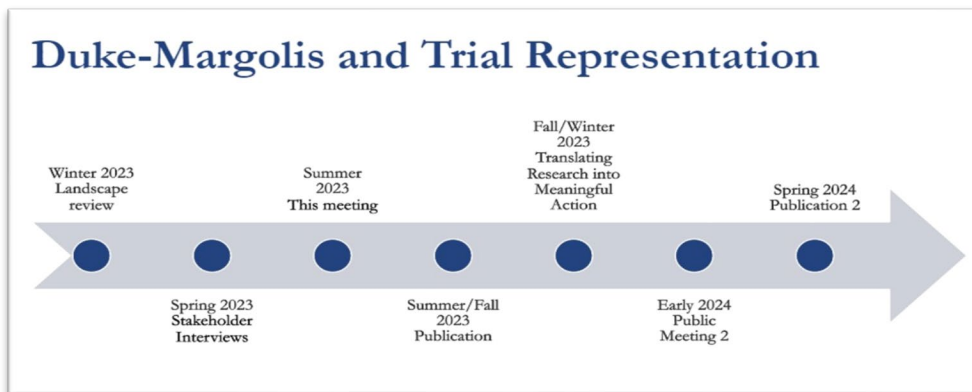


## Advancing Representative Enrollment in Clinical Trials

### Introduction

Clinical trials conducted within the U.S. are affected by structural and systemic complexities that can result in failure to address important clinical research questions quickly, equitably, and efficiently across a range of treatment and disease areas. Data collection burdens on providers, sometimes onerous study protocols, as well as the pressure to enroll narrowly-defined patient populations often render such trials feasible only in well-resourced centers like large academic medical centers — complicating the breadth, quality, generalizability, and equity of clinical trial evidence due to the lack of representation within the trials. In addition, unrepresented populations that clinical trials should enroll often experience systemic exclusion and institutional mistrust. As the need for rapid, rigorous, and generalizable evidence increases, and technology support for clinical data collection improves, there is a growing impetus to reimagine trial conduct to improve trial representation without compromising vital research standards.

The early stages of this project were conducted in two phases including a landscape review phase and an interview phase. The landscape review entailed reviewing extant literature and published materials. The interview phase involved 60-minute virtual interviews with 17 subject matter experts and stakeholders across the research, public, and private sectors. The final outputs for the project will be informed by the landscape review, stakeholder interviews, and workshop insights.



### Key Definitional Components Related to Trial Representation

- **Trial Diversity Vs Representation:** The distinction between trial diversity and trial representation is an essential component of discussions around equity. [An equitable clinical research infrastructure](#) would be comprised of clinical trials and studies that accurately match the demographics of the disease burden under study. Findings from our review indicate that it is important to acknowledge that disease burden as quantified in the research literature or the available data, does not always reflect the true disease burden due to disparities in care access that are a direct result of structural racism and discrimination.
- **Point of Care Trials:** Pragmatic approaches to clinical trial conduct, such as point-of-care trials, may improve representative enrollment for patient populations that are already embedded within a health system or clinic. Two often-recognized components of point-of-care trials include 1) integration of clinical trial conduct with electronic health record (EHR) systems and 2) trial conduct in usual care conditions. Expanding these trial designs across clinical sites may help to expand representativeness within populations with access to healthcare services. It is

important to acknowledge that sustainable change may be difficult in a clinical trials enterprise that is heavily impacted by larger structural and societal problems. For example:

- Pragmatic trial approaches are not a panacea for systemic barriers such as being uninsured/underinsured, lack of provision for health-related social needs, as well as limited bilingual or bicultural clinical personnel and staff, implicit bias, and discriminatory experiences within healthcare settings
- “Recruitmentology” tactics have the propensity to lead to further exploitation of research subjects
- Misaligned funding and power structures continue to serve as barriers to creating longstanding and sustainable partnerships across sectors and stakeholders

### Landscape Review Findings

- A landscape review of current practices in clinical research revealed that most trial cohort demographics are not sufficiently representative, and this lack of representation varies by disease area. Overall, white patients are overrepresented in clinical trials, and a [2022 National Academies report](#) showed little progress in enrolling underrepresented racial and ethnic populations. This lack of representation has been linked to various factors, including medical mistrust; trial availability, access, and eligibility; and lack of education surrounding trial participation. Despite efforts to increase data reporting, many studies do not publish or report data on race/ethnicity, sex orientation and gender identity (SOGI), and other demographic information.
- Past legislative efforts at improving representation in trials, such as the National Institutes of Health Revitalization Act of 1993 and the 21st Century Cures Act, have had little impact. NIH policies do not apply to the private industry-directed trials that account for most premarket studies of investigational products. In addition, NIH reporting requirements for drug sponsors are often not enforced: [the majority of trials on clinicaltrials.gov over the past 20 years have failed to report race/ethnicity data.](#)
- Stakeholders across the clinical trials enterprise, including sponsors, regulators, academics, and payers have proposed and implemented solutions to address the issue of representation in clinical trials with varying success. Rethinking the traditional explanatory trials and opting for more pragmatic approaches to clinical research where appropriate may be important in future efforts to increase representation in trials.

### Relevant Policy Actions

- The federal government as well as private research foundations have set standards and requirements for encouraging representativeness in clinical trials. Under new FDA reform legislation passed by Congress, FDA will require drug sponsors to [submit diversity action plans](#) for their trials.
- In 2020, Congress passed the [Clinical Trial Treatment Act](#), which requires all state Medicaid programs to cover routine costs associated with qualifying clinical trials. This act went into effect beginning in 2022.
- In 2022, the National Academies released a report titled: *Improving Representation in Clinical Trials and Research: Building Research Equity for Women and Underrepresented Groups*.

## Notable Initiatives and Metrics

- Solutions at the payer level may increase trial representation by strengthening community-academic relationships. One [initiative](#) between Harvard Catalyst, Harvard University's clinical and translational science center and Blue Cross Blue Shield of Massachusetts' Community Coalition for Equity in Research will provide input to specifically address diversity and equity on research proposals.
- Academic journals have implemented new, rigorous standards for publishing on health equity topics, and some journals have required that authors include data on trial representativeness when publishing trial results.
- Initiatives by academic groups, such as [Good Pharma Scorecard](#), focus on the idea of public accountability for drug sponsors in ensuring representative trial cohort selection. Good Pharma Scorecard rates drug sponsors on the representativeness of their trials.
- Commercial actors within the drug development space have engaged in voluntary efforts that address clinical trials representation, such as holding investigator training programs, establishing a wider variety of trial site settings, creating tools and templates for trial design, and implementing workplace diversity programs.
- In 2023, the Clinical Trials Transformation Initiative (CTTI) [released recommendations](#) for improving diversity in clinical trials and a corresponding maturity model.
- The Reagan-Udall Foundation for the FDA, in collaboration with FDA's Office of Minority Health and Health Equity, launched the [Real-World Accelerator to Improve the Standard of collection and curation of race and Ethnicity data in healthcare \(RAISE\)](#) project. RAISE intends to elevate the capture and curation of race and ethnicity data in health care settings to ultimately improve the quality of health care and medical products through community workshop and the development of a multi-dimensional tool for improving the capture and curation of race and ethnicity data.
- FasterCures recently released [Mapping the Journey: Building a Mutual Understanding for Health Equity in Clinical Research](#). It details practical recommendations for achieving health equity at different types of trial sites and a visual illustration of how a patient might experience a typical clinical trial.
- The FDA's Office of Minority Health and Health Equity is engaged in a variety of initiatives aimed at improving representation in research, including the [Enhance EQUITY Initiative](#). Enhance EQUITY supports efforts in making trials more representative, increasing research studies about diverse groups, and amplifying FDA's communications with diverse groups.

## Future Directions

- While some of the solutions outlined may improve the representativeness of clinical trial cohorts, meaningful, sustainable change may be difficult in a clinical trials enterprise that is heavily impacted by and helps maintain larger structural and societal problems. Avoiding "[recruitmentology](#)" tactics, or simply using extractive methods to recruit higher levels of historically marginalized patients, is important in not further exploiting research subjects and narrowing the gap in comfort levels between different groups that may participate in clinical trials.
- Systemic barriers such as a lack of insurance, transportation, resources, etc. as well as limited bilingual or bicultural clinical personnel to staff and lead clinical trials, will continue to be a concern for trial participation and may impact retention. Creating longstanding and sustainable partnerships across sectors and stakeholders will be necessary for change.
- No consensus has emerged on enrollment goals or on how to measure adequate demographic inclusion, and thus, how to assess the success of these policies. Without compulsory data reporting, it will be difficult to tell if sponsors are meeting enrollment goals. Going forward, defining

representation goals and streamlining data reporting requirements will be important in measuring progress toward achieving more representative trial participation.

## **Interview Themes**

A number of themes emerged across stakeholder groups and interview participants. An overview of the thematic areas that we will be exploring during our discussions during the workshop is included below.

### ***Theme 1: Measurement considerations for assessing trial representativeness***

Stakeholders identified several measurement considerations for trial representation including (a) the inadequacy of current race and ethnicity measurement (b) acknowledgment that prevalence rates may not be accurate representations of disease burden (c) the need for widespread adoption and consistency in benchmarks used to evaluate representation and (d) the need to synergize representation metrics nationally and internationally.

### ***Theme 2: Barriers and opportunities in sustainable community and patient engagement***

Interview participants noted that there are both historic and current health system and research practices that discourage trial participation. Accordingly, it is important to acknowledge the role of systemic and structural racism in the underrepresentation of marginalized groups (e.g., ethnic and racial minorities, uninsured and underinsured patients).

Interview participants articulated that researchers and sponsors often go into communities to conduct studies without an understanding of the needs/interests of the community. It is essential for researchers and sponsors to establish ongoing relationships with organizations in the community so they can adequately gauge community needs and priorities and build a research network that ensures that they are not restarting the relationship-building process each time there is a new study. Relatedly, awareness, education, and health literacy are under-discussed barriers to trial participation. For example, some members of underrepresented groups would participate in trials if they were aware of their eligibility or had accessible information about the trial, including accessible information about the benefits and risks associated with participation.

Additionally, many interviewees noted that trials sponsors and researchers can make more overt efforts to align incentives and provide broader benefits for participants. Interview participants noted that in many instances, the incentives associated with trial participation are not commensurate with the burden placed on patients and/or communities. Accordingly, there can be more overt efforts to ensure that at a bare minimum, participants and communities are fairly compensated for the time and burden (e.g., transportation costs, childcare costs) associated with participation, and provided with findings from the study in an accessible format. In instances when a study involves the participation of a particular community, sponsors and researchers should consider methods for providing sustainable benefits to the community, either in the form of knowledge or related programs and infrastructure.

### ***Theme 3: Modernizing trial processes by wider implementation of pragmatic design approaches***

Stakeholders frequently highlighted the propensity for pragmatic trial approaches, including point-of-care trials and decentralized trials, to serve as strategies for improving representation of patients that are already embedded within care settings. Modernized clinical trial designs, including pragmatic trials, can be more flexible and accommodating to patients than traditional explanatory trials when they take place in community settings. Pragmatic trials can reduce the amount of resources patients need to participate in

trials, and often leverage existing trusted healthcare provider relationships for increased patient comfort with research. However, stakeholders noted that there are systemic changes that would need to occur to ensure that decision-makers are confident in these approaches and that the appropriate infrastructure is in place for robust data collection and provider and patient support to enable widespread adoption. Additionally, it is important to acknowledge that pragmatic trial approaches are not a panacea to systemic and structural barriers that continue to impede representative participation.

#### ***Theme 4: Importance of instituting formal policies***

Interview participants cited the possibility for regulatory agencies, funders, and research institutions to implement more overt rules and regulations to ensure that representation is not an afterthought in research studies and clinical trials. Many participants also cited new policies and additional potential modifications to existing regulations that may advance representative enrollment. Examples include:

- Regulatory and funding requirements for all applicants to submit a representative enrollment plan that outlines the plan for enrolling and engaging with patients most impacted by a disease or condition *before* conducting a study, including the new guidance from the FDA on diversity plans.
- Enlisting research journals and publishers in instituting representation publication requirements and publishing metrics for representative enrollment.
- Modifying existing funding structures to make it easier to provide compensation to community workers and patient-facing groups.

### **Workshop Objectives and Key Questions**

#### **Session 1: Defining the Current Clinical Trial Landscape**

*Objective:* This session will describe current challenges to achieving representative trial enrollment from the perspective of various stakeholders. Panelists will discuss the best ways to measure success in achieving representation goals, the impact of the current policy and regulatory landscape, and progress made in recent years to advance representative trial enrollment.

1. How can stakeholders such as research institutions, funders (e.g., NIH), and research journals, work together to implement cohesive representation metrics and policies?
2. Based on early efforts, are there any emerging challenges to implementing FDA diversity plans?
3. What are the potential pitfalls of instituting universal representation policies?
4. What metrics are needed to evaluate the success of representation policies?
5. How can we best incorporate intersectionality into our approach to measurement and metrics development?
6. What steps are needed to synergize these measurement dimensions across stakeholder groups?
7. Can real-world data based approaches help? If so, how?
8. How can the FDA best work with regulatory agencies in other countries to unify and harmonize how representation is measured?

## **Session 2: Building Capacity for Representative Trials in Community Settings**

*Objective:* This session will discuss broad strategies and areas of opportunity for improving representative trial enrollment through community engagement and capacity building. Panelists will discuss alternative approaches to clinical trials, explore the role of education and community partnerships in promoting representative enrollment, and consider financial, technological, and cultural barriers to trial implementation in community settings.

1. What strategies can be used to replicate and scale successful community engagement initiatives across various clinical sites?
2. What are examples of initiatives that have helped to build or restore trust among potential trial participants that have experienced historic and contemporary structural racism or discrimination within health systems?
3. What state, federal, or institutional policies are current barriers to fair compensation for trial participants?
4. What resources and funding structures can be mobilized to support access and information barriers faced by potential trial participants?
5. What funding resources can be used to enable resource strained clinical sites/systems to conduct clinical trials?

## **Session 3: Defining the Role of Various Stakeholders in Improving Trial Representation**

*Objective:* This session will discuss actionable next steps for various stakeholders and relevant accountability measures for ensuring progress on trial representation efforts. Discussion will include how to best foster a culture of representative and trustworthy research, the role of point-of-care trial and other innovative trial approaches, opportunities to further introduce or refine policies to encourage representative enrollment, and potential strategies for addressing major remaining gaps to broader representative enrollment.

1. What are the primary factors industry sponsors should consider when implementing representation goals?
2. What steps should researchers, industry, and broader stakeholder groups take to acknowledge historic and current practices that discourage marginalized populations from trial participation?
3. What approach(es) should industry sponsors and academic researchers that do not currently have established relationships with patient groups and communities use to start the relationship-building process?
4. If fair payment for participation in clinical trials becomes more common, what changes need to be made to funding paradigms for clinical trials?
5. What role can journals play as a final opportunity for transparency on trial representativeness?
6. What should stakeholders be doing now to implement point-of-care and decentralized trials to advance more equitable access to clinical research?

*Support for this event was provided by the Robert Wood Johnson Foundation. The views expressed here do not necessarily reflect the views of the Foundation.*