Medical Product Marketing Application:

- Include the sponsor's Plan and details of successes and challenges encountered during implementation.

**With increasing diversity in clinical trial enrollment, sponsors will need to be even more prepared.**

## What Content is Recommended for Plan Development?*


1. **Provide an overview of the disease/condition:**
    a. Describe the pathophysiology of the disease or condition in the underrepresented groups and discuss the current body of evidence pertaining to similar or contrasting characteristics in these groups compared to the general United States population.
    b. Current strategies for prevention, screening, diagnostics, and treatments that are differentially applied in the diversity population.

2. **Detail the scope of medical product development program:**
    a. Provide a brief description for trials or studies intended to be performed and include:
        i. Study design, population and eligibility criteria, endpoints, and geographical location of study or trial sites.
        ii. Analysis of how the aforementioned characteristics may affect enrollment and participation from individuals in underrepresented racial and ethnic populations.
        iii. If applicable and available, summarize any clinical pharmacology study conclusions (e.g., PK/PD and pharmacogenomics data) that may identify pertinent results unique to any of the underrepresented populations.

3. **Define enrollment goals for underrepresented racial and ethnic participants:**
    a. Specify the enrollment goals for those underrepresented racial and ethnic populations presented in Category 1 and assess whether higher enrollment rates are necessary in certain populations to determine potentially unique outcomes in those groups.
    b. Where epidemiological data are sparse, the sponsor should utilize data sources that may be available, such as published literature or real-world data, falling on disease demographics for the overall population if necessary.

4. **Detail the operational plan for enrollment and retention of participants:**
    a. Site location and potential accessibility needs (e.g., reasonable accommodations for language assistance, physical disabilities, and transportation).
    b. Strategies to reduce the burden of trial participation by considering frequency of clinical procedures, telehealth

options, and access to local health facilities (e.g., clinics, laboratories, imaging centers, etc.).

c. Sustained community engagement activities through individuals and groups such as community advisory boards and navigators, community health workers, patient advocacy groups, local healthcare providers, etc.

d. Assign metrics for enrollment goal tracking and achievement, along with an action plan in the event goals are not met.

5. **Evaluate success of the Plan through goal tracking:**

   a. Where applicable, revision of the diversity Plan should be accompanied by regular evaluation of goal progress. Unattained goals established in the Plan by the sponsor should have a rationale presented for post-marketing data acquisition.

* Adapted from *Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials*[1]

**This requires a mindset shift in clinical trial development and an approach of intentionality.**

## Critical Appraisal of Diversity Guidance


Like so many regulatory documents, the diversity plan is simply the summary of a strategy, and all strategies must consider logistics and any dynamic factors that play into and influence the outcomes. A strategy is also inherently sustainable while concurrently aiming to create value for the people invested; it is not a goal or a set of tactics — it's an ongoing and adaptive way of doing. This requires a mindset shift in clinical trial development and an approach of intentionality to ensure the strategy will move beyond the superficiality of a plan. In order to be successful, the plan will require a collective effort by physicians, scientists, and healthcare staff to foster strategic partnerships with individuals or groups who serve or represent communities with a diverse population. This may include community outreach programs, community leaders, and local patient advocacy groups. These relationships will be essential to developing pragmatic strategies to deliver value to the diversity plan. Additionally, sponsors can foster improved trust and confidence in medical establishments and clinical trials by adhering to standard ethical practices.

Recent events involving disparities in representation for sex, race, and ethnicity in COVID-19 clinical trials have also brought to the forefront the importance of representation during medical product development.11 Overcoming a lack of diversity in clinical trial enrollment, however, has been a notable issue for decades. Strategies to promote diversity in clinical trials have been largely unsuccessful despite efforts by the FDA and legislative action, such as the National Institutes of Health (NIH) Revitalization Act of 1993,12 which began establishing guidelines for the inclusion of women and other underrepresented populations in clinical research. The updated April 2022 draft guidance is a result of the FDA further developing prior guidance from *Collection of Race and Ethnicity Data in Clinical Trials* (October 2016),[13] which initially recommended development of a formal diversity and inclusion plan for clinically relevant populations, along with guidelines for collecting and presenting diversity data such as race and ethnicity. Additional guidance was presented in November 2020 to provide general enrollment strategies pertaining to eligibility criteria, enrollment practices, and trial design.[14]

Early establishment of enrollment goals and engagement with the FDA is best practice,[1] particularly for indications within rare disease and oncology[15] where End of Phase 2 meetings may fall relatively later in an already expedited medical product development timeline. To establish and implement enrollment goals that support and encourage a more representative, diverse participant population, researchers must be intentional about developing research questions that foster inclusivity. It has been suggested that patient populations and their caregivers should be directly involved in the development phases of clinical trials in order for researchers to truly understand the concerns and needs of the affected population.[4] This could remedy the fact that for many diseases there is still a lack of epidemiologic data available for underrepresented groups, despite the American College of Epidemiology releasing a Statement of Principles to combat the disparity in health and health risks of underrepresented populations in 1995.[16]

After research questions are established and epidemiologic background review has been addressed to the extent possible, the next phase of clinical trial development in which it is crucial for researchers to intentionally keep diversity in mind is the development of appropriate, but not burdensome, inclusion/exclusion criteria. Clinicians and trial staff can utilize feedback derived from interviews and surveys from community partners to gain insight on the needs of individuals within the target populations and how best to improve their patient experience.[4] Lastly, budgeting considerations should be addressed during protocol development to guide clinical trial operations and diversity plan implementation. To operate efficiently, each site should possess adequate resources and staff to fulfill the needs of the trial, which ultimately stems from sufficient budget allocation.

Successfully implementing strategies to boost diversity in clinical trial enrollment will not come without its challenges, as history has shown. A study conducted in 2015 investigating factors leading to low accrual rates for cancer trials found that physicians did not regularly review available protocols and eligibility criteria, resulting in exclusion of up to one-third of patients who otherwise may have been eligible for trial participation.[17] Of new adult cancer patients, approximately 2% to 7% participate in clinical trials.[18] Some patient-reported reasons for non-participation include the desire for other treatment (34%), distance from the clinic (13%), and insurance denial (8%).[17] Geolocation of trial sites has also been reported as a barrier to clinical trial participation, and there is an unfortunate reality that clinical trial site selection does not always place emphasis on patient location. Those residing in rural areas have limited access to urban sites/centers where clinical trials typically take place.[19] An example of this was shown through an analysis of trial accessibility for 277 active trials in 2012 with 5,011 sites which reported that patients with metastatic breast, prostate, colorectal, and non-small cell lung cancer would have a one-way commute of 1 hour or more to their treatment site.[20] To remediate these issues, decentralizing clinical trials is essential and can be achieved by leveraging local pharmacies as trial access points, employing mobile nurses to collect samples at the patient's home, and utilizing local hospitals and clinics for any necessary specialized services.[21] Simply reducing the patient's perceived barriers to participation has been shown as a positive predictor for a greater frequency of participation, reported by a study measuring the frequency of mammograms for breast cancer screening in rural Appalachia.[22]

As we pivot toward de-centralization of clinical trials, logistics of data collection must be considered and addressed. Sincere efforts to follow established standard operating procedures at satellite clinical trial locations or in the patient's home per protocol needs will help ensure validity of data and mitigate confounding variables that may be encountered. Additionally, staff should be trained to present clinical trial materials that are culturally relevant, age-appropriate, linguistically appropriate, and available in alternative formats.[23] Advertising materials should also possess the same characteristics in order to properly inform and effectively engage potential participants within the target audience. In addition, a staff that is as diverse and collectively representative of the population being served may inherently have mindsets

conducive to establishing better connections, care, and communication with prospective participants, enabling more effective messaging and perhaps greater study recruitment. As diversity plan strategies are implemented and clinical research teams evaluate the effectiveness of their programs, guidance may further evolve and better adapt to overcoming barriers to participation and retaining participants throughout the life of the trial.

## Bridging the Diversity Gap

By considering factors such as barriers to enrollment and working to reduce the burden of participation, sponsors can make participation in clinical trials more accessible and equitable for individuals from underrepresented, and often underserved, populations. Though there have been several iterations of evolving regulatory guidance to enhance diversity in clinical trials in the past, many of those efforts have proven to result only in isolated changes by individual research groups and not the global impact that is needed.[23,24]

Reform of current methodology for clinical trial enrollment is necessary to better enable detection of differences in safety and efficacy of medical products that may be associated with characteristics of race and ethnicity, and early enrollment will expedite this detection. Implementing a structured diversity plan will also help ensure adequate representation of various race and ethnicity populations that will benefit from treatment or use the medical product, which will lead to better generalizability of study data.

Additional outcomes from plan implementation include facilitating greater speed of data acquisition and safer medical product development, while concurrently contributing to a better understanding of how disease processes may differ in these diverse populations. Promoting diversity in clinical trials has the potential to unlock unrealized innovation, collectively benefitting the advancement of medicine and health of society.

Full details on the current draft guidance can be found at FDA.gov.

**Recent events involving disparities in representation for sex, race, and ethnicity in COVID-19 clinical trials have also brought to the forefront the importance of representation during medical product development.**

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