IQVIA INSTITUTE FOR HUMAN DATA SCIENCE

Advancing Diversity in Clinical Development through Cross-Stakeholder Commitment and Action

AN UPDATE ON PROGRESS AND RESULTS

NOVEMBER
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Introduction

The call for achieving representative diversity in clinical trials and development programs is not new — and indeed dates back more than five decades in the United States — but has been amplified over the course of the COVID-19 pandemic as the striking disparities in health outcomes among diverse populations became evident. At the same time, there has been a marked increase in the level of visibility, attention, commitment, and action by multiple stakeholders to address this issue.

The purpose of the research incorporated in this report is to measure the progress that has been made in increasing participation by racial and ethnic groups – with a principal focus on Black/African Americans and Hispanics – in clinical trials. We recognize that "diversity" can be framed in many different ways beyond race and ethnicity, and that there are limitations to what can be measured as well as time lags between action taken and results reported. Nevertheless, we believe that looking at both historical and the latest available information provides a useful evidence base against which future progress can be measured.

We also highlight in this report where we see tangible progress being made, lessons learned and applied, and a positive shift among the many stakeholders involved in pursuing improvements in clinical research representativeness.

The study was produced independently by the IQVIA Institute for Human Data Science as a public service, without industry or government funding. The analytics in this report are based on proprietary IQVIA databases and/or third-party information and insights derived from IQVIA's management of specific clinical trials after the masking of those trials and sponsors.

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Overview

Disparities in patient outcomes across many dimensions — including race, ethnicity, gender, age, and socio-economic status — are significant and persistent in the U.S. and globally. These disparities can be attributed to many intersectional drivers related to healthcare awareness, access, and delivery, in addition to genetic contributions. These disparities extend to clinical development programs for new pharmaceutical medicines. Addressing these disparities in clinical development can help bring earlier insights, expand access to care, advance understanding of optimal patient care, and accelerate innovation. Building an understanding of potential safety and efficacy variability across patient sub-groups is a continuous process, and requires focus from target discovery and exploratory trials, through confirmational clinical trials, to study in post-approval real world settings.

Achieving diversity in clinical programs that aligns to demographics of patients afflicted with any given disease will require partnership across key clinical development delivery stakeholders, including regulators, pharmaceutical sponsors, CROs, laboratory providers, and other clinical trial delivery partners, principal investigators and site staff, patients, communities, caregivers, and patient advocacy groups. Each of these stakeholders has a role to play in addressing diversity, and clinical programs can fall short of diversity objectives and long-term sustainability when stakeholder needs and collective potential are not aligned.

Stakeholders in the U.S. have been discussing diversity in clinical trials for at least the last 50 years and a dramatic increase in diversity data reporting on global Phase II and III trials with industry involvement has occurred in the past six years, peaking in 2018. Specifically, diversity data collection and reporting ranged from 28% of completed trials in 2012 to 40% in 2016, before doubling to more than 80% in 2017 and 2018. Analysis of this data shows both Black/African American and Hispanic participation in Phase II and III trials fall short of 2020 U.S. demographics levels of 13.6% and 18.9% respectively. Black/African American participation has been declining over the past decade, falling from about 12% in 2012 to less than 10% in 2019 and 2020, and to a low 6% in those trials completing in 2021 that have reported data. Hispanic participation increased from 7% in 2012 to a high of just under 10% in 2017 before declining to 8-9% in the past two years.

Notably, clinical trials with only U.S. sites represent about 40% of all Phase II and III trials and are closer to alignment with U.S. demographics. Specifically, trials with U.S. sites only reported as many as 18% of study participants as Black/African American in 2013, but this share has fallen over the decade to 14.3% in 2020 before falling dramatically to just 9% in those trials completed in 2021 for trials reporting data. Hispanic participation rates in U.S.-only trials are only slightly higher than global trials and peaked at 13% in 2017 before falling to less than 10% in the past three years.

Additionally, sub-population inclusion in trials shows variability by therapeutic areas where Black/African American participation in trials completed in 2020 for psychiatry, hematology, and infectious disease, exceeded the overall U.S. demographic level — and in the case of psychiatry reached 30% of the total trial population. Black/African American participation in oncology trials was less than 5% overall. Hispanic participation exceeded the overall U.S. population level for hepatology, as well as for endocrinology and rheumatology when considering trials with only U.S. sites, but oncology, hematology, allergy/immunology and cardiovascular trials had 6% or less representation by Hispanics.

Contextualizing clinical trial diversity based on underlying epidemiology of the relevant disease is important to determine where the largest gaps exist, and tools like the “Inclusivity Quotient” can now provide such comparative measures. This type of tool can help quantify how much a clinical trial departs from real-world distribution of the underlying disease across sub-populations, can compare trials and development programs systematically, and can identify which trial group most contributes to departure from real-world distribution. Applying the Inclusivity Quotient to trials conducted over the past 10 years in a

range of disease areas reveals migraine has the greatest inclusivity on average, while Alzheimer's disease has been the least aligned to the underlying population. The Inclusivity Quotient also reveals very large variability across trials in each disease area, and no notable improvement over the last decade.

In recent times, stakeholders have made significant commitments to support and enable diverse clinical trials, and examples of progress and success cases provide important building blocks for future progress. Starting with regulatory, ongoing clarity from the FDA in the form of guidance, feedback and decisions has increased in the last five years, including the 2022 draft guidance and recent complete response letters or post-approval requirements that are associated with diversity requirements. Payers — notably CMS — have examples of being much more explicit in their requirements, primarily in the case of a drug for Alzheimer's disease where restricted reimbursement under Coverage with Evidence Development was explicitly linked, at least in part, to lack of racial and ethnic representation in current clinical development data.

Most large pharmaceutical companies have also ramped up public commitments to close clinical trial diversity gaps, including establishing clinical trial diversity web pages, generating thought-leadership on the topic, and creating roles and updating organizational structures to operationalize diversity focused initiatives. Operational solutions around inclusive early trial planning, diversity metric tracking, selection of sites, and execution of study participant recruitment programs — often undertaken by CROs or other vendors on behalf of sponsors — have become more sophisticated through the application of data- and technology-driven approaches and show significant impact in recent cases studies.

Success cases from sites that consistently over-recruit study participants relative to their demographics highlight some of the critical factors to engage under-represented populations in the clinical trial process. Building trust with community members at a site was the most often mentioned driver of success in recruiting under-represented populations. Providing trial support that can help participants overcome socio-economic-linked barriers, such as transportation support and scheduling flexibility is critical. Finally, delivering continuous patient value before, during and after a trial is also an important factor to building trust with individuals in the community.

Patient advocacy organizations have taken a prominent role over the past decade in ensuring better representation of sub-populations in clinical trials and have implemented many impactful approaches. These include awareness building and establishment of trust through community-based outreach programs (e.g., Metastatic Breast Cancer Alliance BECOME Research Project), empowerment of patients to pursue clinical trial opportunities through proactive tools that help address critical barriers to participation (e.g., Tigerlily Foundation Barrier Toolkits, ANGEL Advocacy Training (educating, empowering and engaging patients in high-risk underserved communities)), and policy shaping through advocacy around legislation such as PDUFA reauthorization and reimbursement regulations to seek instantiation, accountability and clarity to structurally address known barriers to inclusive research participation.

All biomedical research system stakeholders have significant opportunities to build on the current momentum and achieve greater progress in solidifying and advancing clinical development diversity gains. Setting goals for what "good" looks like and measuring progress against those goals using aligned and objective methods is imperative and requires transparent metrics of activity and outcomes that go beyond current regulatory requirements. Visibility to clinical trial diversity goals and making progress toward them at all levels can help align stakeholders and enable collaboration and support across the ecosystem of players and help drive toward the shared goals of truly inclusive clinical development and reduced disparities in healthcare outcomes.

Imperative for representative diversity in clinical development

+ **Disparities in patient outcomes – across many dimensions – including race, ethnicity, gender, age, and socio-economic status – are significant and can be attributed to many intersectional drivers related to healthcare awareness, access, and delivery, in addition to factors related to genetics**

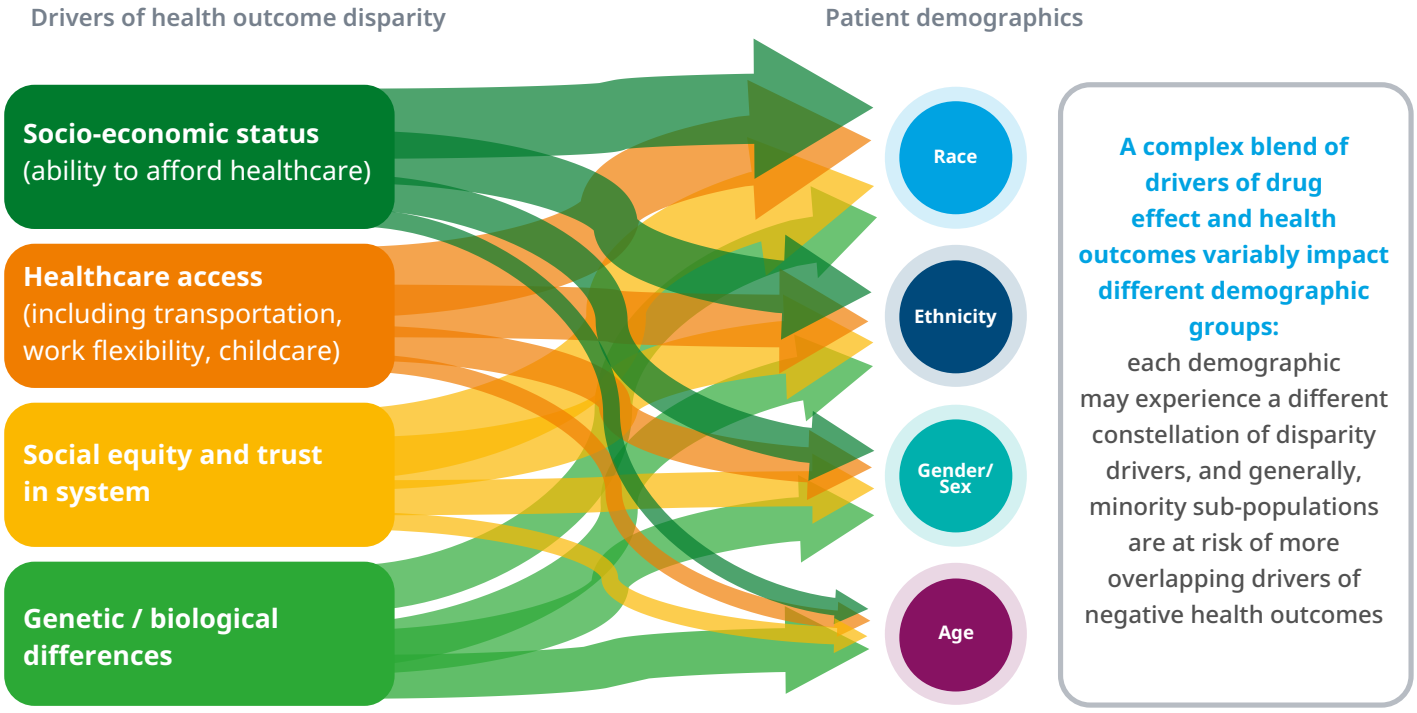
+ **A comprehensive clinical development program that addresses diversity – from early exploratory studies through randomized clinical trials and post-approval studies – can advance understanding of optimal patient care, expand access to care, bring earlier insights, and accelerate innovation**

+ **Multiple stakeholders have roles to play in addressing diversity, and initiatives can fall short of objectives and long-term sustainability when stakeholder needs and collective potential are not aligned**

HEALTH OUTCOME DISPARITIES

Concerns about health outcome disparities across patient sub-populations persist globally and have been accentuated during the COVID-19 pandemic. They are observed across multiple dimensions including gender, sexual orientation, race, and ethnicity.[1–4] Disparities linked to these sub-populations can be attributed to many proximal causes such as diet, exercise, stress, environment, and medical adherence that, in turn, are a function of broader instantiated factors that limit fundamental health and wellness awareness. These broader factors include socio-economic status, access to healthcare — including routine or risk-factor driven screening, diagnosis and healthcare delivery, social equity and trust, and explicit racial bias in the system.[5–7,] Additionally, sub-populations may be predisposed to certain genetic and epigenetic differences that impact response to environmental impacts or medical interventions.

Exhibit 1: Intersectionality of drivers of health outcome and patient demographics



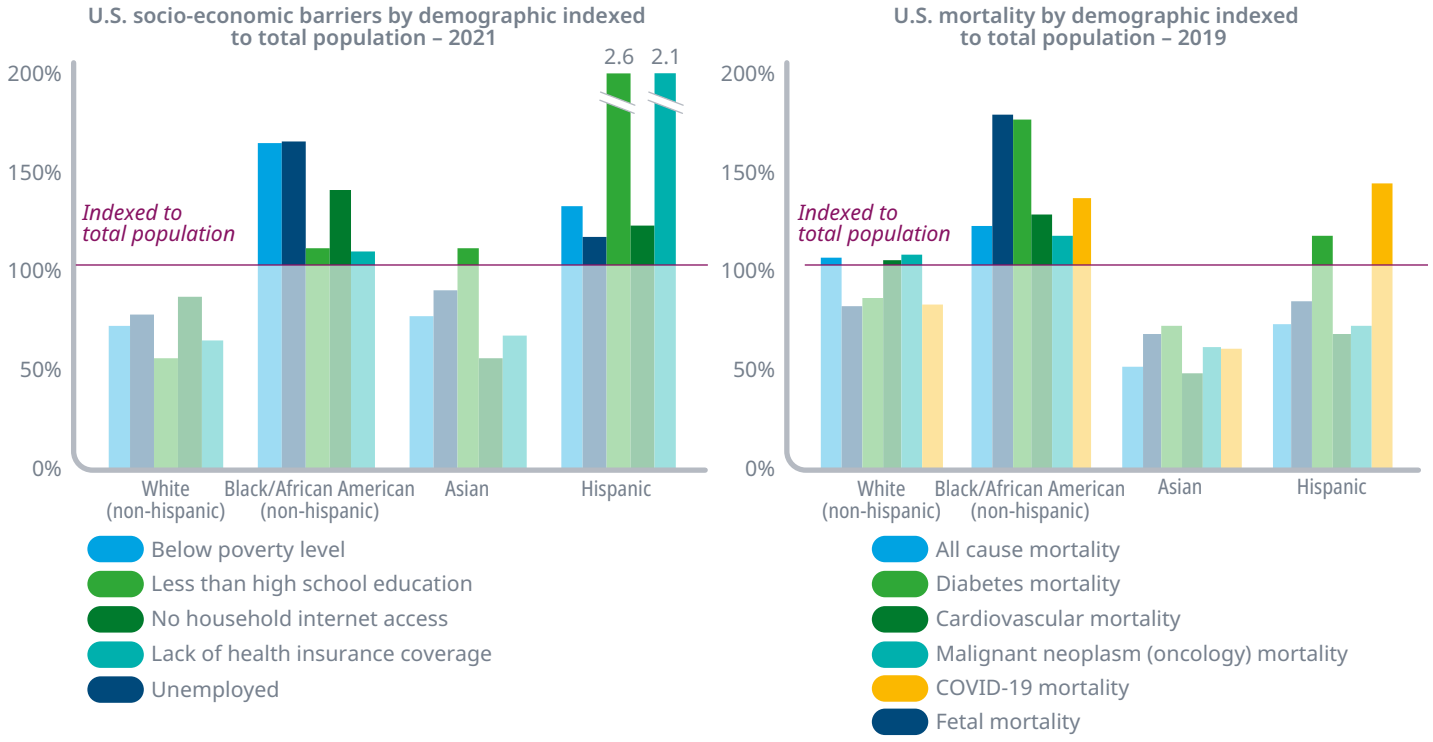
Source: Link BG, Phelan J. Social conditions as fundamental causes of disease. J Health Soc Behav. 1995;Spec No:80-94; IQVIA Expertise; IQVIA Institute, Oct 2022.

All of these factors are at play in a complex intersectionality, with minority sub-populations disproportionately impacted by drivers of health outcome disparity (Exhibit 1). Specifically, socio-economic disadvantages and barriers to healthcare access disproportionately impact Black/African American and Hispanic sub-groups in the U.S. and correlate to comparatively poorer health outcomes when compared to White or Asian counterparts (Exhibit 2).[8,9]

From a socio-economic standpoint, Black/African Americans are exposed to rates of poverty and unemployment 60% higher than the total U.S. population, and the rate of education achievement less than high school graduation or lack of health insurance is nearly double in Hispanic communities compared with the total U.S. population. These socio-economic disadvantages and barriers to healthcare access correlate to comparatively poor health outcomes compared to White or Asian populations. All-cause mortality rates are 20% higher for Black/African Americans, with fetal mortality and diabetes mortality over 90% higher than for the total U.S. population. Diabetes mortality is 30% higher for Hispanics than for the total U.S. population, and both Black/African American and Hispanic communities experienced COVID-19 mortality at rates more than 540% higher than the total population in the early stages of the pandemic.

These negative impacts can be amplified in situations where incidence of disease disproportionately affects a sub-population, and this is known to be the case in several important disease areas, including breast cancer and lupus.[10,12]

Exhibit 2: U.S. racial and ethnic socio-economic and health outcome disparities



Source: U.S. Census Bureau, 2021 American Community Survey 1-Year Estimates; National Center for Health Statistics. Health, United States, 2021: Table Age-adjusted death rates for selected causes of death, by sex, race, and Hispanic origin: United States, selected years 1950–2019. Hyattsville, MD. Available from: https://www.cdc.gov/nchs/hus/data-finder.htm; IQVIA Institute, Oct 2022.

Notes: Rates for races other than White and Black/African American should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate (death rate numerators) compared with population figures (death rate denominators). The net effect of misclassification for these race groups is an underestimation of deaths and death rates.

CLINICAL DEVELOPMENT DISPARITIES

Patient sub-population disparities also extend to participation in clinical development.[12–14] Failure to include adequate representation from key sub-populations risks failing to identify potential differences in therapy efficacy or safety in populations that may have varied response due to intrinsic or extrinsic factors. These gaps in understanding can lead to timeline risks to full regulatory approval and drug availability, while additional sub-population data is collected. Operationally, failure to address diverse sub-populations in recruiting efforts may also be leading to delays in trial completion versus what is possible if untapped patient groups are included.

Additionally, failure to include a representative population in clinical trials reflects and exacerbates health equity gaps, undermining understanding and uptake of new therapies among understudied populations, furthering treatment and health outcome gaps. A key outcome of equitably enrolled clinical trials is physician experience in these trials. Given the central role of evidence-based medicine in medical practice, physician experience with a novel therapy in a particular patient population is an important consideration in ensuring broader use of the novel therapy in that population.

Participation in clinical trials provides patients and providers access to healthcare and firsthand education and experience with novel therapies. Including a broader set of community-based and minority physicians in clinical research will be important to extend the physician experience base with the product, while also extending access and trust with under-represented patients treated by these physicians. Taken together, failure to enroll representative populations drive a risk that clinical trials for new medicines approvals may not provide the necessary information and experience for optimized drug approval, risks delaying or impairing inclusive patient access to new drugs thus reinforcing health disparities within the system.

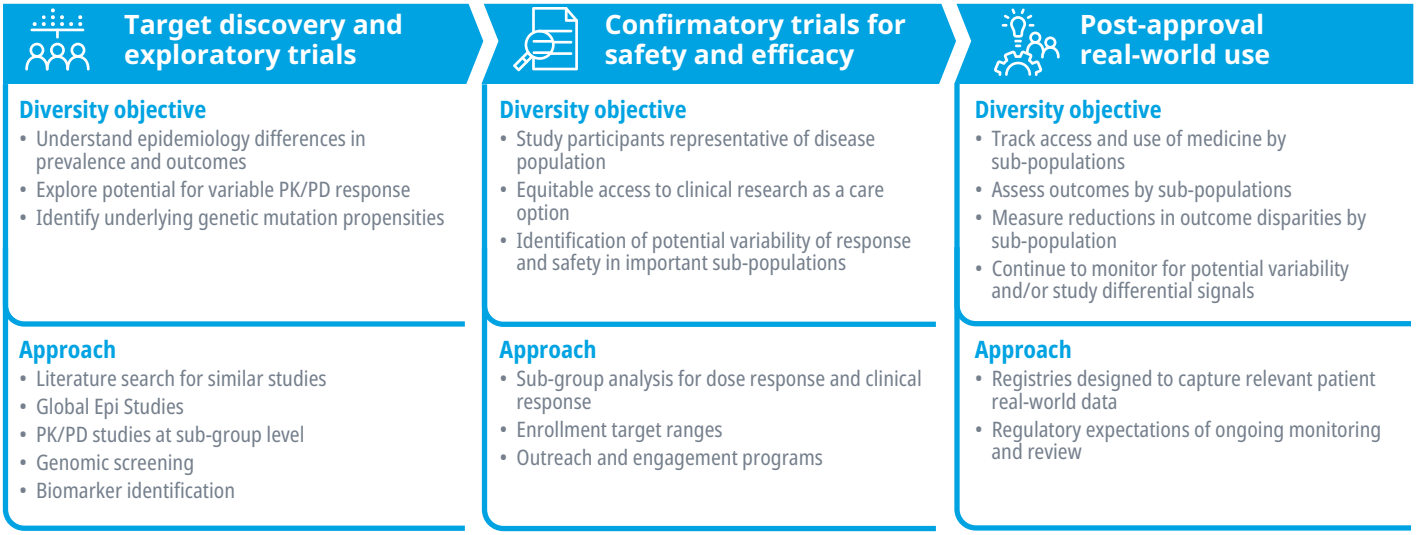
PROGRAMMATICALLY ADDRESSING DIVERSITY IN CLINICAL DEVELOPMENT PARTICIPATION

Building an understanding of potential safety and efficacy variability across patient sub-groups should be a continuous process and requires comprehensive focus across the entire clinical development program of a new therapy– from target discovery and exploratory trials through confirmational clinical trials to study in post-approval real world data collection (Exhibit 3). A key clinical development program goal should be to build a solid evidence base over time that increases confidence that if any clinically meaningful differences in safety and efficacy between sub-population responses do exist, they are identified and explored as early as possible and are factored into each stage of clinical trial planning. The latest draft diversity guidance from the FDA, echoes this concept by renewing the 2016 call for diversity plans to be submitted 'as early as possible' and before the end of Phase II meeting.[15]

Additionally, in the specific format and content recommendations, FDA asks for evidence of any differential findings from clinical pharmacology studies (PK/PD data, pharmacogenomics), underscoring the expectation of earlier and intentional exploration of potential differences in both real-world and program-specific data. The guidance explicitly recommends that sponsors should be using existing research and real-world data in early program planning, and that they should describe any available evidence to support differential in the disease or early study data and be prepared to address any representation gaps in the clinical program via data collection in the post-marketing setting.

A critical objective of early clinical diversity planning is to understand the underlying epidemiology of the disease, and patient demographic and geographic differences in disease outcomes in the real world to ensure research includes a representative patient population. As early as Candidate Drug Nomination, the study of demographic data and multiple real-world data sources to characterize these factors as well as the health outcomes on related therapies should begin.

Exhibit 3: Building diversity into clinical development programs



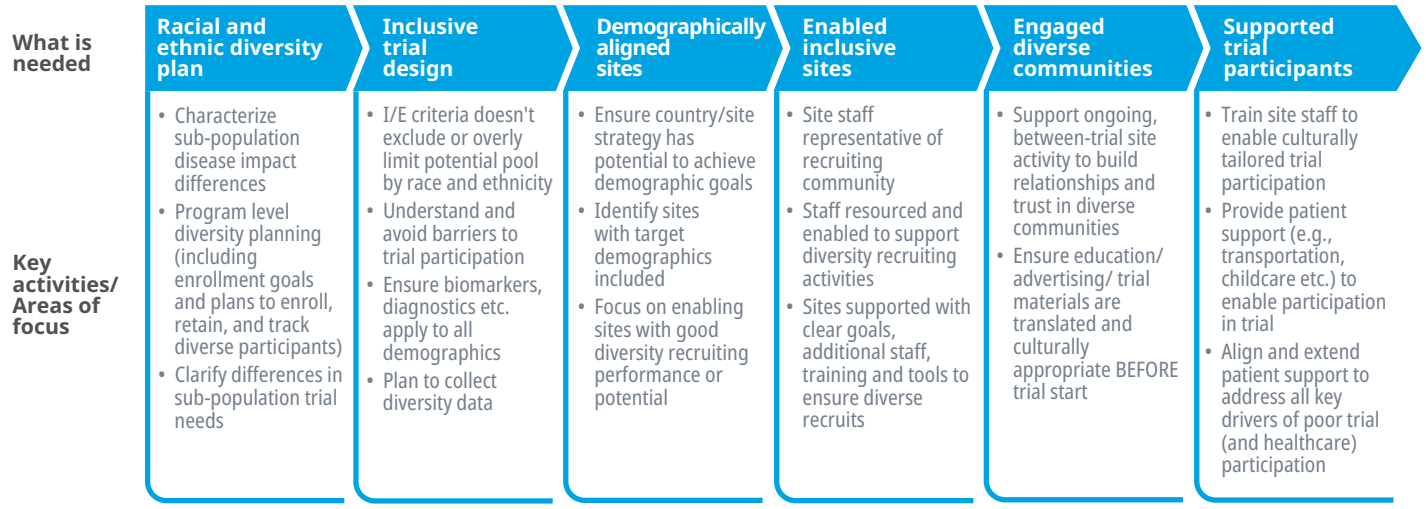
Source: IQVIA Expertise; IQVIA Institute, Aug 2022.

This analysis should seek to identify potential safety signals and/or potential differences in health outcomes that may be relevant to future sub-group analysis. Based on research and pre-clinical findings and literature review of disease and drug mechanisms, researchers may be able to identify pharmacogenomic variability of importance to the program and/or other drivers of safety or efficacy differences by sub-group. Ensuring that pharmacokinetics/pharmacodynamics (PK/PD) studies are conducted in diverse patient groups is also recommended at this point in the program.[14]

Trial diversity planning (Exhibit 4) focuses on assessing endpoints in a disease-representative population by ensuring that diverse participants have access to the trial and that sub-population response signals can be detected in the sample set if present. Planning for program diversity requires looking across all trials in the program, and should detail where patients will be found, how they will be engaged, and what sort of support will be needed to successfully include different diverse study participants in each stage of research. The planning and trial design stage also provides sponsors and contract research organizations (CROs) — which may provide trial planning and execution services to the sponsor company – an opportunity to include real-world data, patient insights and past site experiences to fully interrogate inclusion/exclusion criteria and other trial design elements for impact on patient participation. Critical to the design stage is well thought out inclusion/exclusion criteria and optimization of endpoint collection to maximize patient access, minimize patient burden and ensure sub-population response is part of the ultimate data package.

Planning for program diversity requires knowing where patients will be found, how they will be engaged, and what support they will need.

Exhibit 4: Focus areas for building diversity into confirmatory clinical trials



Source: IQVIA Expertise; IQVIA Institute, Aug 2022.

As part of planning and execution, site selection to optimize diverse patients' inclusion in confirmatory trials is a critical consideration. Beyond placing trials in geographies with representative demographics, attention to site performance along diversity metrics — including diversity of site staff — is very important. Trials with sites that have established community engagement and diversity focus and partner with sponsors or CROs to set enrollment goals and provide tracking and monitoring tools and support strategies are likely to be more successful. Additionally, directly engaging hard-to-reach patients who may be challenged in accessing the trial is important to ensure trials are representative of the underlying population. Finally, plans for data collection and assessment to support the potential for sub-population signal detection within trial, and across trials are also recommended in the recent FDA draft guidance. These strategies will be most successful if implemented and assessed on all program trials — not only on pivotal trials.

Finally, exploration of sub-group risk/benefit must extend beyond drug approval, since some effects are not seen until large numbers of patients have taken a drug. Therefore, there is a need to gather and/or analyze ongoing information on diverse sub-population experience with new medicines post-approval to fill gaps that initial clinical program may not have been able to address. Recent examples of this have been seen with accelerated approvals for oncology drugs umbralisib and infigratinib that included explicit requirements for post approval studies targeting racial/ethnic data questions.[16,17] In the case of these accelerated approvals, the follow-on obligation is additional randomized controlled trials. However, there is also opportunity to characterize sub-group outcomes with novel drugs outside of a formal data collection using prescription claims and medical insurance claims database analysis post- approval. To do so will require careful planning and investment consideration to select the right data methodologies (Exhibit 5). In some cases, claims data may be able to provide insight into utilization via geographic demographics only, while on the other end of the spectrum, investment in post-registrational studies and registries to supplement program diversity analysis may be warranted.

Exhibit 5: Post approval diversity approaches and limitations

RATIONALE	DATA SOURCE	OPTIONS		
		APPROACH	VALUE	LIMITATIONS
• Use of RWE provides an opportunity to continue diversity data collection post approval – - This provides a strategic option to balance RCT recruitment/time to market challenges with support to ensuring diverse access and information on drug impacts • Additionally, analysis of RWE through a diversity lens is critical to confirming that clinical trial diversity efforts are driving improved outcomes across all patient segments	Existing data	**Claims data review**	Ability to track drug utilization linked to demographic data	Lacks diversity data – demographics only inferred by geography
		Electronic Health Record (EHR) analysis	Insight on prescription patterns and outcomes with some race/ethnicity data	Single system EHR data often incomplete – longitudinal analysis challenging and demographic data is varied in terminology and completeness
		Integrated system EHR analysis	More longitudinal insight on prescriptions and outcomes with some race/ethnicity data	Can be very expensive and challenging to work with multiple systems; longitudinal completeness still not guaranteed and demographic data varied
	Prospective study	**Post registrational registry/study**	Ability to track outcomes and safety by demographic; clean and complete longitudinal analysis of outcomes	Expensive and time consuming compared to other options

Source: IQVIA Expertise; IQVIA Institute, Aug 2022.

ALIGNING STAKEHOLDER OBJECTIVES FOR DIVERSITY IN CLINICAL DEVELOPMENT

Achieving optimal diversity in clinical programs will require partnership across key clinical development delivery stakeholders and those with critical roles include regulators, biopharmaceutical and medical-technology sponsors, CROs, laboratory providers and other clinical trial delivery partners, principal investigators and site staff, and patients and patient advocacy groups. Each of these players has a commitment to optimizing diversity in clinical programs but balances this objective with other program goals including speed and efficiency in bringing new medicines through the development cycle and regulatory approval and ultimately to the patient. This need for balance, and management of potential trade-offs on stakeholder objectives underscores the need for coordinated planning when building an optimally diverse clinical development program (Exhibit 6).

While all stakeholders involved are aligned around the central objective of optimizing trial participation to best represent patients who will use the investigational medicine, there are other objectives that stakeholders need to balance to greater or lesser degrees while ensuring diverse research participation. Perhaps central to these is the sponsor/CRO need to optimize for efficiency (optimized speed and cost) in getting a drug to the market while also optimizing for diversity. There is potential for a trade-off requiring greater investment or longer timelines to ensure trials are recruiting patient sub-groups in accurate relation to the underlying disease population.

Engaging broader patient populations may require investments in new sites in alternate geographies, and/or in engaging patients through different channels with a shifted constellation of trial support to ensure successful completion. These activities can drive longer timelines or more expensive trials, especially when diverse recruits are not planned for throughout the clinical program. However, these investments can also actually drive shorter trial timelines when previously under-represented communities of patients are engaged and when development programs have a complete data set to fully assess safety and efficacy and meet regulatory needs after pivotal trial completion.

Furthermore, focus on ensuring representativeness in clinical research leads to a shift in the roles both sites and patients play, and the investments sites make in engaging diverse patients. Because of the intersectionality of

Exhibit 6: Complex mix of diversity objectives across stakeholders

	OBJECTIVES FOR DIVERSITY IN CLINICAL TRIALS			
	INCLUSIVE PLANNING AND TRIAL DESIGN	**DEMOGRAPHICALLY ALIGNED AND ENABLED SITES**		**ENGAGED COMMUNITIES SUPPORTED PARTICIPANTS**
	UNDER-REPRESENTED RACIAL AND ETHNIC GROUPS INCLUDED			
Regulators	**Transparency and diversity focused planning** for entire drug program	Sites with patient populations aligned to U.S. demographic	Clear diversity goals and ability for sites to monitor	Plan for working with key patient sub-groups to enable trial participation
Sponsors **CROs**	Enabled sub-population participation *delivered on time*	**Sites optimized for quality, enrollment speed and diversity** – diversity targets achievable within recruitment budget and timelines		Positive partnership with site and patient – **optimized site staff and tools while remaining in budget** in supporting complex mix of patient populations
Sites	Planned **investments for site and community outreach support** • Consideration of burden on site	Preferential partnership treatment for excellence in diversity	Proactive budget and materials for site support to diversity efforts • Additional patient and community engagement budget • Translated materials • Additional budget for staff efforts to support and retain patients	
Patients / Potential trial participants	Consideration of diverse **patient needs and preferences**	Welcoming, supportive, inclusive and culturally aligned sites		**Sites and sponsors invested in community beyond trial**; Site and trial flexibility, creativity and support to enable access to trials AND medicines post-approval

Source: IQVIA Expertise; IQVIA Institute, Aug 2022.

socio-economic and healthcare access issues with under-represented patient populations as well as lack of trust and implicit bias contributing to trial access issues, focus on enabling and empowering the patient is critical to ensure clinical research inclusiveness. This can require additional work steps, staff time and investment from sites to ensure all eligible and interested patients are able to participate in clinical trial activities. Furthermore, patient support and advocacy groups invest significant effort to ensure patients and sites are educated and empowered to help drive inclusive research.

A return on these collective investments can be expected across all drivers of classically defined drug program value in the long run. An optimally diverse clinical program drives a better understanding of the safety and efficacy of the medicine in the intended patient population. Further to this, pragmatically, given the programmatic approach from the FDA, sponsors and partners can reduce regulatory risk, potential delays and additional real-world data collection obligations by ensuring clinical trials are fully representative of the intended patient population.[18]

Finally, and in summary, as well as enhancing product knowledge and reducing regulatory risk, focus on more inclusive trials has significant potential to ultimately reduce recruitment timelines by broadening patient participation. While engaging under-represented patient populations in any geography may require upfront investments and focus, there is also a very real opportunity to accelerate recruitment as previously under-engaged cohorts of patients are made aware of and provided access to clinical trials. Optimizing patient inclusion early and throughout the clinical research program will drive broader patient and provider experience and trust of the medicine at launch which will likely support a broader uptake of the medicine post-approval to help drive optimized patient outcomes as early as possible, thus realigning all stakeholder objectives around a diverse clinical program.

Measuring gaps in clinical trial representativeness

+ **Stakeholders in the U.S. have been discussing diversity in clinical trials for at least 50 years and a dramatic increase in diversity data reporting has occurred in the past five years, peaking in 2018**

+ **Reported diversity data from the past decade shows both Black/African American and Hispanic participation in Phase II and III trials fall short of the 2020 U.S. demographics levels of 13.6% and 18.9% respectively**

+ **Trials run entirely in the U.S., which represent about 40% of all Phase II and II trials, are closer than global studies to alignment with U.S. demographics**

+ **Sub-population inclusion in trials shows variability by therapeutic areas with allergy/immunology, and oncology showing lower Black/African American and Hispanic inclusion in 2020 versus other therapeutic areas like infectious disease**

+ **Contextualizing clinical trial diversity based on underlying epidemiology of the relevant disease is important to determine where the largest gaps exist, and definition of 'success' will vary by disease area with some diseases impacting racial minorities at different rates vs underlying population demographics**

+ **The Inclusivity Quotient (IQ) is a tool designed to measure clinical trial deviation from real-world demographics, and over the past 10 years in a range of disease areas, it reveals migraine has the greatest inclusivity on average, while Alzheimer's disease has been the least aligned to the underlying population**

DECADES OF U.S. GOVERNMENT ACTIONS ON DIVERSITY IN CLINICAL TRIALS

Diversity in clinical trials, or lack thereof, is not a new topic among U.S. policymakers and advocacy groups. Gaps in trial participation across racial and ethnic lines mirror significant health disparities and efforts to address them date back to the 1970s in the U.S.[19–21] Multiple cycles of legislation, many tied to the five-year reauthorization cycle for the FDA Prescription Drug User Fee Act (PDUFA) have led to new regulations, FDA guidance and reporting systems that have progressively increased transparency and encouraged inclusiveness in clinical trials.

The current diversity in the clinical trials regulatory landscape began taking shape in the U.S. in the late 1980s with the publication of the U.S. NIH Guide for Grants and Contracts, which requires NIH/ADAMHA clinical research grants, cooperative agreements, and contracts to include minorities and women in study populations[22] and the passage in 1993 of the National Institutes of Health Revitalization Act, which required investigators who used NIH funds for clinical research to include both women and minorities in their clinical research (Exhibit 7).[23]

Notably, ClinicalTrials.gov was created with the Food and Drug Administration Modernization Act of 1997 and the site launched in February 2000. Since then, subsequent regulations on registration requirements and diversity focus beyond NIH funded trials have paved the way for clinical trial transparency generally, and more recently, visibility into demographic sub-group enrollment.

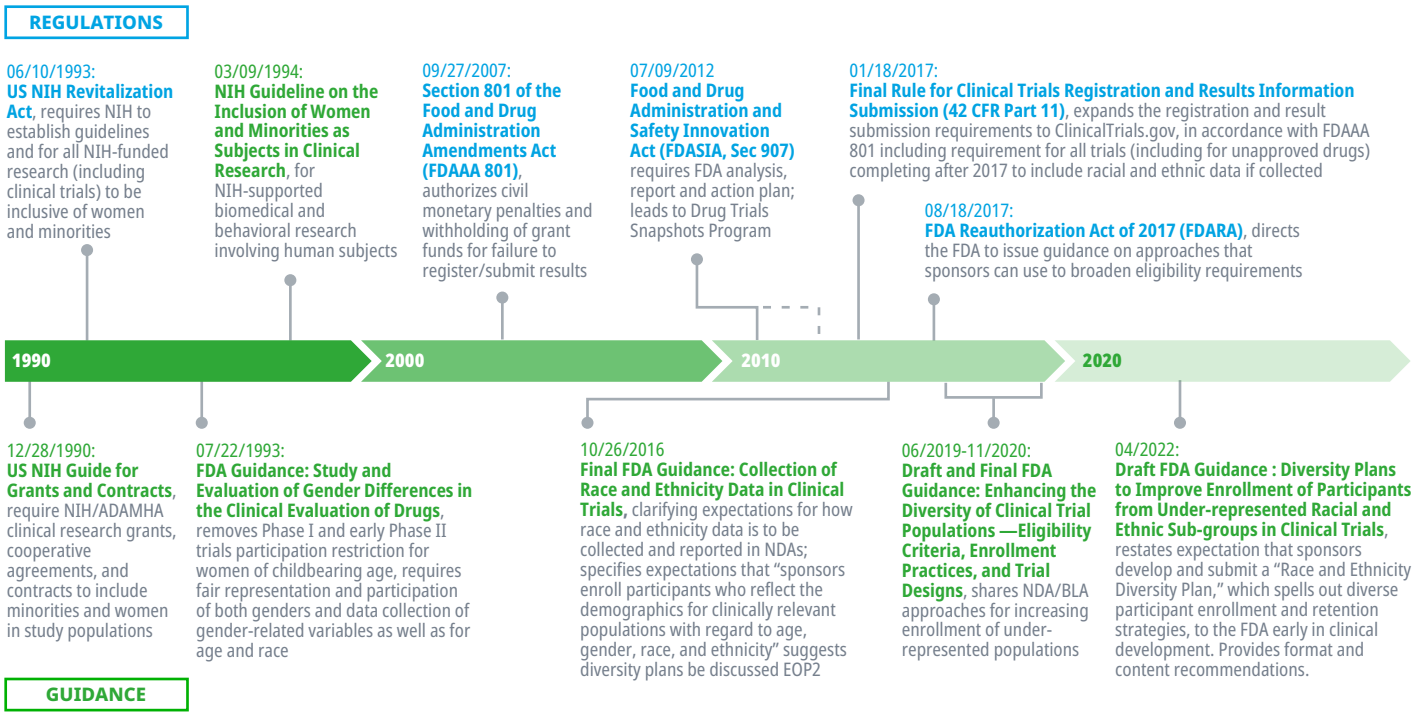
In a subsequent PDUFA cycle, advocates secured Sec. 907 in the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA), which directed the FDA to 1. Study and report on the extent of clinical trial participation and the inclusion of safety and effectiveness data by demographic sub-groups (sex, age, race, ethnicity) for marketing applications approved by the FDA and 2. Create an action plan for addressing demographic sub-group data gaps. Among the actions resulting was the FDA Drug Trials Snapshot Program[24] which specifically increased transparency on diversity of

pivotal trials for FDA approved drugs. At the start of 2015 the FDA began posting the diversity data for the pivotal trial(s) within 30 days of the approval of a new molecular entity (NME). Though FDA and other stakeholders acknowledge the limitations of Drug Trial Snapshots as a diagnostic for industry performance, the availability of individual views of trials and low percentages of minority inclusion frequently reported in these Snapshots have further fueled calls for more regulatory action.

The final FDA guidance on Collection of Race and Ethnicity Data in Clinical Trials[25] in 2016, which also resulted from FDASIA, reiterated a standardized approach for collecting and reporting racial and ethnic patient data for U.S. and global clinical research on FDA regulated medical products and stated FDA expectations that "sponsors enroll participants who reflect the demographic for clinically relevant populations with regard to age, gender, race and ethnicity." The following year saw passage of the Final Rule for Clinical Trials Registration and Results Information Submission,[26] which clarifies and expands the regulatory requirements and procedures for submitting results information for certain trials to ClinicalTrials.gov. This final rule included civil monetary penalties for responsible parties for failure to register applicable clinical trial information within a year of the primary completion date.

The FDA added more focus around diversity in 2019 when they issued draft guidance on "Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices and Trial Designs."[27] Part of a broader PDUFA VI directive to explore the impact of inclusion/exclusion criteria on accessibility of trials, the FDA guidance discussed approaches for industry sponsors to improve eligibility criteria and consider both medical and demographic diversity. The final version of Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices and Trial Designs was issued amid the COVID emergency in 2020 and provided a platform for more FDA advocacy on the topic. In April 2022, FDA issued draft guidance "Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Sub-groups in Clinical Trials",[28] which provides further detail on methods and focus for early submission by sponsors of diversity plans as a drug moves through the clinical development lifecycle.

Exhibit 7: Timeline of U.S. diversity guidance



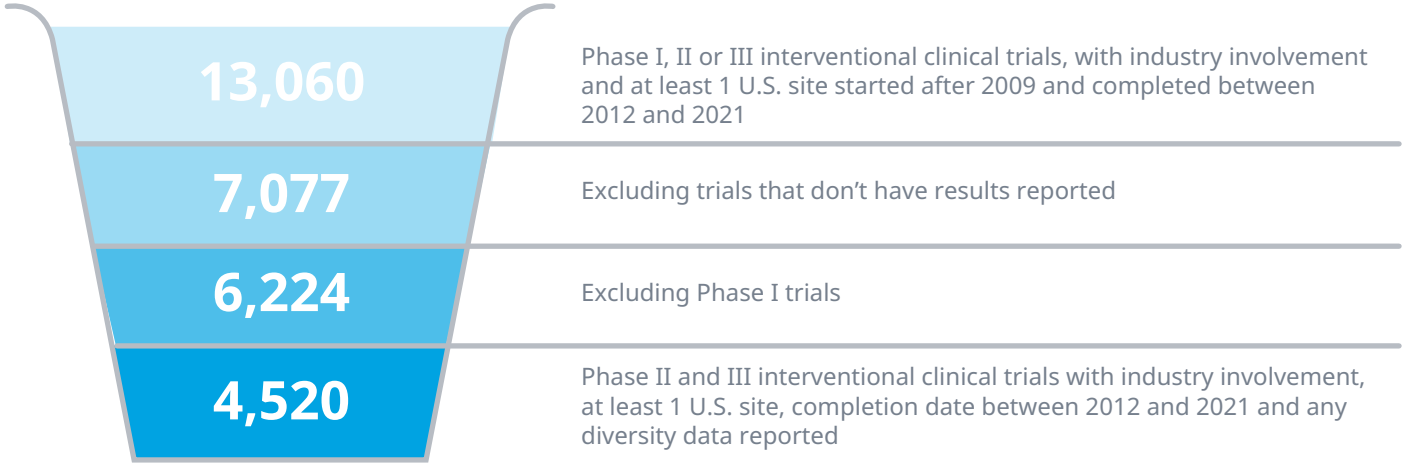
Source: U.S. Department of Human Health Services, U.S. FDA, U.S. Congressional Record, IQVIA Institute Analysis, Aug 2022.

DIVERSITY DATA COLLECTION AND REPORTING TRENDS

Data publicly available from ClinicalTrials.gov provide a way of assessing how industry trial data collection and reporting generally, and race and ethnicity data collection and reporting, specifically, has changed over time.

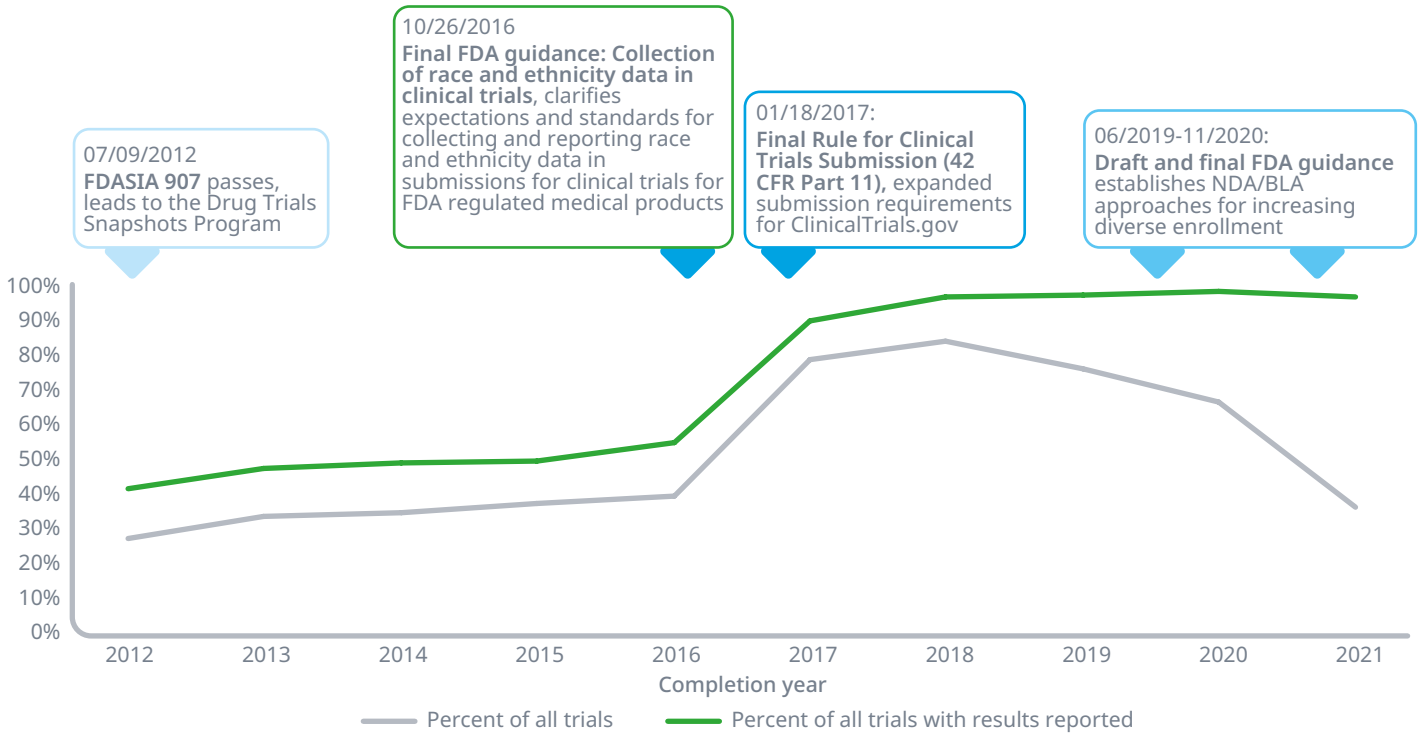
Review of trials posted to ClinicalTrials.gov in the past decade, with a focus on completed Phase II and III clinical trials with at least one U.S. site and industry involvement (e.g., industry funding), suggests that there has been a significant increase in racial and ethnic data collection (Exhibits 8 and 9). In the first half of the

Exhibit 8: Number of trials found on ClinicalTrials.gov



Source: ClinicalTrials.gov June 1,2022.

Exhibit 9: Diversity data reporting in Phase II and III trials completed 2012–2021



Source: ClinicalTrials.gov June 1, 2022.

Notes: Includes all interventional Phase II and III trials with industry involvement and any U.S. sites listed on ClinicalTrials.gov starting after January 1, 2009 and completing between the start of 2012 and the end of 2021. A total of 8,604 trials analyzed across time period, 6,224 of which had results.

decade, the percentage of trials reporting any race or ethnicity data ranged from 28% to a maximum of 40% in 2016. This reporting doubled to 80% of trials in 2017 and 2018. This correlates with both the passage of the Final FDA guidance for Collection of Race and Ethnicity Data in Clinical Trials and the Final Rule for Clinical Trials Submission which implemented an enforcement mechanism for trial data reporting.

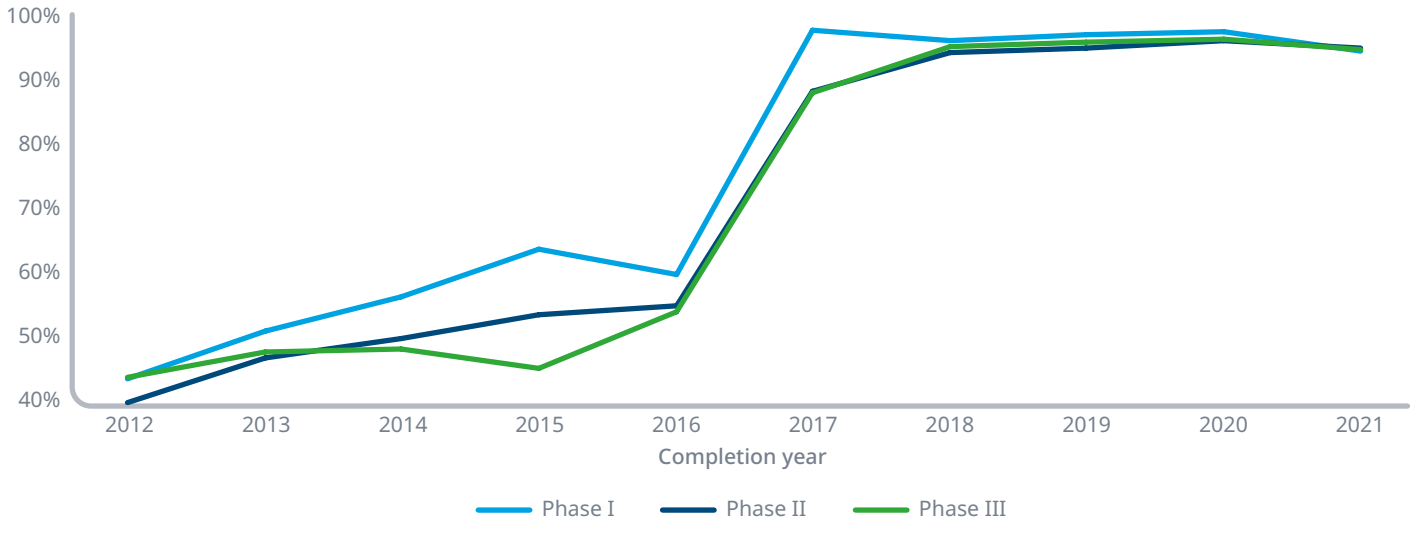
Reporting of race and/or ethnicity data peaks for trials completed in 2018 and is followed by a decrease in diversity data reporting, with a dramatic drop for trials completed in 2021. The drop in 2021 is likely at least partially explained by the regulations for ClinicalTrials.gov data submission, which allows for one year post primary completion date for the majority of trials to submit results. This does not fully explain the trial reporting decline which starts in 2019 and 2020. While COVID-19 driven staffing challenges may be partially to blame, it also has been attributed to a broader compliance issue as we move further from the date of regulation implementation with minimal apparent accountability.[29–31]

Notably, when only trials that reported data are analyzed, a consistently higher percentage of trials include at least some facets of racial and/or ethnic data, and this remains consistent through the second half of the decade. Thus, when looking at the full data set, the drop off in diversity data reporting observed post 2018 is a function of a decline in any data reporting on the trial. For trials that report data, an average of 96% include some racial and/or ethnicity data for each of the years 2018–2021. This is nearly double the level of diversity data reporting in the earlier half of the decade where an average of only 49% of the trials reporting data between 2012-2016 include diversity data of any sort.

Examination of these results by phase with a focus on trials with any data reporting shows that racial and/or ethnic data collection and reporting is consistent for all stages of clinical development (Exhibit 10).

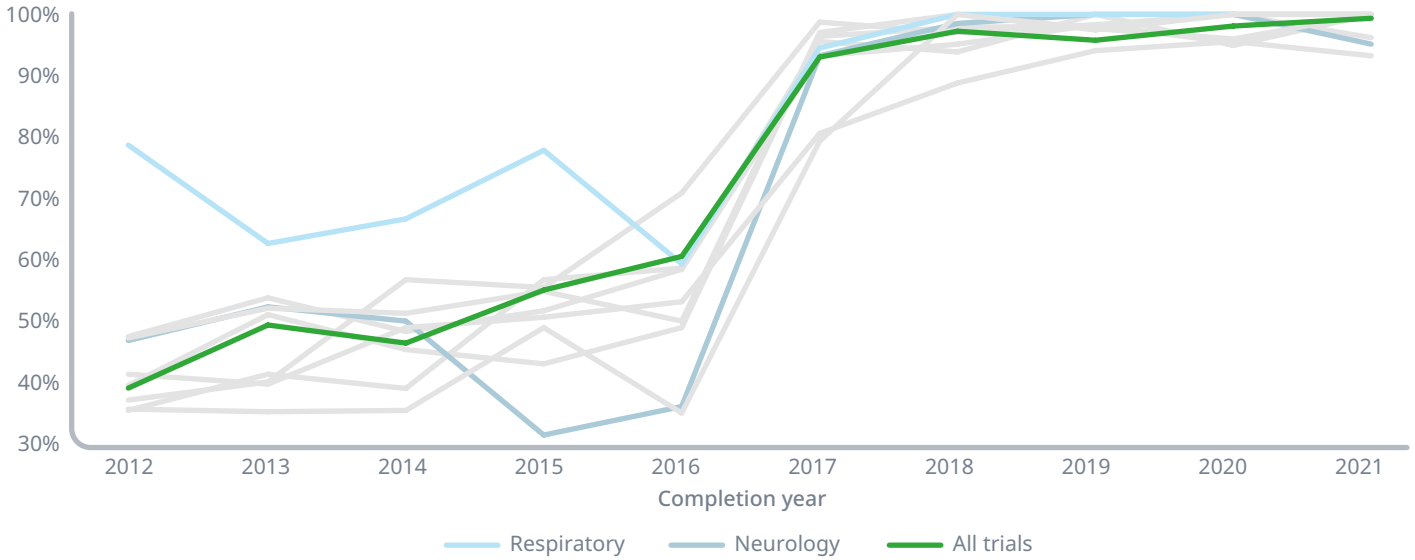
Differences between therapeutic areas in inclusion of racial and/or ethnic data when results are included in the ClinicalTrials.gov records were notable prior to 2016, with greater variability in diversity collection and reporting.

Exhibit 10: Diversity data in completed trials with reported results, by phase



Source: ClinicalTrials.gov June 1, 2022.
Notes: Includes all interventional Phase I-III trials with industry involvement and any U.S. sites listed on ClinicalTrials.gov as starting after 2009 and completing between the start of 2012 and the end of 2021. A total of 7.077 trials analyzed over the time period.

Exhibit 11: Diversity data in completed Phase II and Phase III trials with reported results, by therapeutic area



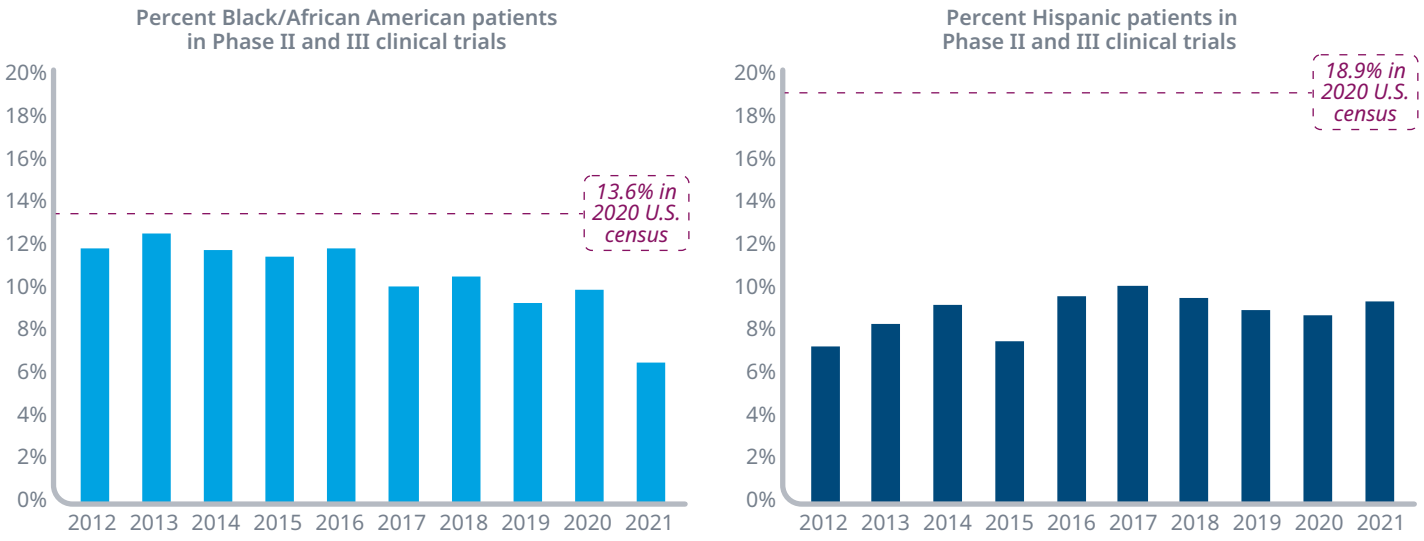
Source: ClinicalTrials.gov June 1, 2022.
Notes: Includes all interventional Phase II and III trials with industry involvement and any U.S. sites listed on ClinicalTrials.gov as starting after 2009 and completing between the start of 2012 and the end of 2021. Analysis includes 6,224 trials over time frame.

Respiratory, in particular, reported diversity data at a higher rate than the other therapeutic areas (Exhibit 11). Since 2017, differences between therapeutic areas have been minimal.

RACIAL AND ETHNIC INCLUSION IN CLINICAL TRIALS

The increased reporting of diversity data in the ClinicalTrials.gov dataset provides increased transparency and more detailed insight into how the industry is performing on clinical trial diversity. Analysis of this data shows that relative racial and ethnic inclusion on clinical trials has remained steady or has decreased slightly over the past decade for interventional Phase II and III trials with industry involvement and at least one U.S. site (Exhibit 12).

Exhibit 12: Racial and ethnic inclusion in Phase II and III clinical trials — 2012–2021



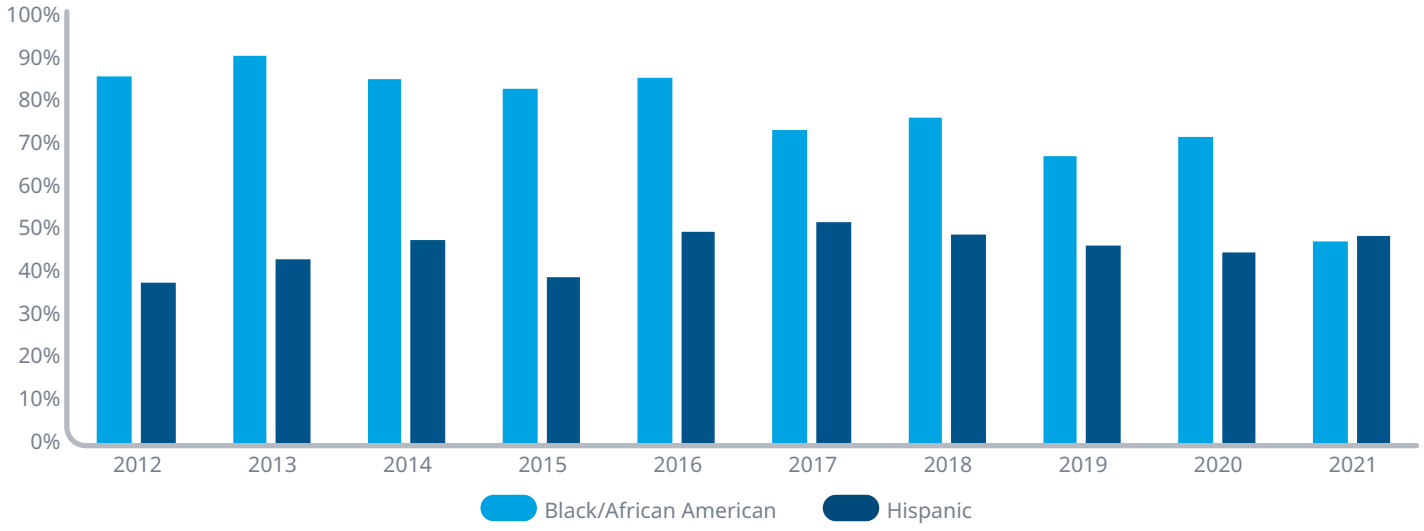
Source: ClinicalTrials.gov June 1, 2022; U.S. Census Bureau.
Notes: Includes all interventional Phase II and III trials with industry involvement and any U.S. sites listed on ClinicalTrials.gov as starting after 2009 and completing between the start of 2012 and the end of 2021. Only trials with racial or ethnic data collected were included in calculation of minority inclusion. Analysis includes 4,520 trials over the time period.

Analysis of both Black/African American participation, and Hispanic participation shows trials on average falling short of the 2020 U.S. demographics. Specifically, Black/African American participation has been declining over the past decade – including a 15% drop in 2017 from a 2013 peak of 12.3% and a 35% decrease in 2020–2021 from 9.8% to 6.5%. Hispanic inclusiveness varied over the timeframe, ranging from 7.4% in 2015 to a high of 9.9% in 2017. Considered in concert with the data on diversity data reporting trends, the 15% drop in 2017 coincides with the increase in total diversity trial reporting. A potential explanation for this is that the trials that were voluntarily reporting diversity data prior to regulated requirement were already more focused on recruiting diverse patients onto their trials. That said, Hispanic recruitment may be increasing slightly over the past decade, though this could be a function of a more rapidly increasing underlying population versus specific focus or actions in clinical trial recruitment.

Indexing the average recruitment rate for Black/African American and Hispanic patients to the underlying U.S. demographics across trials reinforces the view that neither is being recruited at representative levels (Exhibit 13). By 2021, both sub-populations are included in clinical trials at about 50% of the underlying U.S. demographic.

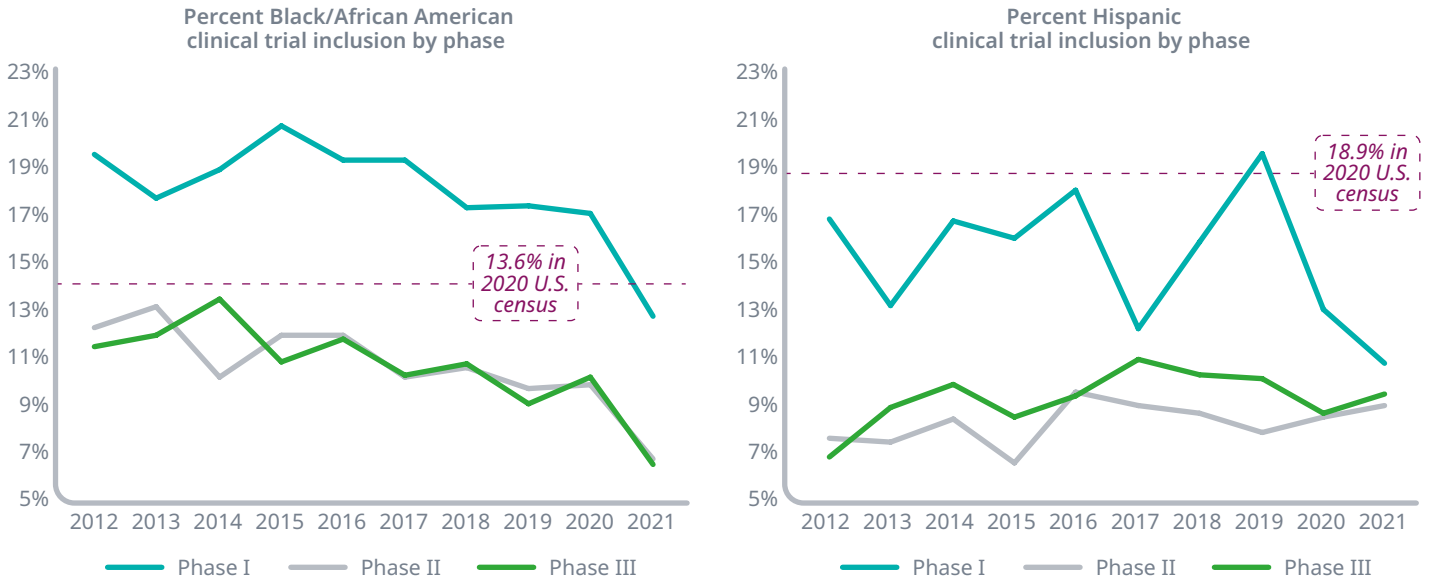
Examination of the recruitment levels of each sub-population by phase of trial shows that the trend is similar for Phase II and Phase III trials, but Phase I trials show a much higher inclusion rate for Black/African American and Hispanic patients (Exhibit 14). On average across trials for most of the decade, Black/African American patients are over-enrolled in Phase I studies relative to their underlying population. Over-enrollment of Phase I trials may be a function of higher participant payments and socio-economic drivers leading to higher proportion of minority volunteer enrollment in Phase I trials.[32] Phase I unit location and community engagement strategies may also be driving higher minority engagement. These divergences between Phase I and later-phase studies should be a consideration in building strategies based on ongoing assumptions about barriers to sub-population trial participation for later stage trials.

Exhibit 13: Phase II and III racial and ethnic inclusion indexed to U.S. demographics — 2012–2021



Source: ClinicalTrials.gov June 1, 2022; U.S. Census Bureau.
Notes: Includes all interventional Phase II and III trials with industry involvement and any U.S. sites listed on ClinicalTrials.gov as starting after 2009 and completing between the start of 2012 and the end of 2021. Only trials with racial or ethnic data collected were included in calculation of minority inclusion. Analysis includes 4,520 trials over the time period.

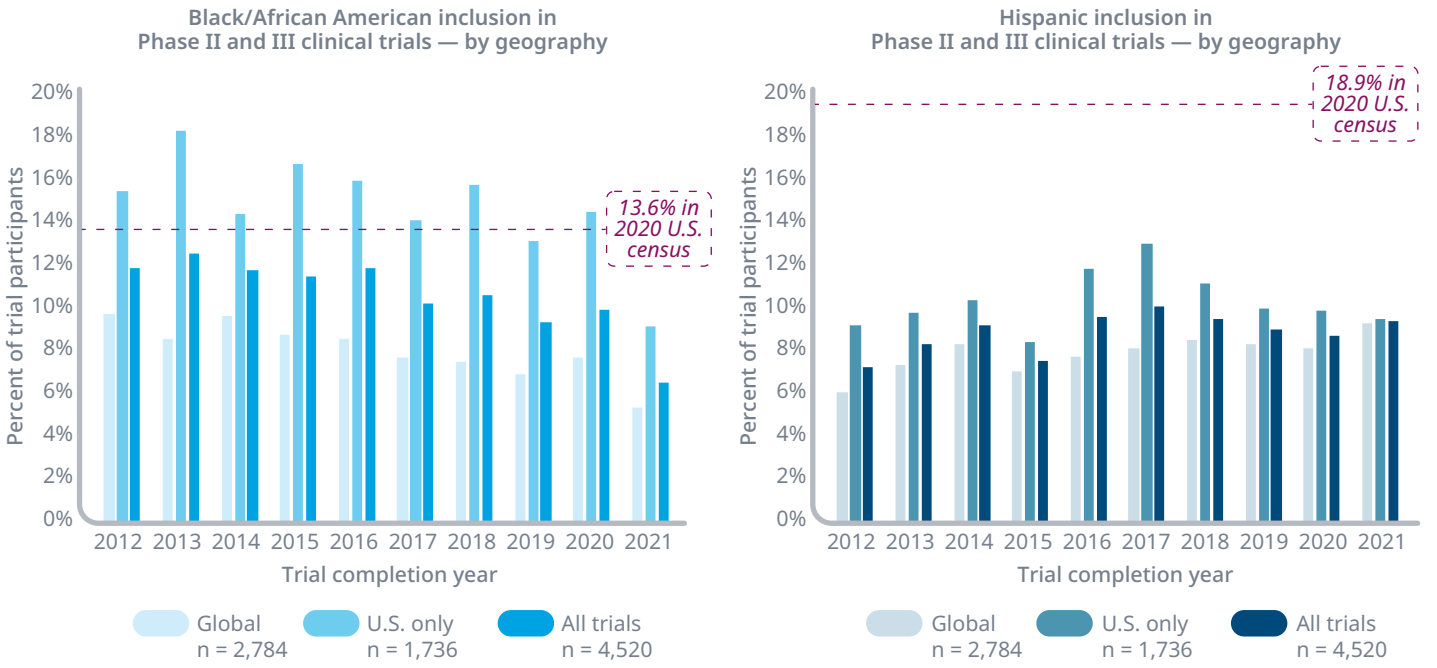
Exhibit 14: Racial and ethnic inclusion in clinical trials, by phase — 2012–2021



Source: ClinicalTrials.gov June 1, 2022; U.S. Census Bureau.

Notes: Includes all interventional Phase I, II and III trials with industry involvement and any U.S. sites listed on ClinicalTrials.gov as starting after 2009 and completing between the start of 2012 and the end of 2021. Only trials with racial or ethnic data collected were included in calculation of minority inclusion.

Exhibit 15: Phase II and III racial and ethnic inclusion — U.S-only versus global



Source: ClinicalTrials.gov June 1, 2022; U.S. Census Bureau.

Notes: Includes all interventional Phase II and III trials with industry involvement and any U.S. sites listed on ClinicalTrials.gov as starting after 2009 and completing in 2020. Global includes any trial that had U.S. sites and ex-U.S. sites; U.S. Only are trials with only U.S. sites and All Trials is all of the trials in the data set (Global and U.S. Only combined).

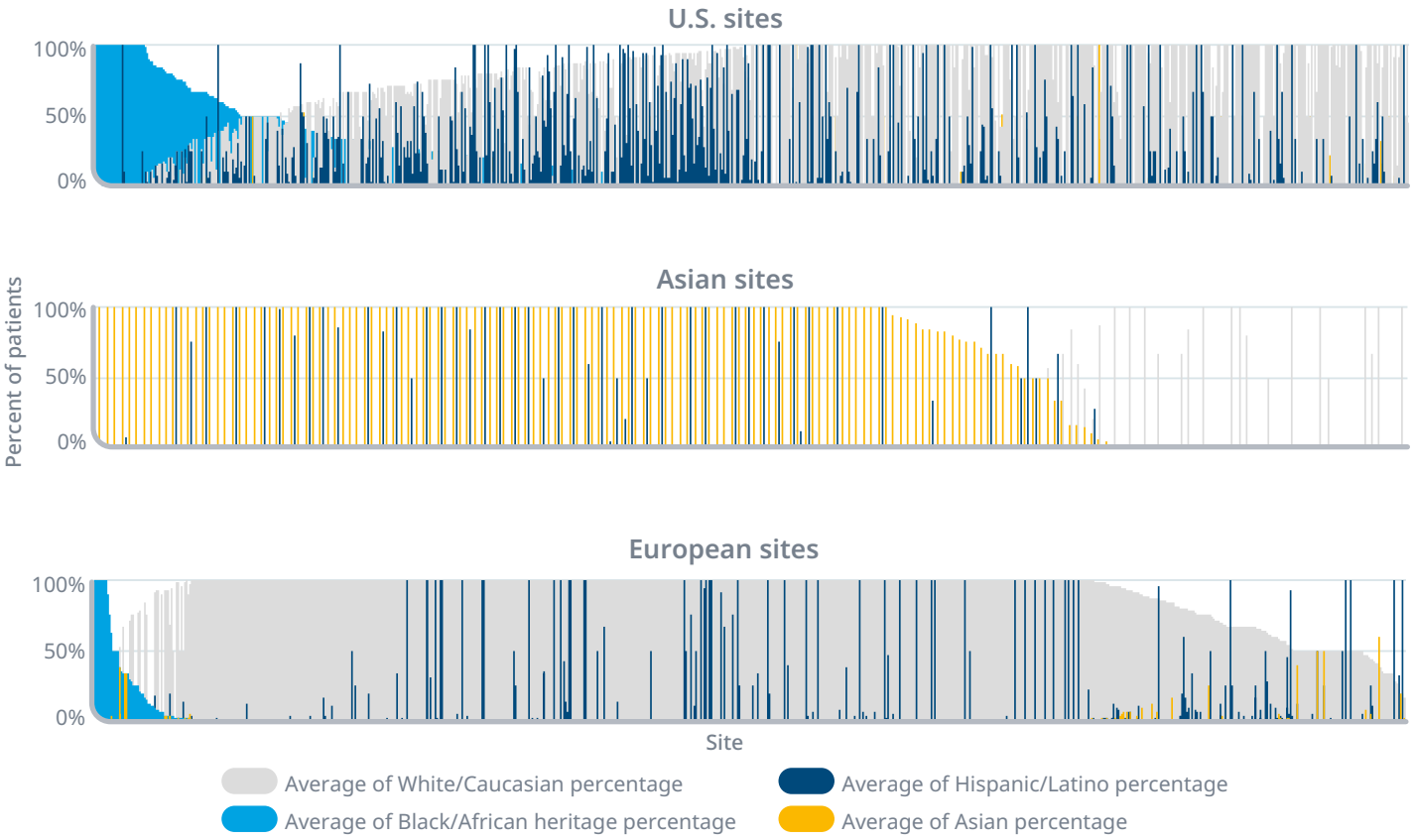
While this analysis is focusing on trials found in the ClinicalTrials.gov database which inherently suggests a U.S. focus, many trials are for drugs being developed for other markets as well and/or include non-U.S. research sites. In fact, trials with only U.S. sites make up about 40% of the analyzed data set (Phase II & III, industry involved, completed clinical trials) and have comparable rates of study results and diversity data reporting to 'global' trials (trials with a mix of sites from the U.S. and from ex-U.S. countries) (not shown). Importantly, analysis of trial inclusiveness shows that trials run entirely in U.S. sites are much closer to alignment to underlying U.S. demographics on average than trials run in a mix of U.S. and ex-U.S. sites ("Global") (Exhibit 15). This is especially true for Black/African American enrollment where entirely U.S. run trials meet or exceed U.S. demographic levels. While U.S. only trial enrollment of Hispanic patients is higher than 'global' studies, even with U.S. sites only, the average inclusion across the last decade never meets or exceeds the U.S. demographic level.

An analysis of global site-specific recruiting across IQVIA-run studies further illustrates the importance of site location on patient enrollment diversity (Exhibit 16). Analysis of race and ethnicity of recruited patients by site from all IQVIA supported Phase II and III completed trials initiated between 2016 and 2018 shows a very distinct recruiting profile by region. Sites located in the U.S. showed the most Black/African American recruiting, with approximately 5% of the sites recruiting between 10–15% Black/African American patients and 30% recruiting greater than 15%. Asia-Pacific sites have nearly entirely Asian patient representation, and European sites are very weighted toward White patient recruiting with a small percentage of Black or Hispanic focused sites.

This analysis highlights the importance of considering race and ethnicity representation in global programs seeking U.S. approval with a high percentage of ex-U.S. sites. This is also one of the reasons it is so challenging to place a finite regulatory 'target' for program diversity for drugs seeking approval in the U.S. (or any geography) in the context of a global program. This type of complexity continues to be a challenge for global programs and is another reason early partnership with regulatory agencies in each geography where the drug will be used and where program planning will include an explicit focus on diversity are important.

Strategies that are leveraging Asian or Eastern European sites to help drive recruiting efficiencies or market access may end up significantly below representative levels for key U.S. racial and ethnic populations.

Exhibit 16: Site specific diversity by region for completed Phase II and III trials started between 2016–2018

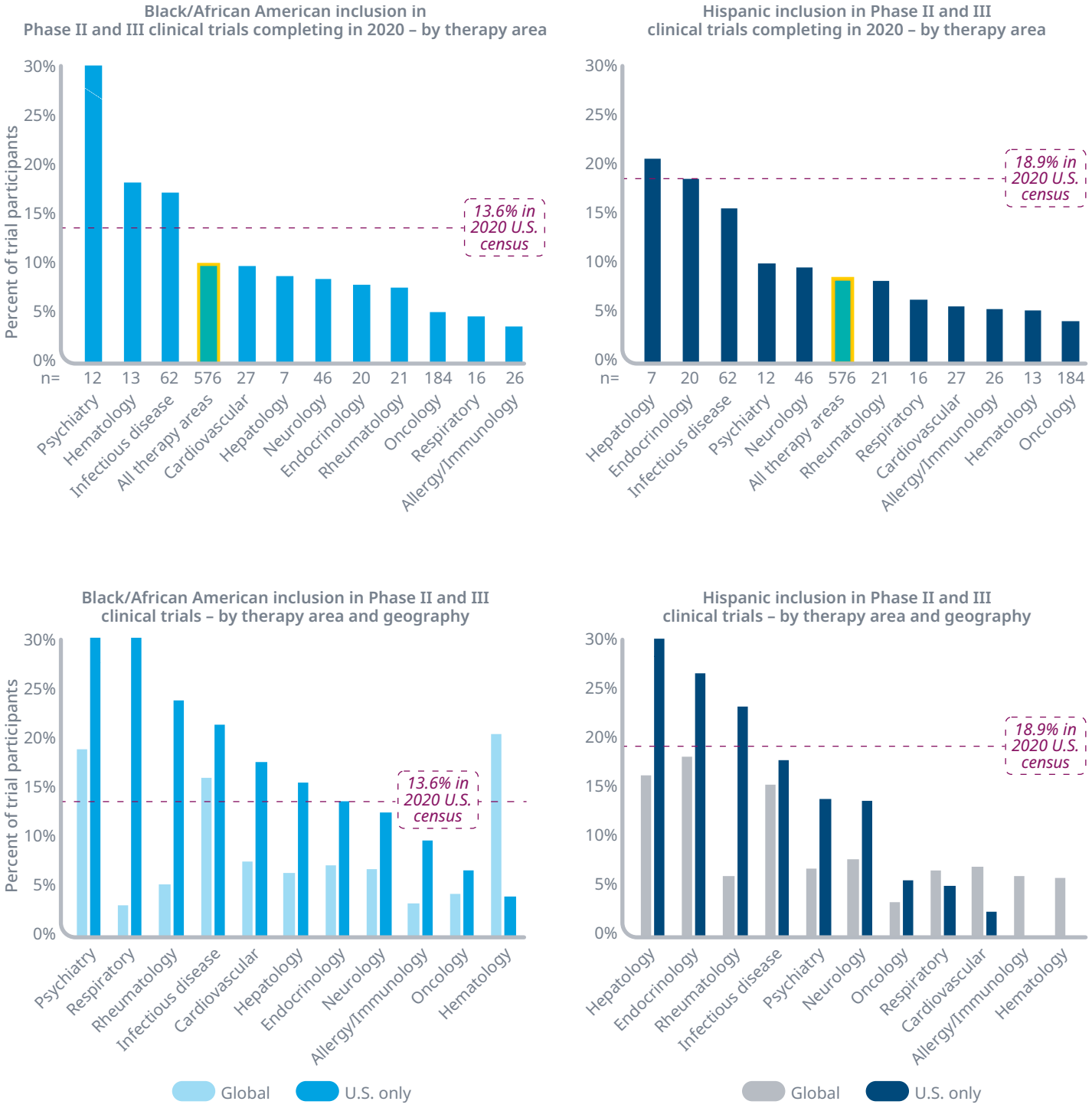


Source: IQVIA historical trial data.
Notes: Graphs created by plotting average diversity across all recruiting done by each unique site with activity on IQVIA Phase II and III, completed trials that started enrolling between Jan 1 2018 and Jan 1 2019. Trials limited to those in allergy, cardiovascular, endocrinology, hematology, infectious disease, inflammatory disease, nephrology, neurology, oncology, respiratory and rheumatology.

Focus on therapeutic area shows further differences between Black/African American and Hispanic inclusion on clinical trials (Exhibit 17). In all (U.S.-only and global) Phase II and III trials completed in 2020, Hematology, Infections Disease and Psychiatry trials all reported Black/African American patient inclusion significantly above the U.S. demographics. Conversely, Black/African American patients represented less than 5% of the enrollment in completed allergy, oncology or respiratory trials in 2020. Focus on global versus U.S. trials shifted these results slightly and made clear that for some therapeutic areas such as respiratory, rheumatology U.S. cardiovascular, there are significant differences between U.S. and 'global' trials in inclusion of Black/African American patients.

In the case of Hispanic trial participation, endocrinology and infectious disease trials reported Hispanic inclusion at nearly the level of the underlying U.S. population, but a significant underrepresentation in most of the other therapeutic areas versus the U.S. demographic. The data shows similar need for strategic focus on global programs with inclusion of Hispanic accessible/focused sites in the U.S. and inclusion of Latin geographies to ensure reporting of diversity data that meets the U.S. regulatory needs.

Exhibit 17: Phase II and III minority inclusion by therapeutic area — all trials, and U.S.-only versus global — 2020

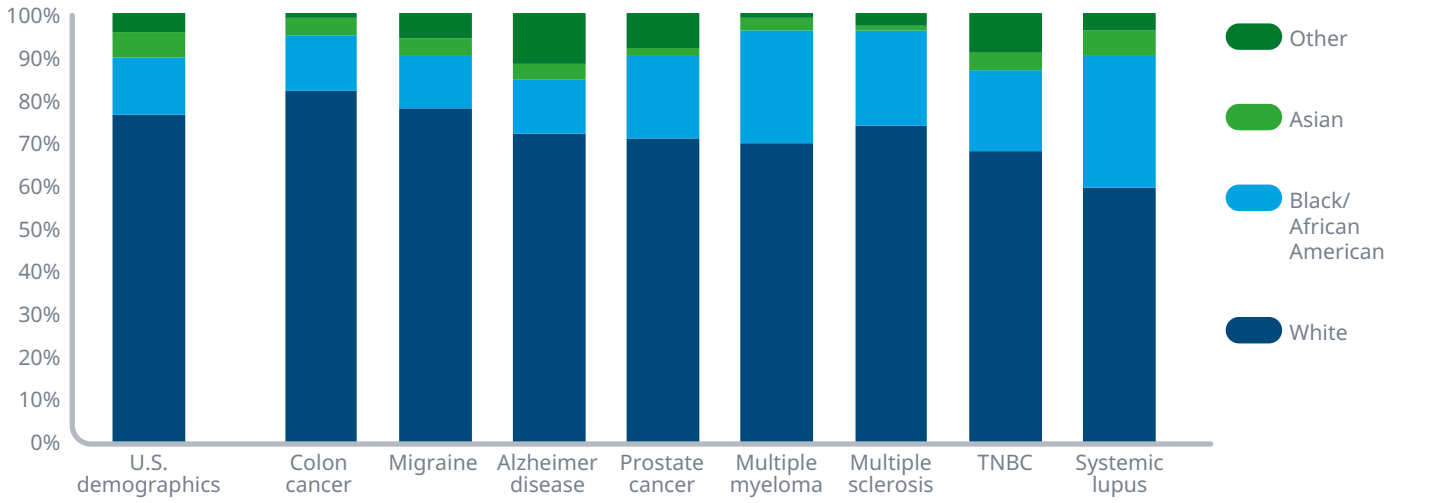


Source: ClinicalTrials.gov June 1, 2022; U.S. Census Bureau.
Notes: Includes all interventional Phase II and III trials with industry involvement and any U.S. sites listed on ClinicalTrials.gov as starting after 2009 and completing in 2020.

A further complexity to optimizing inclusiveness in clinical research is that the 'optimal' patient demographics shift by the disease being researched. At an industry pipeline level, achieving trial participation on par with underlying geographic demographics is a surrogate target. The reality is that for any given clinical research program, optimized inclusivity will differ based on demographics of the population that is 'clinically relevant' to that therapy. Many diseases are known to impact patients at different levels than underlying geographic demographics would suggest (Exhibit 18), and examples include lupus, triple-negative breast cancer (TNBC) and multiple myeloma.[10,11,33–35] Taken a step further, many drugs currently being tested in today's pipeline are focused on rare diseases and may enroll relatively small numbers of very specific patients in their clinical trials — and these types of trials will have entirely different and critically important targets around 'inclusivity' than the underlying geographic race/ethnicity proportions. In each of these cases, thoughtful planning, recruitment goals stated as ranges based on rigorous analysis, and ongoing measurement of progress to goals can drive successfully inclusive programs.

Currently, key industry-wide diversity measurement and baselining efforts such as the FDA Drug Trials Snapshots program are challenged by the fact that they reference underlying U.S. population demographics rather than the real-world race and ethnicity epidemiology of a disease. To achieve and capture progress toward consistent inclusivity across disease areas, tools which can flexibly articulate inclusiveness to target are needed.

Exhibit 18: 2021 U.S. demographic and disease specific epidemiology for select disease areas



Source: U.S. Census, July 1, 2021; FDA Drug Snapshots, Dec 2021; ClinicalTrials.gov; IQVIA Institute, Oct 2022.

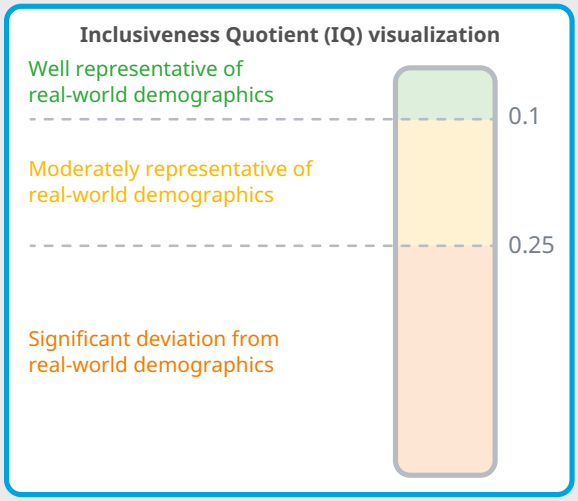
Methodology: Inclusivity quotient

Tools that can describe observed patient inclusion in relation to the expected underlying community are critical to enabling measuring and tracking true patient diversity. An example of this sort of tool that has been developed to provide a contextualized measure of inclusivity is the IQVIA Inclusivity Quotient (IQ). The IQ is a straightforward and intuitive data-based metric that quantifies the magnitude of departure from disease-specific demographics for any clinical trial or program and identifies the factors contributing to this deviation, thus enabling both monitoring of progress and informing strategies to address inequities or gaps at a program or portfolio level. Importantly, this instrument accounts for both the absolute and relative differences between the observed trial sample and expected real-world population, which is central to ensure a more meaningful understanding of departure from expected representation across races and ethnicities.

Exhibit 19: Inclusivity Quotient equation and scoring

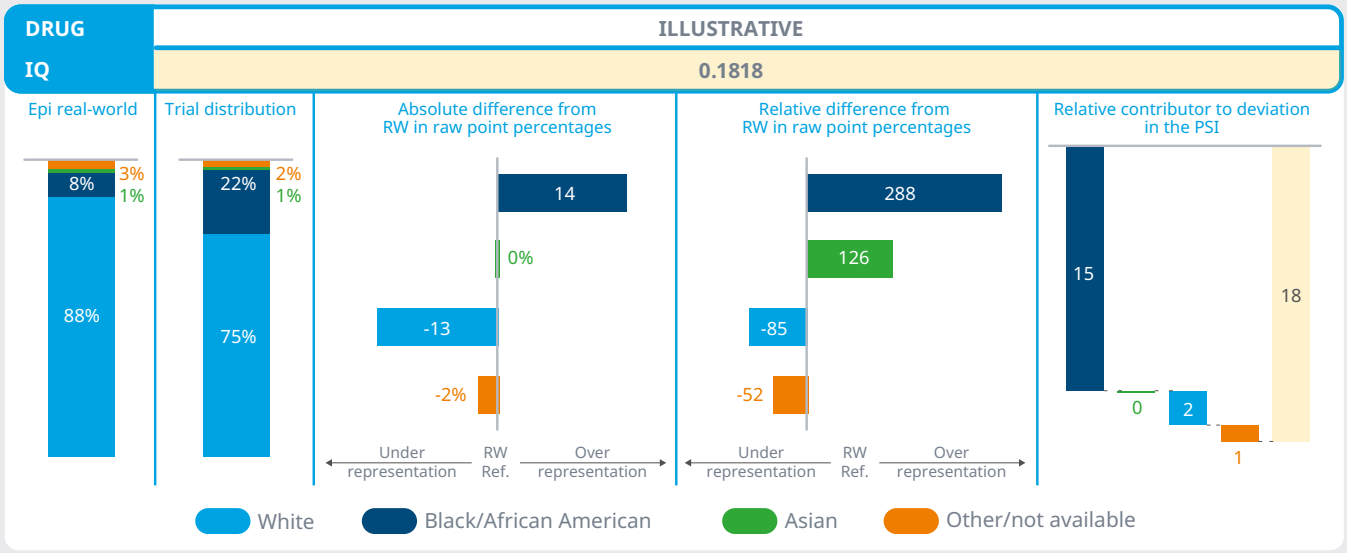
- The IQ is a **data-driven** tool that quantifies how much a clinical trial departs from real-world patient distribution by indication, and compares across trials/drugs
- The IQ uses the **Population Stability Index (PSI)** metric to measure the ***absolute*** and the ***relative*** difference between real-world (expected) and clinical trial (observed) demographics:

  The equation for the PSI is (sum of Obs-Exp * Natural log of Obs/Exp)
- PSI enables examination of each trial group (or other population) to identify which ones most contribute to departure from real-world distribution



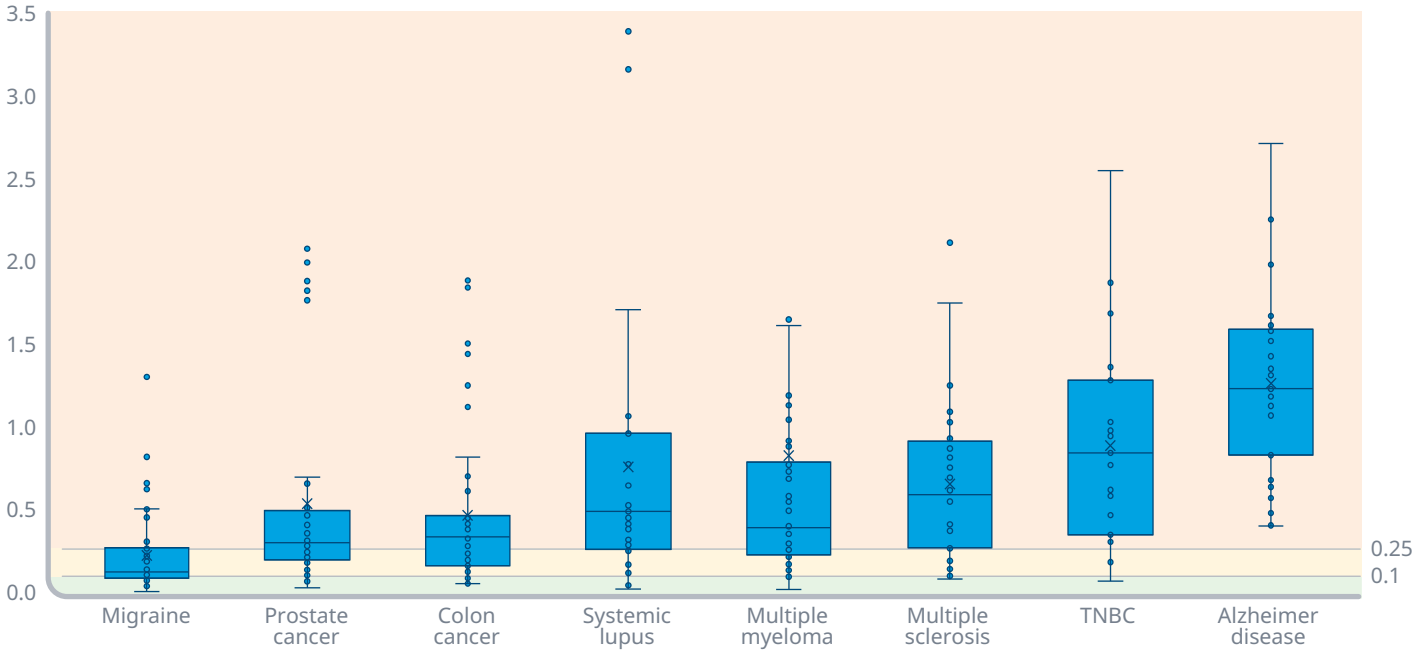
Source: IQVIA Analysis.

Exhibit 20: Inclusivity Quotient detailed readout



Source: ClinicalTrials.gov June 1, 2022; U.S. Census Bureau.
Notes: Includes all interventional Phase II and III trials with industry involvement and any U.S. sites listed on ClinicalTrials.gov as starting after 2009 and completing between the start of 2012 and the end of 2021. Only trials with racial or ethnic data collected were included in calculation of minority inclusion.

Exhibit 21: Median Inclusivity Quotient score and variances for trials run 2012–2021 in selected indications



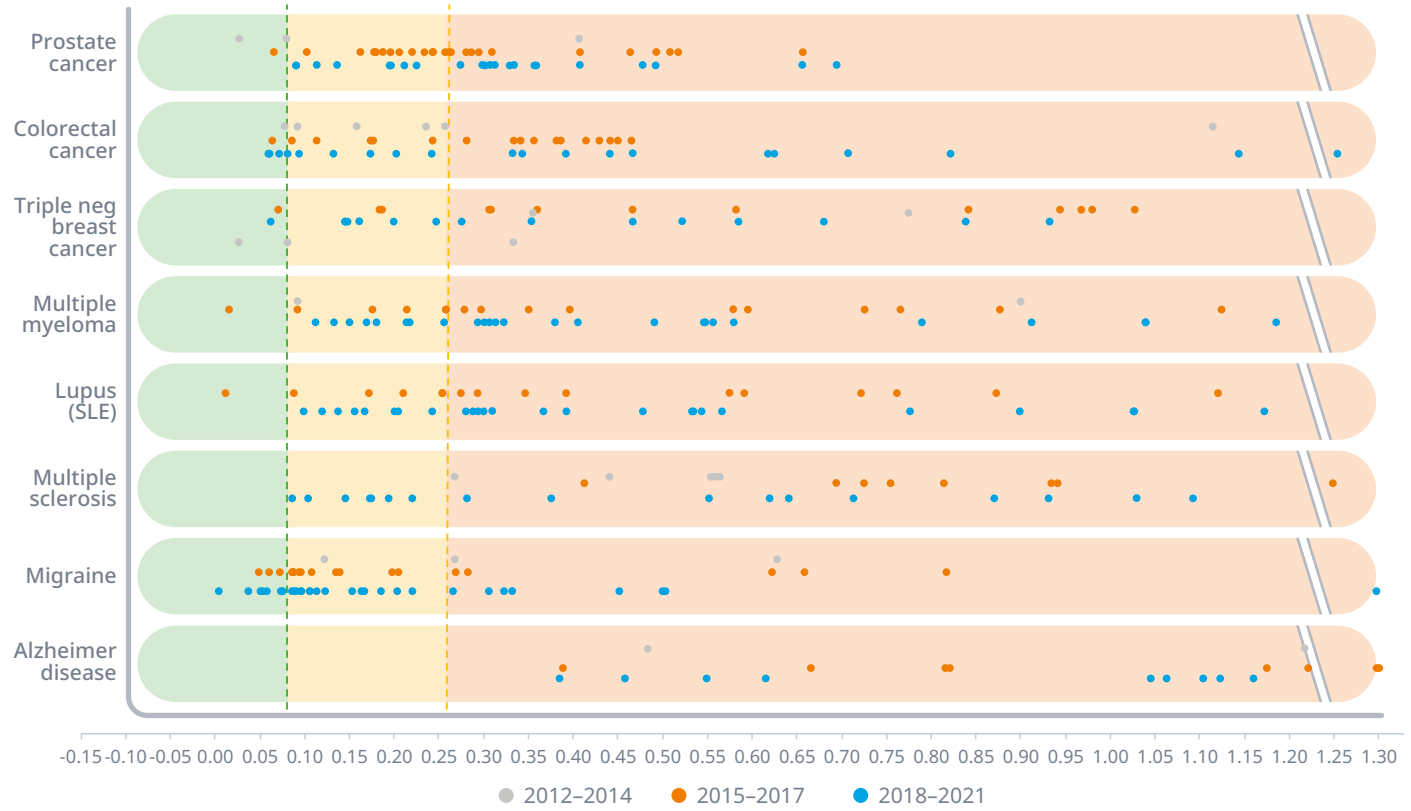
Source: ClinicalTrials.gov June 1, 2022; U.S. Census Bureau.
Notes: Includes all interventional Phase II and III trials with industry involvement and any U.S. sites listed on ClinicalTrials.gov as starting after 2009 and completing in 2020. Only trials with racial or ethnic data collected were included in calculation of minority inclusion.

Analysis using the IQVIA Inclusivity Quotient (Exhibits 19 and 20) as one such tool to look at a set of disease areas that disproportionately affect minority patient populations in the U.S. reveals a wide range of alignment to underlying patient populations (Exhibit 21). Across eight selected disease areas with a range of sub-population impact, migraine is showing the greatest inclusivity on average while Alzheimer's disease is least aligned to underlying population. In the case of Alzheimer's disease this is consistent with well-documented under-representation of Black/African American patients.[36–39]

IQ analysis of the portfolio of trials in three-year increments across the timeframe does not demonstrate any notable improvement in inclusivity over time in any of these key diseases (Exhibit 22).

"Under-represented and marginalized populations-particularly those identifying as a racial or ethnic minority, those with low socioeconomic status, or living in rural areas-have been historically underrepresented in ongoing [Alzheimer's disease] clinical trials despite overwhelming evidence that such populations are at increased risk for developing dementia." [39]

Exhibit 22: Inclusivity Quotient analysis of focus indication diversity over three time periods between 2012–2021



Source: U.S. Census, July 1, 2021; FDA Drug Snapshots, Dec 2021; ClinicalTrials.gov; IQVIA Institute, Oct 2022.

Notes: Includes all interventional Phase II and III trials with industry involvement and any U.S. sites listed on ClinicalTrials.gov as starting after 2009 and completing in 2020. Only trials with racial or ethnic data collected were included in calculation of minority inclusion.

Inclusivity Quotient analysis of the portfolio of trials in three-year increments across the timeframe does not demonstrate any notable improvement in inclusivity over time in a specific set of diseases.

Advances in critical stakeholder commitments and activities

+ **Enabling diverse clinical trials requires cross-stakeholder commitment and success cases show that progress can and is being made toward more inclusive clinical development**

+ **Analysis of pharmaceutical sponsor focus on diversity shows a variety of company specific and collaborative efforts are being made to ensure inclusivity in clinical trials, although correlation of company specific public "diversity footprint" to relative sub-population inclusion has not yet been detected due to completed trial lag**

+ **Clinical sites with highly successful engagement from under-represented patient segments focus on building trust at a community and individual level, including investing in meeting culturally diverse patient needs**

+ **Patient advocacy groups have been taking a more prominent role over the past decade in ensuring better representation of sub-populations in clinical trials; recent examples of diversity in clinical trials specific patient outreach, patient and provider education, and multiple forms of patient advocacy demonstrate ongoing momentum**

The opportunity and need for ongoing clinical development trial population diversity remains clear based on progress in the last decade. Recent developments including the drastic COVID outcome disparities seen in early 2020,[40-42] along with a general 'racial reckoning' in the U.S. and elsewhere that has fueled a sense of urgency and has shifted conversations from the policy arena to the operational level.

With increasing focus on improving clinical development diversity and progress on trial results transparency, the healthcare ecosystem is poised to make appreciable gains in clinical development inclusivity. At the same time, examples of progress toward more inclusive clinical development are being demonstrated across stakeholders and an integrated model of action has started to emerge (Exhibit 23) with pharmaceutical sponsors and their partners, sites, patients, and regulators all playing a critical part in advancing a more equitable clinical innovation system.

Consideration of each stakeholder's role, objectives, and examples of progress sets the stage for building more diverse clinical programs going forward.

Looking at success stories across stakeholders makes it clear that the building blocks exist to systematize inclusive clinical trial participation if the current level of focus and will to enact change persists.

Exhibit 23: Cross-stakeholder commitment to enable diverse clinical trials

What is needed	Racial and ethnic diversity plan	Inclusive trial design	Demographically aligned sites	Enabled inclusive sites	Engaged diverse communities	Supported trial participants
Sponsors & CROs	• Characterize sub-population disease impact differences • Plan for program level diversity (including enrollment goals and plans to enroll, retain, and track diverse participants)	• Confirm I/E includes all demographics • Understand and avoid barriers to trial participation • Ensure biomarkers, diagnostics etc. apply to all demographics • Plan to collect diversity data	• Analyze country and site mix demographics and fit to diversity goals	• Articulate clear diversity goal ranges • Supplement staff with additional FTEs and training as needed to ensure successful focus and enrollment • Provide enrollment tools to monitor progress	• Support ongoing, between-trial site activity to build relationships and trust in diverse communities • Ensure education/ advertising/trial materials are translated and culturally appropriate BEFORE trial start	• Train site staff to enable culturally tailored trial participation • Provide patient support (e.g., transportation, childcare etc.) to enable participation in trial
Sites	• Provide input on trial barriers and investments needed to reach diverse patients	• Provide input on trial participation challenges and design flaws	• Research and community practices in diverse areas participate in clinical trials • Develop referral mechanisms from more community -based practices	• Staff includes (bi-lingual) minorities • Align (increase) staff for focused minority enrollment (including outreach)	• Align (invest in) staff for between trial community engagement	• Align and extend patient support to address all key drivers of poor trial (and healthcare) participation
Patient organizations	• Amplify areas of health outcome disparities • Clarify differences in sub-population trial needs	• Provide input on trial participation challenges and design flaws	• Monitor clinical trial 'pipeline' and lobby for local and community site participation	• Engage in community outreach; trial awareness • Enable diverse patient to advocate for diagnosis and participation in trials • Educate sites and physicians on implicit and explicit bias, inclusion inequities and barriers to sub-population trial participation		• Amplify need for patient support and help focus activities to be most effective
Regulators/ Government	• Finalize guidance, share best practice, publish Q&A	• Guidance and feedback on trial design: share known areas of impact	• Enable community site participation	• Support staffing and investment actions targeting minority patient support (e.g., align FMV to accommodate additional support activities)		

Source: IQVIA Institute Analysis.

REGULATORS AND PAYERS

Policymakers and the FDA specifically, have been pushing industry to improve diversity in clinical trials for well over two decades, and under current leadership is vocally committed to ensuring trial diversity keeps pace with U.S. population diversity. FDA Commissioner Robert Califf recently stated, "The U.S. population has become increasingly diverse, and ensuring meaningful representation of racial and ethnic minorities in clinical trials for regulated medical products is fundamental to public health".[43] Additionally, FDA draft guidance issued in spring 2022 provides a structured set of recommendations targeting clinical program planning to ensure optimized diversity.[28] This guidance highlights the focus of the FDA on planning to enable inclusive programs while still supporting the mandate to get safe and effective medicines to patients as fast as possible.

This represents a notable amplification in the FDA's position on the need for industry-wide focus on delivering clinical trials with representative patient inclusion but continues to acknowledge the complexity and need for specific diversity plan/approach for each program. The critical point is that each clinical program needs a well-considered diversity plan. To that end, this most recent guidance builds on past guidance to reiterate that all clinical research should be considering inclusivity throughout the entire program and provides a more detailed framework for planning and design to ensure diverse patients are engaged (Exhibit 24).

Exhibit 24: Comparison of 2016 FDA trial diversity guidance and 2022 draft guidance detailing 'Diversity Plan' expectations

2016
Diversity plans mentioned

...“FDA expectations are that sponsors enroll participants who **reflect the demographics for clinically relevant populations with regard to age, gender, race, and ethnicity.**

A plan to address inclusion of clinically relevant sub-populations **should be submitted for discussion** to the Agency at the earliest phase of development and, for drugs and biologics, **no later than the end of the phase 2 meeting.”**

Source: 2016 Guidance on Collecting Race/Ethnicity Data; echoed in 2020 Guidance on Enhancing Diversity in Clinical Trials

2022
Guidance details format & content expectations for diversity plans

Given the importance of increasing enrollment from historically under-represented racial and ethnic populations, FDA is publishing **this guidance to provide detail on what sponsors should include in a Race and Ethnicity Diversity Plan**

- General considerations for **format and content**
- Plan to enroll representative population submitted to IND application
- **Discuss with agency** as soon as practicable, no later than **end of phase 2 feedback discussion on pivotal trials**

Source: April 2022 Draft Guidance on Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials

Source: U.S. FDA website, IQVIA Analysis.

In addition to issuing its most detailed and sweeping guidance on the topic, there are numerous recent examples of FDA decisions linked to lack of patient representation in line with U.S. demographic and/or disease prevalence (Exhibit 25). In the last two years, the FDA issued multiple complete response letters (CRLs) indicating that currently submitted data packages do not support an approval in the U.S. in oncology for sintilimab in non-small-cell lung cancer,[44] surufatinib in pancreatic cancer[45] and retifanlimab in squamous cell carcinoma of the anal canal.[46] In each of these cases, FDA feedback made clear that the decisions were at

Exhibit 25: Recent examples of oncology CRL or post-approval requirements linked to lack of clinical program diversity

FDA ACTION	DRUG	INDICATION	DIVERSITY RELATED REASON FOR ACTION
Complete Response Letter (CRL)	sintilimab	NSCLC	CRL cited multiple issues including lack of patient diversity due to use of single-country foreign data to support U.S. filing[44]
	surufatinib	pancreatic tumor	CRL indicated that a multi-regional clinical trial (“MRCT”) is required for U.S. approval[45]
	retifanlimab	squamous cell carcinoma of the anal canal	CRL cited multiple data issues including lack of data on diverse patients[46]
Post approval requirements	infigratinib	cholangiocarcinoma	Post-approval diversity requirement: accelerated approval with post-marketing confirmational RCT to include racial and ethnic representation “proportional to the FGFR2 sub-groups in the U.S. population"[16]
	umbralisib	lymphoma	Post-approval diversity requirement: accelerated approval with post-marketing confirmational RCT to include sufficient numbers of racial and ethnic patients to better reflect U.S. patient population[17]

least partially due to lack of patient representativeness relative to U.S. demographics. Additionally, examples of accelerated approvals with post-marketing requirements that include explicit guidance to ensure diverse patient representation in ongoing trials include infigratinib[16] therapy for cholangiocarcinoma and umbralisib[17] for lymphoma. These are important examples, because while the FDA has stopped short of specifying diversity thresholds, they have reiterated the need to meaningfully demonstrate planning and action appropriate to the medicine in development to ensure that drug safety and efficacy information, access, and experience is equitably aligned to the patient population that will be using the medicine post approval.

Finally, beyond explicit FDA expectations for sponsors to explore the potential for differential effect pre-market, there are also ongoing indicators and examples of national payer focus on drug effect in underserved patient populations.[47,48] The recent decision from CMS to provide limited coverage of aducanumab in Alzheimer's disease (AD), known as coverage with evidence development (CED), is partially attributed to lack of efficacy data in a broadly applicable patient population.[49,50] A key criteria for Centers for Medicare & Medicaid Services (CMS) coverage of Aduhelm will be that ongoing clinical trials include a racially and ethnically representative set of patients. CMS lays out very clear rationale for its directive to ensure underserved populations are included, which could signal increased scrutiny of the representativeness of evidence behind FDA approved medicines moving forward: "...In order to address these barriers in coverage and care, it is critical that these patients are engaged, recruited, and retained in future trials. Due to the lack of diversity in previous trials, the higher prevalence of AD in Black and non-White Americans, and the directives in Executive Order 13985, Advancing Racial Equity and Support for Underserved Communities Through the Federal Government, CMS is proposing as a trial requirement that the diversity of patients included in each trial must be representative of the national population diagnosed with AD".[51]

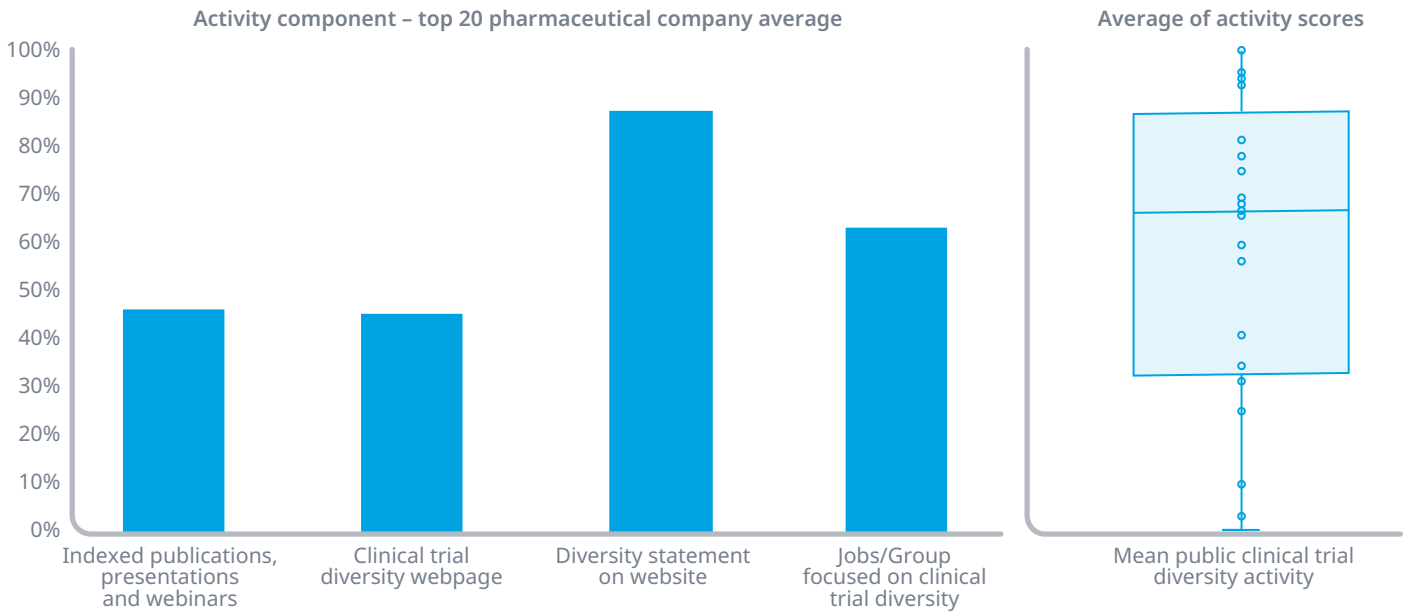
While the FDA has stopped short of specifying diversity thresholds, they have reiterated the need to meaningfully demonstrate planning and action appropriate to the medicine in development.

SPONSORS, CROs AND CLINICAL TRIAL DELIVERY PARTNERS

Existing pharmaceutical sponsor and delivery partner responses to racial and ethnic disparities in clinical trials have been amplified as the last few years have seen an increase in focus on racial injustice. In addition, the COVID-19 crisis around the world exposed great health disparities along racial lines and highlighted the need for inclusive clinical development (Exhibit 2). Most large pharmaceutical companies have made public commitments to efforts that are intended to close clinical trial diversity gaps. Related to this renewed focus, many have dedicated clinical trial diversity webpages, generated thought-leadership on the topic, and created roles and organizations to reinforce focus on diversity in clinical development operations.

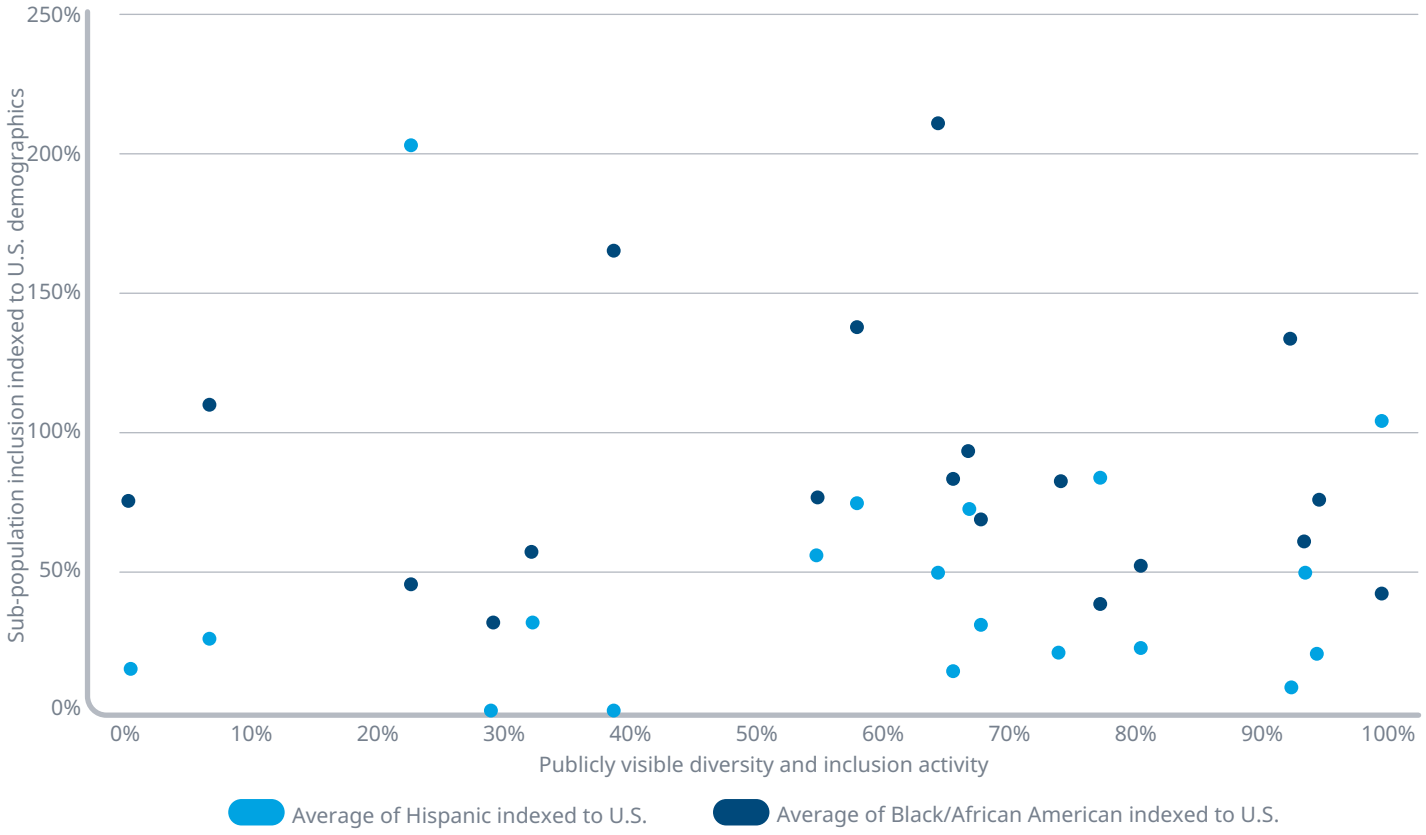
An analysis of publicly visible clinical trial diversity activities of the top 20 pharmaceutical companies included four broad dimensions including thought leadership in the public domain, clinical trial diversity webpage development, a visible clinical development diversity mission, and organizational groups or roles focused on clinical trial diversity (Exhibit 26). Each company showed multiple components of diversity 'presence' although there is a relatively broad array of depth of publicly stated commitments and activities. Examination of Phase II and III trials run by these

Exhibit 26: Top 20 pharmaceutical sponsor public clinical trial diversity activity — 2021



Source: Top 20 pharmaceutical websites; 2022 IQVIA and IQVIA Institute Analysis.
Notes: Visible 2021 activity for each attribute tallied and indexed score generated for each pharmaceutical company for each activity. Average 'Activity Score' calculated based on each of the components and mean across the top 20 pharmaceutical companies plotted along with all individual data points to demonstrate broad range of activity.

Exhibit 27: Correlation of pharmaceutical visible focus on diversity to minority recruiting – Phase II and III, 2018–2021



Source: Top 20 pharmaceutical websites; 2022 IQVIA and IQVIA Institute Analysis; ClinicalTrials.gov June 1, 2022; U.S. Census Bureau.
Notes: Visible 2021 activity for each attribute tallied and indexed score generated for each pharmaceutical company. Average 'Activity Score' calculated based on each of the components and mean across the top 20 pharmaceutical companies by pharmaceutical drug sales plotted along with all individual data points to demonstrate broad range of activity. Includes all interventional Phase II and III trials with industry involvement and any U.S. sites listed on ClinicalTrials.gov as starting after 2009 and completing between the start of 2012 and the end of 2021. Only trials with racial or ethnic data collected were included in calculation of minority inclusion.

companies in the last four years compared to these activities shows no topline correlation between key sub-population recruiting (of Black/African American or Hispanic patients) to publicly visible clinical trial diversity focus (Exhibit 27) although it should be noted that it is likely too early to see completed trials with recruitment data yet for trials started in the last few years.

Despite current lack of top line correlation of publicly visible pharmaceutical sponsor diversity efforts and increasing trial diversity, there are many examples of how this activity is helping drive specific programs and cross-industry collaborations that are targeting key action areas expected to yield improvements to industry ability to access and enroll traditionally underserved communities, including diversifying research workforce and supporting sites in underserved communities, (Exhibit 28). One such partnership is Beacon of Hope, a 10-year initiative involving Novartis, Sanofi and Merck & Co. to support collaboration with 26 historically Black colleges and universities and their Clinical Trial Diversity Centers of Excellence. Sponsor trade associations PhRMA and BIO and consortia TransCelerate have redoubled their prior efforts starting in 2020, with principles statements, multi-stakeholder workshops and various initiatives to support members with tools and infrastructure investments. TransCelerate, launched its Diversity of Participants in Clinical Trials Initiative in 2021

Exhibit 28: Examples of recent pharmaceutical sponsor commitment to increasing diversity in clinical trials in past three years

ENTITY TYPE	ENTITY	ACTION	TIMING	LINK
Industry trade or working group	**Beacon of Hope** (Novartis, Sanofi, Merck partnership with 26+ Historically Black Universities & Medical schools)	10-year collaboration to co-create programs that address the root causes of disparities in health and education, and create greater diversity, equity, inclusion and trust across the research and development ecosystem	Jun-21	https://www.novartis.com/news/beacon-hope-addressing-health-disparities-through-holistic-community-based-collective-action
	DiME (Digital Medicine Society)	Acclinate, Amgen, GSK, Lightship, Medable, Rubix LS, Sage Bionetworks, Savvy Cooperative, and THREAD Research to drive inclusion in digital clinical trials	Mar-22	https://www.dimesociety.org/tours-of-duty/diversity-equity-inclusion/
	MRCT (Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard University)	3-year, 50+-member, international, multi-stakeholder workgroup published "Achieving Diversity, Inclusion, and Equity in Clinical Research" guidance document and toolkit	Aug-20	https://mrctcenter.org/diversity-in-clinical-research/guidance/guidance-document/
	PhRMA (Pharmaceutical Research and Manufacturers of America)	Industry-wide "Commitment to Enhancing Diversity in Clinical Trial Participation" principles	Nov-20	https://catalyst.phrma.org/just-released-phrma-members-new-clinical-trial-diversity-principles
	TransCelerate	Diversity of Participants in Clinical Trials initiative providing sponsors with actionable tools	May-21	https://www.transceleratebiopharmainc.com/initiatives/diversity-of-participants/
Top 20 pharmaceutical company	**Amgen**	RISE: Dedicated internal team dedicated to improving representation on clinical trials	Oct-20	https://www.amgen.com/stories/2021/02/inside-amgens-push-for-greater-diversity-in-clinical-trials
	BMS Foundation	$100M commitment to train and develop 250 new clinical investigators who are racially and ethnically diverse or who have a demonstrated commitment to increasing diversity in clinical trials	Nov-20	https://diversityinclinicaltrials.org/in-the-news
	Eli Lilly	$500,000 of seed money toward a new network focused on community public health research in Indiana aimed at increasing diversity in clinical trials	Jul-22	https://indianapublicradio.org/news/2022/06/eli-lilly-announces-500k-to-improve-diversity-in-clinical-trials/
	GSK	2022 target to ensure over 75% of our interventional clinical trials have a clear demographic plan aligned with disease epidemiology	Jan-22	https://www.gsk.com/en-gb/innovation/trials/diversity-in-clinical-trials/
	Johnson & Johnson	Race to Health Equity initiative with $100M commitment to promote health equity solutions in the next 5 years	Jan-22	https://www.jnj.com/our-race-to-health-equity
	Pfizer	3 year, $10M grant to establish Columbia-Pfizer Clinical Trials Diversity Initiative, targeting under-representation of minorities in clinical trials and as clinical researchers	Sep-21	https://www.cuimc.columbia.edu/news/columbia-university-and-pfizer-establish-clinical-trials-diversity-initiative

Source: Company websites and IQVIA Institute Analysis.

to "move beyond prior awareness-building activities and equip sponsors and ecosystem stakeholders with actionable tools and resources to improve outcomes through diversification of participants in clinical trials." In July 2022, PhRMA announced a $10 M grant to fund The Equitable Breakthroughs in Medicine Development in partnership with Yale School of Medicine, Morehouse School of Medicine, the Research Centers in Minority Institutions Coordinating Center at Morehouse School of Medicine and Vanderbilt University Medical Center, with the goal of building a sustainable network of community-based sites within a pilot program. The Association of CROs (ACRO) created its principles statement in 2021 and launched a multi-week rollout in 2022 to highlight how member CROs and technology companies could help advance diversity in clinical trials.

Internal efforts within companies have also been increasing with creation of clinical trial inclusion and diversity teams for governance and accountability to drive more inclusivity during study design. Staff and leadership diversity within and across pharmaceutical teams is increasing while cultural competency training and employee support is emphasized to further align teams around diversity objectives. Since the pandemic, many sponsors have realigned diversity staff or created roles in trial operations to work directly with study teams. Others have established enrollment goals or portfolio metrics to drive change. As these efforts continue to build momentum, examples of pharmaceutical sponsors and CROs implementing solutions across planning and design, site selection and execution innovation to improve diversity are becoming more and more prevalent and gaining operational traction.

The planning and design of inclusive clinical trials has become a high priority with recent FDA guidance and recognition of the importance of building in diversity from the start to help optimize the balance of inclusiveness and efficiency. Teams are improving and consistently leveraging planning and design tools that consider the needs of the patient and optimizing protocols to minimize patient burden through surveys and even advanced analytics that estimate protocol patient burden. Likewise, the importance of considering the impact of inclusion/exclusion criteria on diversity has become central to protocol design.[52-54] A striking example of increasing planning and design focus on diversity, GSK has set a global demographics & diversity goal that more than 75% of all trials initiated in 2022[55] will proactively plan, design and enroll appropriately diverse trial participants consistent with the disease epidemiology while enabling access to the clinical needs of those most burdened by disease.

Additionally, sponsors and CROs continue to focus on finding the best sites for their study using data and analytics, and increasingly this now includes optimizing for racial and ethnic demographics to ensure inclusive trial recruitment. Many large pharmaceutical companies are turning to trial site selection in regions where Black/African American, Indigenous, and People of Color (BIPOC) and socially disadvantaged populations live. Such is the case of Bristol Myers Squibb (BMS), which committed in 2020 to locating 25% of its U.S. clinical trial research sites in racial or ethnically diverse communities (defined as > 30% non-white) by 2022. As optimized sites are identified, it is critical to ensure that they are recruiting diverse patients in line with their anticipated site potential, while also keeping an eye on the total trial enrollment picture, which requires a mechanism for ongoing visibility and a plan for mitigation to reach trial-level diversity goals.

Finally, sponsors and their partners continue to look for ways to supplement existing sites with community outreach and patient support throughout the trial and, ideally, between trials. Here again, the balance between time, cost, and quality (with diversity being the quality factor here) is a key focal point and activities around

Accessing communities of under-engaged patients in clinical trials is a fundamental opportunity to improve trial speed and quality.

community outreach and patient support are part of reducing the time and cost side of the equation.

Other strategic improvements being deployed by biopharmaceutical companies include the use of technology for decentralizing trial activities that allows for engagement of the patient in new ways — which in many cases may help with access by reducing barriers. These include allowing patients to participate in clinical trials at least in part from home, or from a community-based care settings, to reduce the barrier of in-person visits to a central clinical research site. Proven for its effectiveness in COVID-19 trials where industry needed to reach beyond traditional research sites to access the volume of patients needed, the concept of meta-sites, satellite, mobile, or temporary sites can physically bring studies to populations that live greater distances from, or otherwise might have trouble accessing traditional clinical trial sites. Earlier this year, a non-profit for the digital medicine community (Digital Medicine Society (DiMe)) announced their collaboration with a number of stakeholders of the industry (Acclimate, Amgen, GSK, Lightship, Medable, Rubix LS, Sage Bionetworks, Savvy Cooperative, and THREAD Research) to drive inclusion in digital clinical trials by developing a fit-for-purpose framework that clinical study teams can use to ensure the inclusivity of all participants in the way their trials incorporate technology.

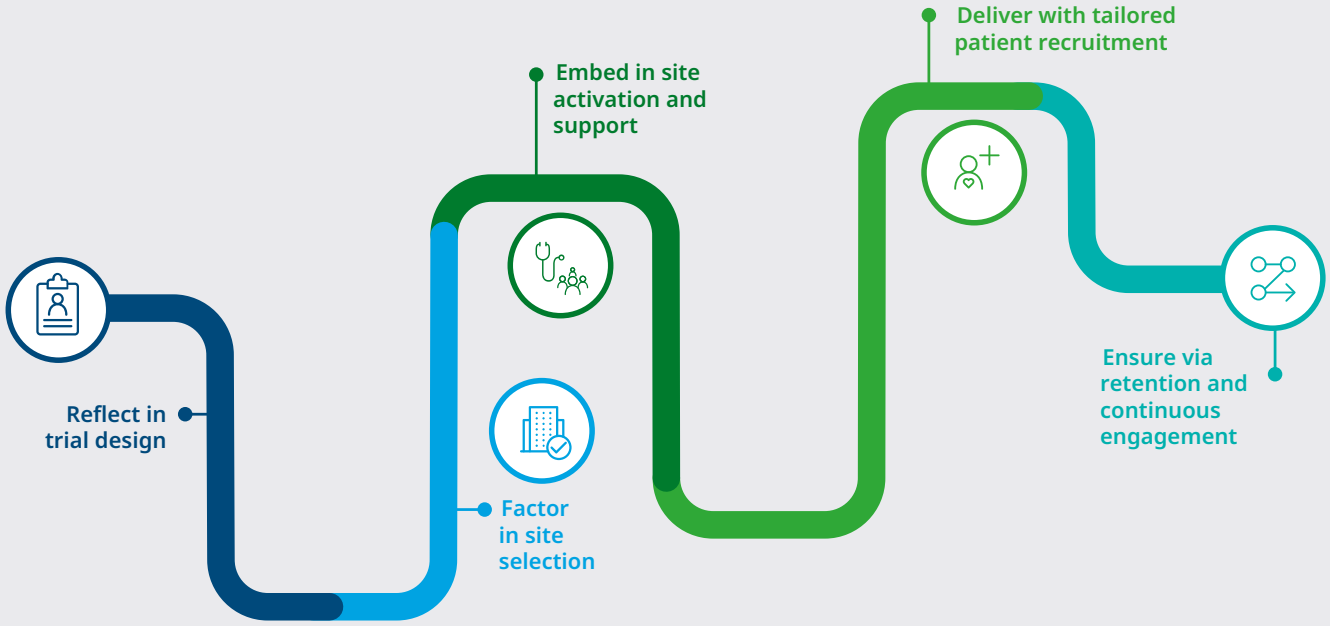
In the case of a recent COVID-19 vaccine trial, a pharmaceutical company and CRO executed each of these component strategies in the context of a global pandemic and historic urgency and scale (Exhibit 29). In this example, the IQVIA CRO team partnered with the sponsor in a very intentional manner to prospectively plan for ensuring diverse participation in the trial. This included extensive analysis of geographic site placement and performance to find sites that would be successful in rapidly engaging minority patients. Operationally, this planning was supported by the project team and site training as well as a multi-channel, community-specific set of patient outreach campaigns. Additionally, project and site-based monitoring and analytics that allowed for real-time tracking and adjustment of site balance ensured very purposeful recruiting to ensure trial patients represented patients most impacted by the virus. As a result, both Black/African American patients and Hispanic patients were recruited at levels that exceeded U.S. Census demographics and this was better aligned with COVID impact.

Use of technology to monitor trial enrollment progress is not new, yet its tailored use for achieving diversity goals proved to be a key success factor in a trial predating today's current focus. An example where intentional planning for diversity and tracking to established targets was a particular enabler of success is the C-EDGE program, executed by Merck & Co. and supported by the Spark Portal, developed by DrugDev, now an IQVIA clinical technology platform (Exhibit 30). Planning for the execution of this program included factoring a trial level diversity goal in site selection and prioritizing inclusion of sites with the ability to recruit diverse patients. Operational success factors included explicit goal setting at site level and use of a dynamic site-facing platform that included dashboards that showed both site and sponsor progress to targets. Feedback and clear guidance on real time recruiting progress and priorities were provided to each site on the dashboard and through regular email communication. These operational support structures helped the team to exceed minority enrollment goals of 20% with randomization of 26.5% minority patients on a very tight timeline.

Case study: COVID-19 vaccine trial example of pharmaceutical and CRO focus on diversity in clinical trials

APPROACH TO DIVERSITY & INCLUSION

Exhibit 29: Key process points to ensure diversity in clinical trials



CRITICAL SUCCESS FACTORS

- ✓ Early strategic Diversity & Inclusion (D&I) planning and feasibility
- ✓ Customized analytics and precision modeling
- ✓ Culturally tailored approaches
- ✓ Agile and adaptive delivery mechanisms

RESULTS

COVID-19 Vaccine D&I Enrollment Exceeded Industry Average

Enrollment of COVID-19 EUA Vaccine Trials was meaningfully more inclusive than other similar trials:

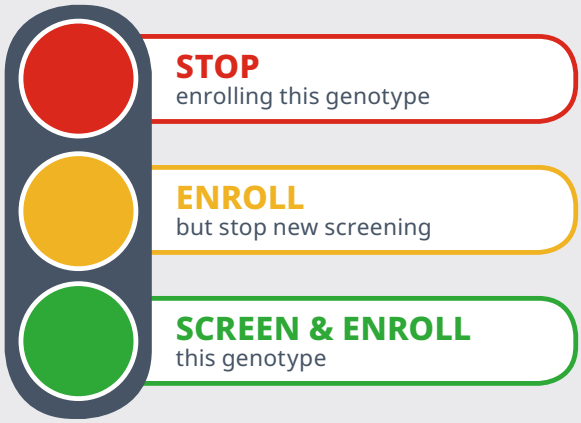
- 16% Black/African American participants (compared to 10% average)
- 35% Hispanic participants (compared to 23% average)

Source: IQVIA Analysis.

Case study: Dynamic enrollment tracking for a Hep-C clinical trial – using technology for dynamic enrollment tracking

SITUATION

- The investigator portal provided sites with enrollment status based on current diversity metrics
- Using twice-daily IVR feeds to update the portal with current diversity enrollment numbers, the **tracker acted as a virtual traffic light** for the screening and randomization of various genotypes at each site so sites could focus their efforts on patients with specific genotypes

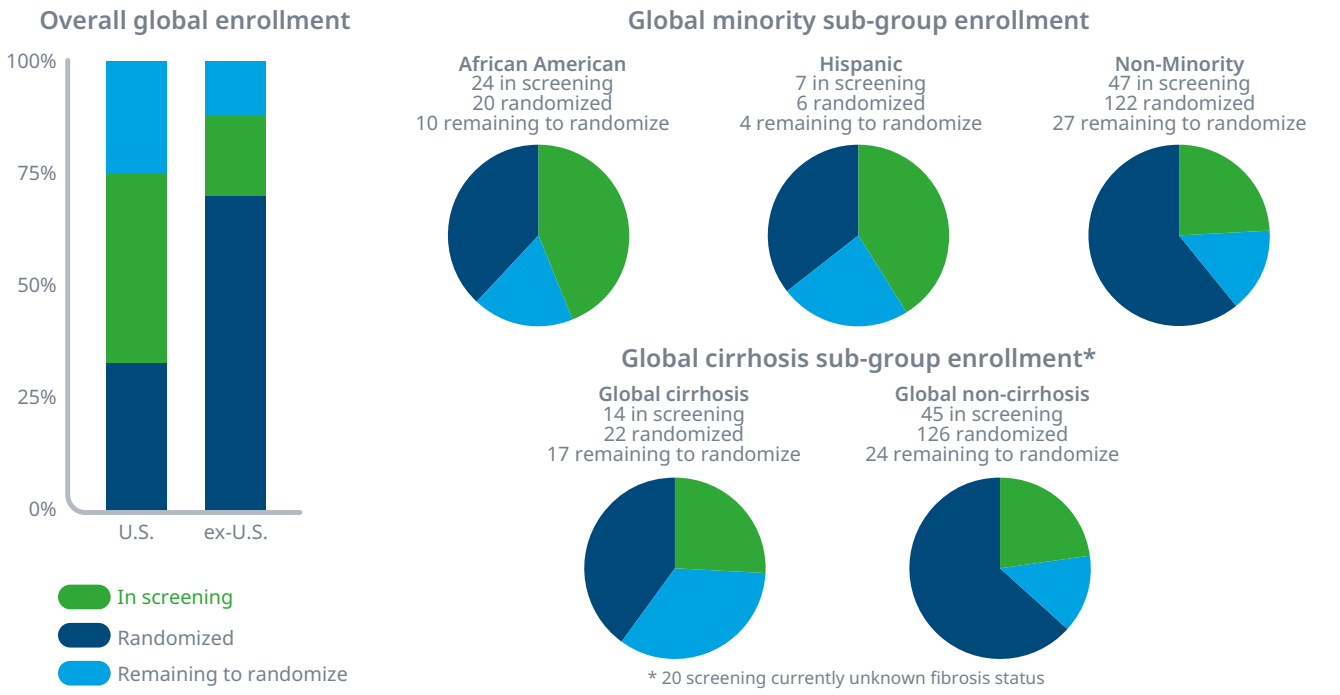


RESULTS

With an outstanding **26% actual minority participation rate**, the sponsor **surpassed the diversity goals** set by the FDA through the combination of its commitment, educational materials, and this portal for dynamic real-time enrollment tracking and ongoing site engagement.

"The combination of education information along with technology tools allowed us to far surpass our goal. It was something that my team and I took pride in and something we think is worth sharing with the industry."
Head of Global Operations

Exhibit 30: Enrollment dashboard — global



Source: IQVIA Analysis; https://www.drugdev.com/uncategorized/merck-improved-clinical-trial-patient-diversity-using-dynamic-enrollment-tracker/

Site interviews

DR. ROBERTO AGUIRRE CPI/CCRP, Chief Medical Officer, AGA Clinical Trials
A multispecialty research facility conducting Phase I-IV clinical trials in Miami, Florida

BEN KARSAI, Co-Founder and Chief Business Development Officer of Monroe Biomedical
A dedicated clinical research facility in Monroe, North Carolina

DR. FABIAN SANDOVAL, MD. President and CEO Emerson Clinical Research Institute
Community based clinical research facilities in the Washington, DC metropolitan area

As clinical research sponsors and their partners focus on diversity on their trials, one of the most important decisions is where to conduct the trial. In depth analysis of geographic patient densities to inform site focus is a key first step, starting with trial country selection (Exhibit 15). To further align to intended patients, sponsors and CROs often leverage more detailed demographic data to select sites that are located within higher densities of under-represented patients and analysis of historical recruitment of under-represented sub-populations shows that some sites far 'out-perform'.[56-58] These sites are extremely valuable to helping ensure trials reach representative inclusivity, and as such they are viewed as important partners in clinical research diversity strategies. Sponsors often use rigorous screening processes to identify and partner with these sites and site staff diversity, alignment to diversity goals, and use of proven enrollment strategies are all characteristics that are looked for to identify sites that will be make strong contribution to trial diversity.

Sites that recruit key sub-populations at rates that exceed their underlying demographics provide critical insights into how best to engage under-represented populations in the clinical research process. Structured interviews with leaders of a few of these sites reiterate and provide examples of fundamental focus areas to drive site success in engaging under-represented communities. These fundamentals are linked and include building trust and connectivity with patient communities, providing value and continuity to the patient and community, and providing flexibility and culturally-relevant support to ensure equitable patient access to clinical research.

Community Trust
Building trust within communities at the site was the most often mentioned driver of success in recruiting under-represented patients to clinical research.

"A patient centric approach in clinical research recognizes an important distinction—there is a fundamental difference between patients seeking treatment out of necessity and volunteers offering their time for a clinical trial. Trust is the foundation of a patient's decision to participate in a study."

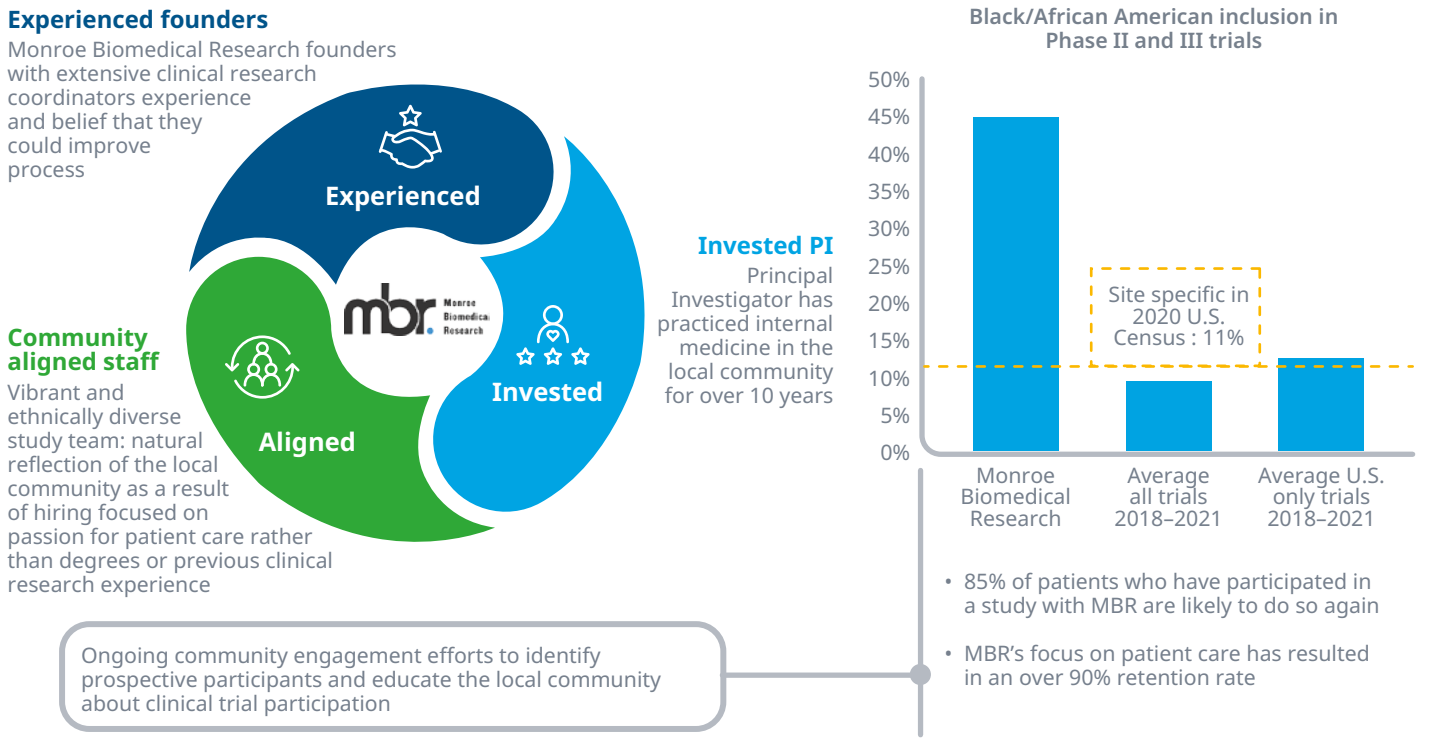
"Trust goes hand in hand with comfort and satisfaction. In our experience, regardless of race or ethnicity, trust is garnered through excellent service and patient care. A study site should always strive for low wait times, a comfortable environment, and a patient centric site staff."

— Ben Karsai, Monroe Biomedical

One key is employing staff that reflects the community being served, and ensuring a cohesive team aligned around the mission of supporting patient care and ease of access. Monroe Biomedical Research is an example of a site that that responded to the call to include more Black/African American patients in clinical trials and has seen its patient-centered approach result in enrollment rates exceeding expectations relative to the local demographics (Exhibit 31). Ben Karsai, one of the co-founders, attributes the company's recruitment and high patient satisfaction to an organically-grown, patient-oriented staff and a thoughtfully designed trial environment.

Creating this trust and comfort is tightly linked to patients' reassurance that their racial background will not impact the care they will receive over the course of their study participation. Here, Mr. Karsai explained that patients' trust stems from the experience they have with the site's study team. If a patient works with site staff that demonstrate excellent service, including diligence, reliability, and a clear passion for patient care, then the patient will expect the same in turn. However, due to historic abuses and inequities minorities have suffered from research and medical institutions, patients of color require additional assurances that their race will have no bearing on their medical oversite during a study. If a patient observes a racially diverse site staff cooperating and respecting one another, patients of color will expect the same treatment as a result. Mr. Karsai further explained that his site achieved such a study team through a hiring philosophy focusing on diligence, reliability, and passion for healthcare, rather than previous study experience or educational pedigree. This approach has resulted in a site staff that is not only more representative of the local community, but also share a passion for patient care.

Exhibit 31: Monroe Biomedical Research focus on committed and diverse study team



Source: Monroe Biomedical Research interview and recruiting data August 2022; ClinicalTrials.gov June 1, 2022; U.S. Census Bureau.
Notes: "All Trials: includes any trial that had U.S. sites and ex-U.S. sites; U.S. Only are trials with only U.S. sites and All Trials is all of the trials in the data set (Global and U.S. Only combined). Includes all interventional Phase II and III trials with industry involvement and any U.S. sites listed on ClinicalTrials.gov as starting after 2009 and completing in 2020.

"Whenever the topic of ethnic diversity in clinical trials is discussed, someone will inevitably say, 'minority groups will only trust professionals that look like them.' This is such a gross oversimplification. If a patient observes a study team composed of many ethnic backgrounds, interacting and trusting one another, then the patient will know that their racial background will have no bearing on the care they will receive."

— Ben Karsai, Monroe Biomedical

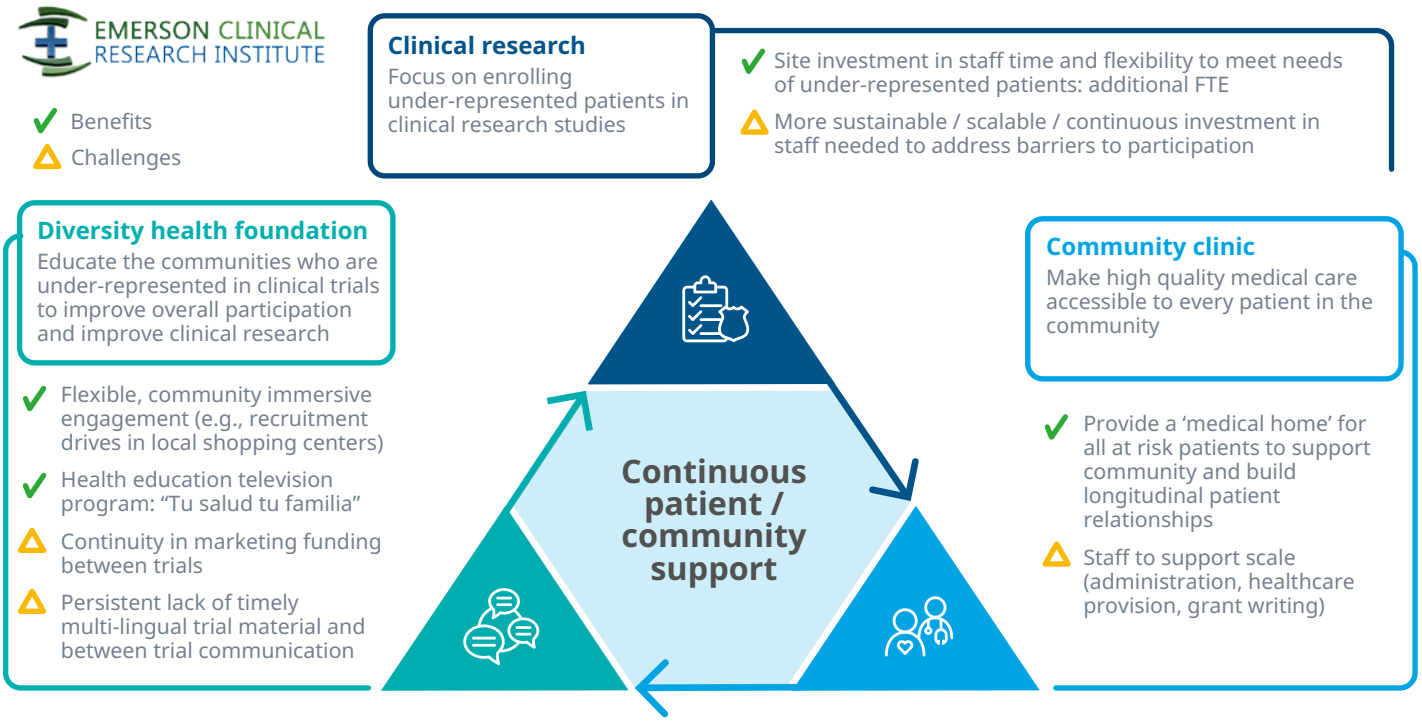
Communication is also a critical part of building trust for sites and partnering with existing community resources to identify the right channels, forums, and formats to share information is highly recommended. In some cases, this will mean using a variety of communication methods including social media, print and even television to reach different segments of the population and in all cases, it will mean making sure to proactively have site, general medical, and research specific materials translated into the right languages to serve communities of focus. As an extension and potential amplifier of all these approaches, building trust through word-of-mouth communication is an important but often overlooked mechanism to driving further community engagement and is a very powerful channel for reaching under-represented patients in the community. Dr. Roberto Aguirre, Principal Investigator at AGA Clinical Site points out that word of mouth can cut both ways — a positive experience can generate multiple referrals, while word of a negative experience can spread even faster. He points out the importance of basic reciprocity and courtesy in thanking volunteers for their contribution to the research.

Flexible Trial Support

Under-represented demographic groups are disproportionately likely to also face socio-economically linked barriers to clinical research participation. Those who work hourly jobs, multiple jobs, or second shift are challenged to attend appointments during standard first shift working hours. Finding childcare, or parent care, to be away from the home to attend research appointments is another common logistical barrier as are transportation issues in getting to sites for screening and follow up research appointments. All the sites interviewed for this work point to the importance of site staff flexibility and commitment to help the patient address these challenges. While there are some examples of clinical development marketing budget including some funding for additional staff support to some of these activities, research directors from Monroe Biomedical Research and Emerson Clinical Research Institute pointed to sites being forced to make their own investments in staff and staff hours to meet patient needs, and both pointed to a challenge in sustaining these investments without support from other stakeholders in the system. Emerson noted that investment does not have to mean a big budget at every site accounting for every patient; it can be a flexible fund to use for those otherwise willing patients who just need a ride or even a babysitter to meet the study visit schedule.

Some of the logistical barriers to participating in clinical trials have the potential to be at least partially addressed through decentralized research activities and tools. As 'virtual trial' solutions work to optimize the balance of at-site and in-home trial activities, site managers caution against relying too heavily on these solutions to fix diversity challenges. Many of the barriers that exist with optimizing under-represented patient participation at sites (trust, lack of awareness, language barriers, health literacy, and lack of economic resources to access the Internet) will still be present and possibly exacerbated with decentralized solutions, and new variables around technology literacy and technology quality will be introduced.

Exhibit 32: Emerson Clinical Research Institute three-tiered patient engagement model



Source: Dr Fabian Sandoval interview, Jun 2022.

Continuous Patient Value

As part of building trust and creating longitudinal patient community engagement, sites interviewed for this research all pointed to the importance of providing continuity in care — and not just providing that care when a patient meets clinical trial inclusion/exclusion criteria. Dr Fabian Sandoval of Emerson Clinical Research Institute (ECRI) in Washington DC, a multi-tiered research, clinic and community engagement model (Exhibit 32) points out that providing access to basic healthcare and screening including blood work, mammograms and ultrasounds in addition to clinical trial opportunities is extremely impactful in helping patients from under-represented communities gain trust in the healthcare system.

These steps help patients see that they can afford to take control of their own healthcare and to start to see better outcomes. This also helps to build trust by providing longitudinal engagement with patients in and out of the context of a clinical trial. Similarly, Dr Aguirre points out that an important aspect of this is to ensure access to multiple trials at a site at any given time so that when a patient screen fails for one, there is still an option for them to participate in another.

Concerted engagement with the community outside of the clinic is also a part of the ECRI model. Maintaining a separate Health Foundation for community outreach provides another way for under-represented patients to be engaged in the healthcare system. The site's foundation works with existing trusted community structures, including faith-based groups, schools, places of commerce and even local consulates to reach potential patients. Sites see a real opportunity to drive

"It's that they're getting ultrasounds, they're getting blood work to see what they're cholesterol is look like.... so that access to care that they would otherwise not have access to is a big bonus that we tried to promote to our communities"

— Dr. Fabian Sandoval, Emerson Clinical Research Institute

this sort of in-person community visibility and pre-screening activity, but caution that it cannot be only for a specific trial — this sort of engagement needs to be ongoing to engender trust and maintain a connection between the site and the community.

Ongoing site improvement opportunities

Discussions with high performing sites highlighted some common missteps that also represent practical opportunities for ongoing optimization of patient participation in clinical trials. Some of the most straightforward center around sponsor and CRO planning and investment in recruiting under-represented patients. One of the most common is failure to have translated trial materials available for Hispanic populations at the onset of trial recruitment leading to delays that can be extremely detrimental to achieving equitable representation. Often a trial's recruitment period closes before IRB-approved, translated materials are made available to sites, undermining the site's ability to deliver on a trial opportunity otherwise promoted to the community.

Additionally, recruitment/trial marketing budgets often fail to cover multiple communication channels needed to reach underserved patients and create gaps in community access to the trial. Sites note that leveraging their experiences and insights about best channels to engage local communities — and not just those selected by a national agency — is a missed opportunity.

Fundamental to establishing true community relationships is early and ongoing engagement and reciprocity, yet site revenue streams to fund these activities are trial specific. Funding for between-trial activities to maintain engagement with diverse communities is a recognized gap in need of a multi-stakeholder solution.

"We have situations with trials that are starting up and mass text messages are sent and patients know that the trial started — but they are in essence being told 'but it's not for you' because they don't have a Spanish translation even two months after the trial has started"

— Dr. Roberto Aguirre, AGA Clinical

"It makes it very hard to do highly effective patient outreach like screening patients at the mall, or meeting them at the consulate with no trial budget - we lose a lot of money at it, but it's the only way that I know we can reach those patients that need our help"

— Dr. Fabian Sandoval, Emerson Clinical Research Institute

Finally, sites often must fund staff overtime to enable patient-centric flexibility at a higher rate on highly diverse clinical trials, and sites report these extra efforts are rarely funded in trial site grants — thus diverse sites end up operating on a thinner profit margin than sites that do not provide incremental services or hours to ensure under-represented patient inclusion in their trials.

Another area of opportunity that was discussed with high-performing sites is building better sponsor to site partnerships for highly diverse sites. These partnerships could focus on providing preferred, trust-based engagement including streamlined qualification processes, contracting and operational start-up. This sort of partnership would also help to address technology issues as direct-to-patient outreach and patient-centered data collection are implemented on more trials. Multiple data vendors are being used per trial to implement these new technologies and are creating prohibitive complexity, bottlenecks, and quality risks. From a site perspective, the number of vendors and interfaces rapidly proliferates across multiple studies and creates significant extra work and potential quality issues. Focus on streamlined technology is particularly critical for patient-facing technology usage in under-represented patient populations that may not be as tech savvy and/or for whom English is a second language as decentralized trial capabilities continue to be part of clinical research solutions going forward.

Patient advocacy interview

MAIMAH KARMO, President and CEO, Tigerlily Foundation

A national non-profit breast cancer foundation that is dedicated to educating, advocating for, empowering and proving hands-on support to young women affected by breast cancer

As with sites, patients and patient advocacy groups have been playing a more prominent role in advancing equitable representation on trials especially in the past few years. Efforts to improve inclusive patient access are coming from a variety of patient group types including those that are disease focused (e.g., American Cancer Society, Tigerlily Foundation, and Metastatic Breast Cancer Association (MBCA)) to those that are ethnically aligned health advocates (e.g., National Alliance for Hispanic Health). These efforts cover the spectrum of research and awareness building and patient and critical stakeholder education on tools and approaches to empower patients and drive more inclusive patient engagement, in addition to policy advocacy to continue driving progress and lessen systemic barriers to equitable patient participation.

Awareness and trust

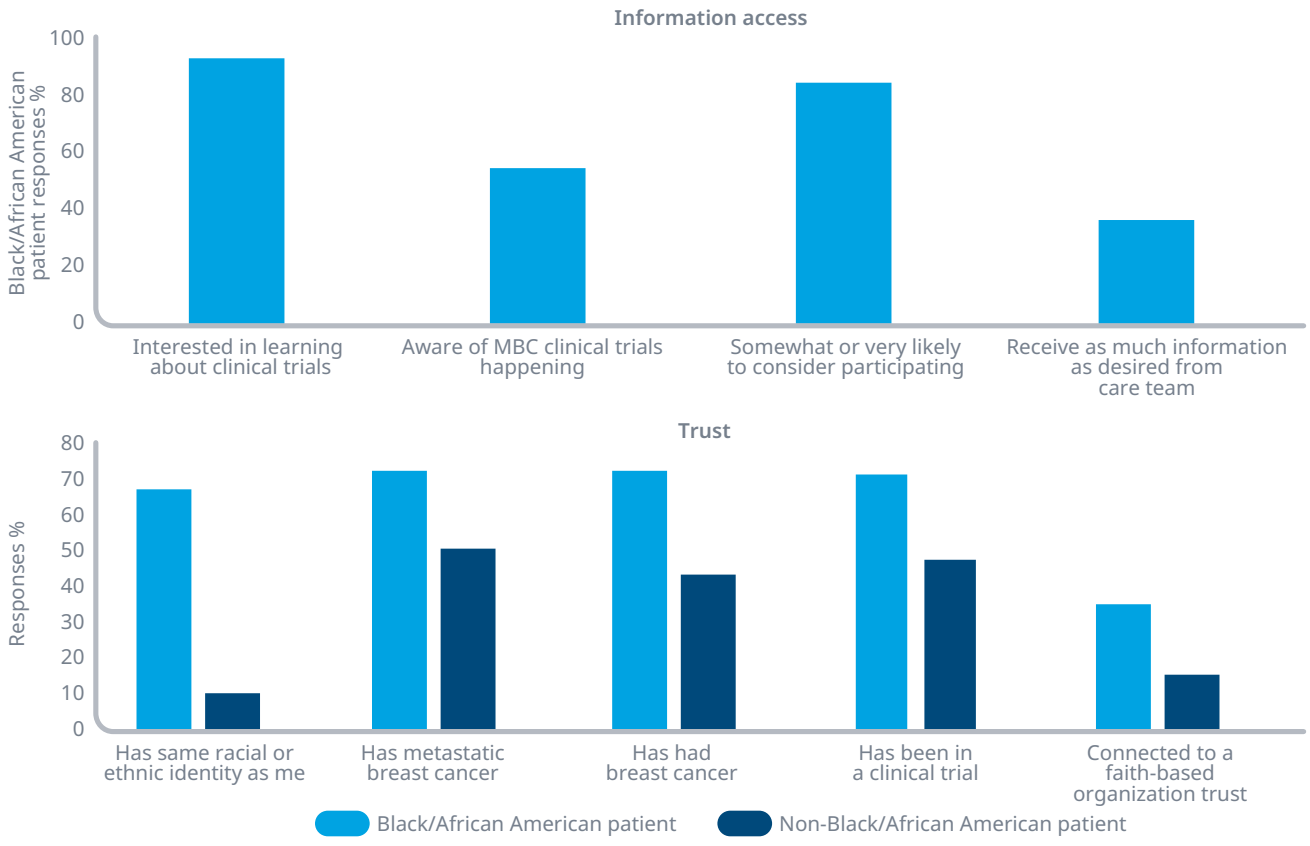
Awareness building has been a key focus for patient advocacy groups working to improve diversity in clinical research. Efforts have been focused not just among patients, but also with providers and investigators. This work is targeting implicit and explicit bias that limits who is asked to participate in clinical research. Recent research from the BECOME initiative[59] in metastatic breast cancer — a disease that disproportionately impacts Black/African American women[4] — demonstrates that low Black/African American participation is linked to a failure of the system to include these patients, even when patients are highly motivated to participate. In the survey, 92% of the Black/African American respondents indicated interest in participating in clinical trials, while just 54% were aware of cancer trials that would be available to them (Exhibit 33). These results point to an urgent need for clear communication with sites about the intent to enroll representative populations and challenging the perception that minority patients are not willing or otherwise likely to enroll. Critical to the method of outreach, the survey also found that Black/African American patients were much more willing to trust information from sources with whom they shared experience.

Efforts to improve inclusive patient access are coming from a variety of patient group types including those that are disease focused.

BECOME survey results and actions

The Black Experience of Clinical Trials and Opportunities for Meaningful Engagement (BECOME) research project from the Metastatic Breast Cancer Association (MBCA) was undertaken to better understand Black patient experience with, and interest in clinical research. The survey was designed to explore and compare attitudes and experiences with clinical research and to better understand disparities between patients who self-identify as Black versus White. The results are from a web-based survey of adults in the U.S. living with MBC and respondents were weighted toward highly educated patients with high socio-economic status and access to social media but still reveal significant distinctions in Black versus White access to clinical research information and opportunities.

Exhibit 33: The BECOME (Black Experience of Clinical Trials and Opportunities for Meaningful Engagement) project



Source: Metastatic Breast Cancer Alliance. Black Experience of Clinical Trials and Opportunities for Meaningful Engagement, Oct 2022.

Empowerment

Patient groups are also focusing on providing specific tools to empower patients in pursuing clinical trial opportunities to help address a critical barrier to participation. Maimah Karmo, CEO of the Tigerlily Foundation explains that patients do not just need to be educated or empowered when they get a disease and would benefit from enrolling in a clinical trial, but they also need to be empowered before they require therapies. With this basic tenant in mind, Tigerlily Foundation has been working on multiple community-oriented solutions to help proactively build this empowerment — particularly with women of color.

> *"What's been helpful is empowering patients to realize 'I can get that [clinical trial]. I can ask these questions. I have rights to keep my job. I can get transportation'."*
>
> *— Maimah Karmo, Tigerlily Foundation*

As an example, The Tigerlily Foundation has been disseminating Barrier Toolkits (Exhibit 34) to support their breast cancer patients in navigating the health system and clinical research system to support equitable inclusion and treatment. These toolkits were developed after extensive patient interviews and listening sessions and are designed to address the information and communication gap with Black/African American communities where triple-negative breast cancer (TNBC) is being underdiagnosed and patients are heavily under-represented in clinical trials. The toolkits are designed to provide culturally accessible information to help patients to understand the importance of clinical trials as a potential treatment option, to enable them to find trials, and learn how to advocate for themselves. Notably, these toolkits contain provider focused information that patients can share with their providers to increase understanding of healthcare system bias and their own inherent bias and barriers to Black/African American patient clinical trial participation.

In addition to toolkit information targeted to providers, Tigerlily has been having success engaging providers at the community level in patient listening sessions via the Pull up a Seat program. This program is proving to be extremely powerful in dispelling inherent bias and helping providers understand the unintended impacts of some of their actions. These sessions provide an opportunity for patients to feel safe sharing their experience, concerns, and fears — and critically, they validate and model speaking up in the doctor's office with concerns and questions going forward.

Finally, the Toolkits and listening sessions are complemented through another highly impactful patient empowerment solution called ANGEL Advocates. In this program, Tigerlily is recruiting and training women of color, who are at high risk, and those who have been impacted by breast cancer to act as informed advocates for themselves and on behalf of others in their community. These women are resources to their community and can provide community specific feedback to other stakeholders in the clinical research system to ensure all aspects of clinical trials (e.g., outreach channels, content, site experience, specific barriers to participation, etc.) are relevant to the diverse patients within the community.

Tigerlily Foundation Barriers Toolkit: Enabling patients and providers

As a response to highly disparate breast cancer outcomes across patient populations, Tigerlily Foundation has created a toolkit with 13 modules to support, educate and empower patients and providers in the breast cancer space. These modules address the topic of barriers to clinical trial participation from a top-level view, but also address the drivers of disparate participation and outcomes.

Patient toolkits focus on holistic view of the clinical trial process and FAQs, geographical barriers, enabling trust building with healthcare team, healthy lifestyle choices, addressing environmental disparities, addressing socio-economic barriers, mental health considerations and health literacy challenges.

Provider toolkits focus on the issue of racial disparity in clinical research and specifically works to raise provider focus on disparities in health care access, the ongoing reality of medical racism, bias in media portrayal of minority races and the importance of representativeness in the healthcare workforce.

Exhibit 34: Tigerlily Foundation Barrier Toolkits

Source: Tigerlily Foundation Barriers Toolkits: https://www.tigerlilyfoundation.org/barrier-toolkits/ (accessed Sep 2022).

Policy

Patient advocacy groups have been a consistent force in influencing regulatory policy over the years, including diversity related changes outlined earlier in this chapter. For example, a coalition of cancer patient and provider organizations were successful in garnering changes to Medicaid coverage policy to include routine care for clinical trial participants in the Clinical Treatment Act of 2020.[60] Two years after joining Congressional leaders in calling for COVID trials to be diverse, patient advocacy groups are keeping clinical trial diversity at the top of their public policy agendas and that of their Congressional supporters. In 2022, advocacy groups were successful in getting many priority provisions included in the U.S. House version of PDUFA VII, though the Senate and conference negotiators eventually opted to reauthorize user fees without any policy riders.

As of publication of this report, Congressional leaders have agreed to consider many of the proposed PDUFA VII policy riders along with expiring FDA programs before the end of the year. It remains to be seen whether these measures will advance in this Congress or resurface in the next. Regardless, the July 11 letter (Exhibit 35) demonstrates broad consensus across these groups that diversity needs to be addressed, and crystallizes advocacy focus on enabling community-based and decentralized trials, more accountability for diversity planning, and better clarity on patient reimbursement to help remove financial barriers for trial participation.

In addition to providing a robust patient perspective, the visible assembly of this broad coalition of patient advocacy groups further underlines the urgency and opportunity of the moment and provides a formidable patient foundation for ongoing advocacy and empowerment toward equitable clinical research participation.

Two years after joining Congressional leaders in calling for COVID trials to be diverse, patient advocacy groups are keeping clinical trial diversity at the top of their public policy agendas and that of their Congressional supporters.

Exhibit 35: Patient advocacy groups' letter to Congress to support diversity in clinical trials provisions in 2022 PDUFA

Three critical provisions

Meet patients where they are

- Build on COVID-19 legislation which removed barriers to trial access by enabling remote trial methods to bring trials to community settings and into patients' homes
- Increase resources to build out community-based clinical research network

Proactive planning

- Build on FDA draft guidance encouraging sponsors to develop diversity plans to make plans mandatory as part of final PDUFA legislation

Addressing financial barriers

- Provide clarity on safe harbor on kickback statutes to ensure sponsors can alleviate financial barriers that disproportionately prevent socio-economically constrained patients from participating in clinical trials (e.g., including travel costs and internet access)

Signed Patient Advocacy Groups

- American Cancer Society Cancer Action Network
- National Comprehensive Cancer Network
- The Leukemia & Lymphoma Society
- American Association for Cancer Research
- American Heart Association
- American Kidney Fund
- American Liver Foundation
- American Lung Association
- American Society for Radiation Oncology (ASTRO)
- American Society of Hematology
- Arthritis Foundation
- Association for Clinical Oncology
- Association of American Cancer Institutes
- Association of Community Cancer Centers (ACCC)
- Association of Oncology Social Work
- Asthma and Allergy Foundation of America
- Bladder Cancer Advocacy Network
- Breastcancer.org
- CancerCare
- Cancer Support Community
- Children's Cancer Cause
- Colorectal Cancer Alliance
- Debbie's Dream Foundation: Curing Stomach Cancer
- DEnali Oncology Group
- Epilepsy Foundation
- Fight Colorectal Cancer
- Florida Society of Clinical Oncology
- FORCE: Facing Our Risk of Cancer Empowered
- Friends of Cancer Research
- Global Liver Institute
- GO2 Foundation for Lung Cancer
- Hemophilia Federation of America
- Illinois Medical Oncology Society
- International Myeloma Foundation
- JDRF
- KidneyCAN
- Livestrong
- LUNGevity Foundation
- Lymphedema Advocacy Group
- Maryland/DC Society of Clinical Oncology
- Men's Health Network
- Michigan Society of Hematology and Oncology
- National Brain Tumor Society
- National Cancer Registrars Association
- National Eczema Association
- National Health Council
- National Hemophilia Foundation
- National Kidney Foundation
- National Marrow Donor Program/Be The Match
- National MS Society
- National Organization for Rare Disorders
- National Patient Advocate Foundation
- National Psoriasis Foundation
- Oklahoma Society of Clinical Oncology
- Oncology Nursing Society
- Patient Access Network (PAN) Foundation
- Pennsylvania Prostate Cancer Coalition (PPCC)
- Prevent Cancer Foundation
- Susan G. Komen
- The AIDS Institute
- The ALS Association
- The Tigerlily Foundation
- Triage Cancer
- U.S. Against Alzheimer's disease
- Winship Cancer Institute of Emory University
- WomenHeart: The National Coalition for Women with Heart Disease
- ZERO - The End of Prostate Cancer

Source: ASCO, https://www.fightcancer.org/releases/eighty-seven-patient-groups-urge-congress-pass-legislation-would-improve-clinical-trial.

Maintaining momentum and progress

+ **The biomedical ecosystem has an opportunity to build on current momentum to solidify and advance clinical development diversity gains**

+ **Setting goals for what "good" looks like and measuring progress against those goals using aligned and objective methods, is central to sustained focus on improving diversity in clinical trials and requires a set of transparent metrics of activity and outcomes that go beyond current U.S. FDA requirements**

+ **Tools such as the Inclusivity Quotient can be used to baseline, track, and assess progress toward diversity goals as clinical trials and programs — and the industry — progress**

+ **Continued collaboration among sponsors, CROs, site and patient organizations and government is critical to capitalize on the recent industry-wide momentum, align objectives for shared success and accelerate progress toward truly inclusive clinical development and reduced disparities in healthcare outcomes**

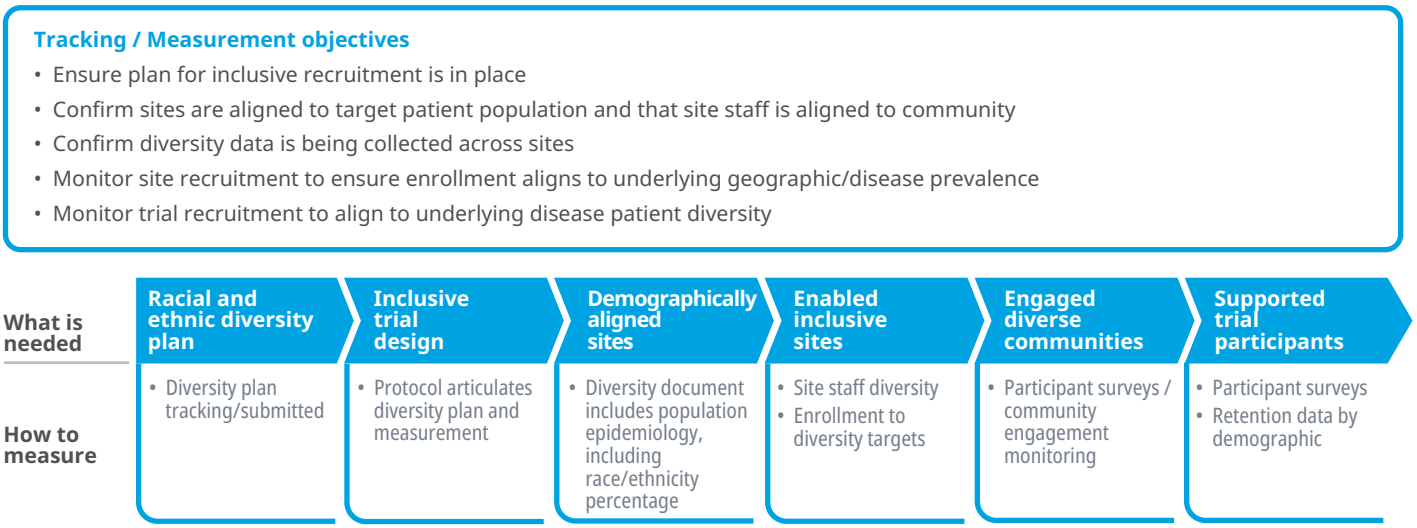
With broad cross-stakeholder attention to actions to support diversity in clinical trials including policy and guidance updates, the industry has seen a dramatic increase in clinical trial diversity data reporting in the last half decade. More concerted ClinicalTrials.gov reporting requirements, and implementation of the FDA Snapshots program have increased transparency and importantly, this increased transparency has shown that an imbalance in clinical trial participation persists. Characterization of diversity in clinical trials over the past decade has highlighted the complexity of optimizing trial inclusivity with therapeutic and geographic differences driving wide variability in what success means for each drug program and set of trials. The discourse on this issue has long focused on the constellation of barriers, which are rooted deeply in personal, societal, health system and trial operations levels. Since 2020, the discussion has shifted toward action to work around those barriers and embed solutions as operational norms. Given the complexity and time for change to surface as results, cross-stakeholder partnership is going to be needed to deliver on current momentum.

Looking across stakeholders, one of the clearest opportunities to improve diversity in clinical development is through better trial and program diversity tracking, analysis, and reporting with aligned and objective metrics. Sponsors, CROs, sites, advocates, and policymakers would all benefit from a shared view of what good looks like and how far off any site, trial, program, therapeutic area, or sponsor are from that target. Without the ability to define a measurable goal and show progress, it is impossible to improve.

All stakeholders will benefit from a better view of what good looks like so the industry dialogue can advance from agreement that there is a problem, to specifically addressing the problem.

The challenge is — and has been — that given the trial-size, disease, and geography specific complexities for clinical development diversity, there is no simple 'one size fits all' inclusivity target. Each trial will need to have targets that fit with the objective of patient representativeness at the right level for the disease being treated and in the context of the objective of patient representativeness at the right level for the disease being treated and in the context of the broader clinical development program. Building on recent FDA Guidance,[28] sponsors, CROs and sites have an

Exhibit 36: Measuring progress to drive clinical trial diversity success



Source: IQVIA Expertise; IQVIA Institute Analysis, Aug 2022.

opportunity to set agreed program and trial-specific enrollment diversity goals in the trial planning process (Exhibit 36). These targets can then be factored into program specific plans, processes and accountabilities that together will help the industry further advance toward meaningful inclusivity in clinical development.

Another key challenge faced by each of the stakeholders working on this issue is that trial diversity measurements taken out of context can lose meaning. An average that is measured from the entire pipeline composed of drugs seeking approval across a range of geographies will not fully align to the patient demographic for any of the geographies in which the drugs are intended to be used. A clinical trial for a drug being developed for a rare disease, or a disease that disproportionately affects sub-populations of patients will not be representative if the national racial/ethnic demographic is emulated. Likewise, a particular trial may not meet a diversity target for the market or disease area it is seeking to enter, but the program of trials (or other components of the program) that it is a part of may meet diversity objectives. For these reasons, partnering and discussing with regulators and key stakeholders to determine and optimize the levels of diversity will be important for the program and each trial of each new drug.

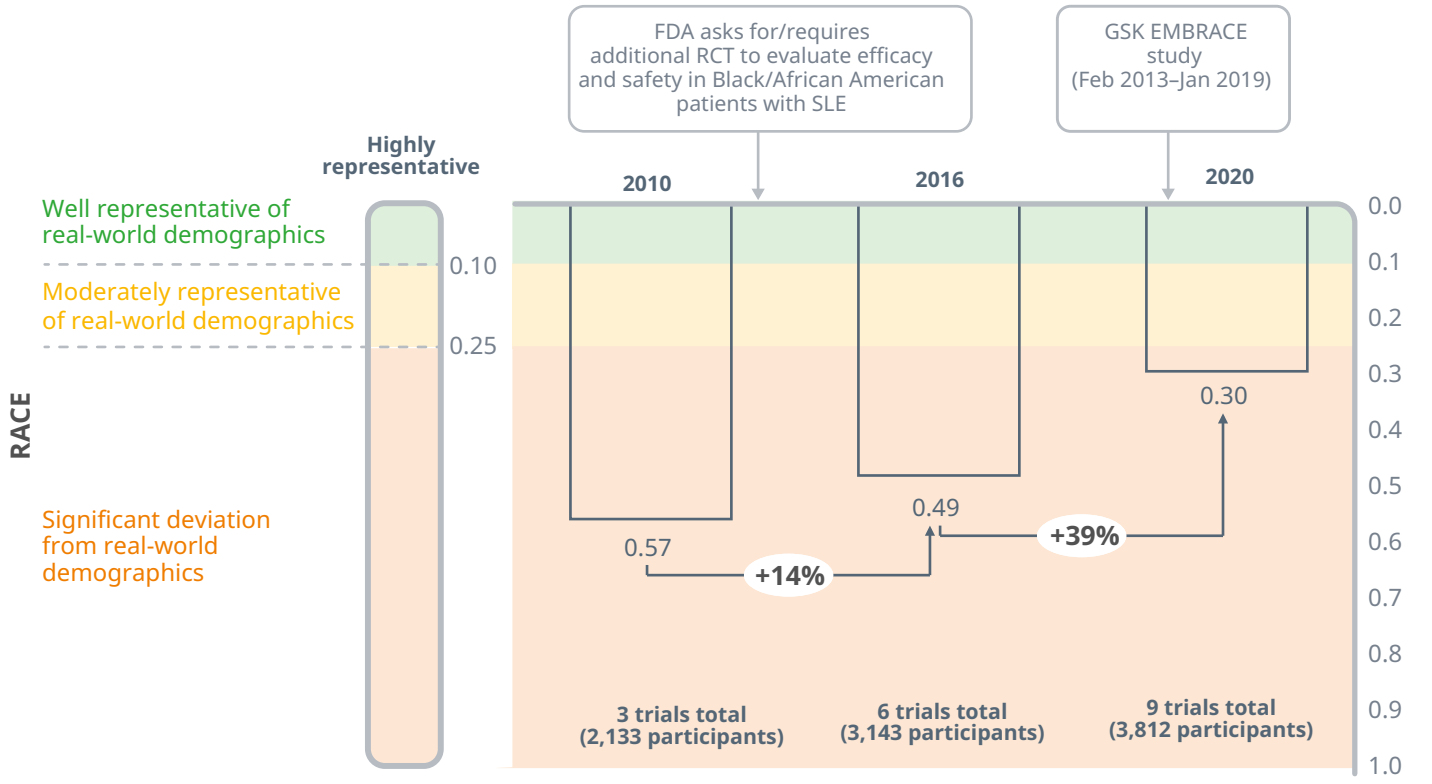
Because each therapeutic area, disease area and drug will have slightly different diversity targets, each trial should have its own contextualized target for success. Industry-wide metrics may need to focus on the number of programs that reach a specific target versus looking at pipeline-wide average sub-population percentages recruited. For this to work, tools like the Inclusivity Quotient (Exhibits 19 and 20) that measure absolute and relative deviation of sub-population inclusion in a trial against underlying disease levels will be needed. This type of tool gives an indexed top-line score of inclusivity across all sub-groups analyzed individually and allows for comparison across drugs being developed for disparate diseases and for use in a range of geographies.

A final example of cross-stakeholder roles, and the impact of cross-trial measurement in ensuring diversity in a clinical program is the belimumab (Benlysta) drug development program. When belimumab was originally approved for the systemic lupus erythematosus (SLE) indication in 2010, the FDA called out a need for further diversity, due to an under-enrollment of minority patients in the original pivotal trials. The under-enrollment was particularly significant because SLE disproportionately affects Black/African American and Hispanic patients (Exhibit 18). As part of the resulting

post-approval commitments, the sponsor designed and successfully executed a 500-patient trial entirely in Black/African American patients to establish the ability to label the drug for use in all patient demographics (the EMBRACE study). Based on the FDA feedback and lessons learned in executing the EMBRACE trial,[61] subsequent trials for Benlysta follow-on indication expansion were very concertedly focused on meeting or exceeding diversity at the same level of disease prevalence in the Black/African American community in the U.S. A retrospective analysis using the Inclusivity Quotient shows that over a span of 10 years, Benlysta's clinical development program-wide minority inclusivity has shown dramatic improvements since the original launch trials (Exhibit 37). This is a higher profile example of FDA requiring post-marketing studies for a lack of diversity, and shows how a tool like the Inclusivity Quotient could give industry a way to show progress and reassure both prescribers and minority patients when evidence meaningfully included "people like them".

On the foundation of decades of experience, tracking and working to improve diversity in clinical development to help remove disparities in the health outcomes in the U.S. and globally, today's clinical development stakeholders have an opportunity to turn current momentum into step-change inclusivity improvements. As stakeholders such as sites, patient advocacy groups, and payers become more central to clinical development success, and pharmaceutical companies' diversity objectives and business outcomes continue to move into alignment, space is being created to change some long-standing assumptions about patient engagement and enrollment. The current sense of shared urgency, the shifts in the clinical development ecosystem, and advances in technology put discernable advances in clinical development diversity that drive better and faster patient outcomes within reach.

Exhibit 37: Inclusivity Quotient analysis of Benlysta clinical program diversity over time



Source: ClinicalTrials.gov; IQVIA Analysis.

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About the authors

MURRAY AITKEN
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Murray Aitken is Executive Director, IQVIA Institute for Human Data Science, which provides policy setters and decisionmakers in the global health sector with objective insights into healthcare dynamics. He led the IMS Institute for Healthcare Informatics, now the IQVIA Institute, since its inception in January 2011. Murray previously was Senior Vice President, Healthcare Insight, leading IMS Health's thought leadership initiatives worldwide. Before that, he served as Senior Vice President, Corporate Strategy, from 2004 to 2007. Murray joined IMS Health in 2001 with responsibility for developing the company's consulting and services businesses. Prior to IMS Health, Murray had a 14-year career with McKinsey & Company, where he was a leader in the Pharmaceutical and Medical Products practice from 1997 to 2001. Murray writes and speaks regularly on the challenges facing the healthcare industry. He is editor of Health IQ, a publication focused on the value of information in advancing evidence-based healthcare, and also serves on the editorial advisory board of Pharmaceutical Executive. Murray holds a Master of Commerce degree from the University of Auckland in New Zealand, and received an M.B.A. degree with distinction from Harvard University.

NICOLE CONNELLY
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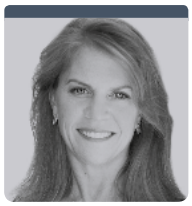
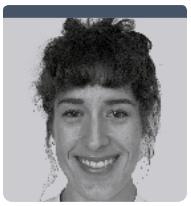
Nicole serves as Research Director for the IQVIA Institute for Human Data Science, leading Institute research focused on global pharmaceutical R&D-related topics. In this work, she partners with team members, IQVIA experts, and industry thought leaders to bring insights on R&D performance and ongoing innovation. Prior to joining the Institute in late 2021, she was Senior Director of R&D Strategy at IQVIA, where she partnered with the organization's leaders to frame corporate and therapeutic growth strategies. She also worked in the IQVIA Consulting organization from 2008 to 2014, leading projects with pharmaceutical and biotech clients and helping to optimize cross-functional drug development solutions. Before coming to IQVIA, Nicole worked in R&D organizational effectiveness at Pfizer, and began her career in 2008 in the Pharmaceutical and Medical Product practice at McKinsey & Company. Nicole holds a Ph.D. in Microbiology from Duke University and a B.S. in Biology from the State University of New York at Fredonia.



RACHEL FONES
Director, Government and Public Affairs, and Strategic Advisor for Diversity in Clinical Trials, IQVIA

Rachael Fones serves as Director, Government and Public Affairs, and Strategic Advisor for Diversity in Clinical Trials for IQVIA. With 17 years at the company and 8 in her current role, Rachael works with trade associations, advocacy groups and government officials to identify opportunities to advance the clinical research ecosystem. Rachael has been an active participant on numerous diversity in clinical trials initiatives over the past seven years, including with the Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard University's (MRCT) workgroup since 2017, and serves on the planning committee for the Society for Women's Health Research 2016 workshop, "Achieving Meaningful Sub-group Data in Clinical Trial Design and Development." Rachael is a frequent speaker on the topic and serves as the Chair of the Association of CROs (ACRO) Diversity & Inclusion in Clinical Trials Committee. Prior to joining IQVIA (then Quintiles), Rachael worked on healthcare policy and advocacy for Blue Cross and Blue Shield of Florida and as the Executive Director of the Health Care Quality Alliance in Washington, DC, a member organization founded by PhRMA, American Medical Association, medical specialty societies and patient, minority health, and issue advocacy organizations. Rachael holds a B.A. in in Political Science from Tulane University.



JULIA KERN
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IQVIA Institute for Human Data Science

Julia Kern serves as a Research Analyst for the IQVIA Institute for Human Data Science, conducting research, data analysis, and supporting the publication process for IQVIA Institute reports. Prior to joining IQVIA in 2021, she held positions at Boston Medical Center, Cargill R&D, and Columbia University. Julia combines her field research, clinical, regulatory affairs, consulting, and academia expertise to contextualize data and investigate trends. She holds a B.S. in Anthropology from the University of California, Los Angeles, and an M.P.H in Epidemiology from Boston University School of Public Health.

About the Institute

The IQVIA Institute for Human Data Science contributes to the advancement of human health globally through timely research, insightful analysis and scientific expertise applied to granular non-identified patient-level data.

Fulfilling an essential need within healthcare, the Institute delivers objective, relevant insights and research that accelerate understanding and innovation critical to sound decision making and improved human outcomes. With access to IQVIA's institutional knowledge, advanced analytics, technology and unparalleled data the Institute works in tandem with a broad set of healthcare stakeholders to drive a research agenda focused on Human Data Science including government agencies, academic institutions, the life sciences industry, and payers.

Research agenda

The research agenda for the Institute centers on five areas considered vital to contributing to the advancement of human health globally:

- Improving decision-making across health systems through the effective use of advanced analytics and methodologies applied to timely, relevant data.
- Addressing opportunities to improve clinical development productivity focused on innovative treatments that advance healthcare globally.
- Optimizing the performance of health systems by focusing on patient centricity, precision medicine and better understanding disease causes, treatment consequences and measures to improve quality and cost of healthcare delivered to patients.
- Understanding the future role for biopharmaceuticals in human health, market dynamics, and implications for manufacturers, public and private payers, providers, patients, pharmacists and distributors.
- Researching the role of technology in health system products, processes and delivery systems and the business and policy systems that drive innovation.

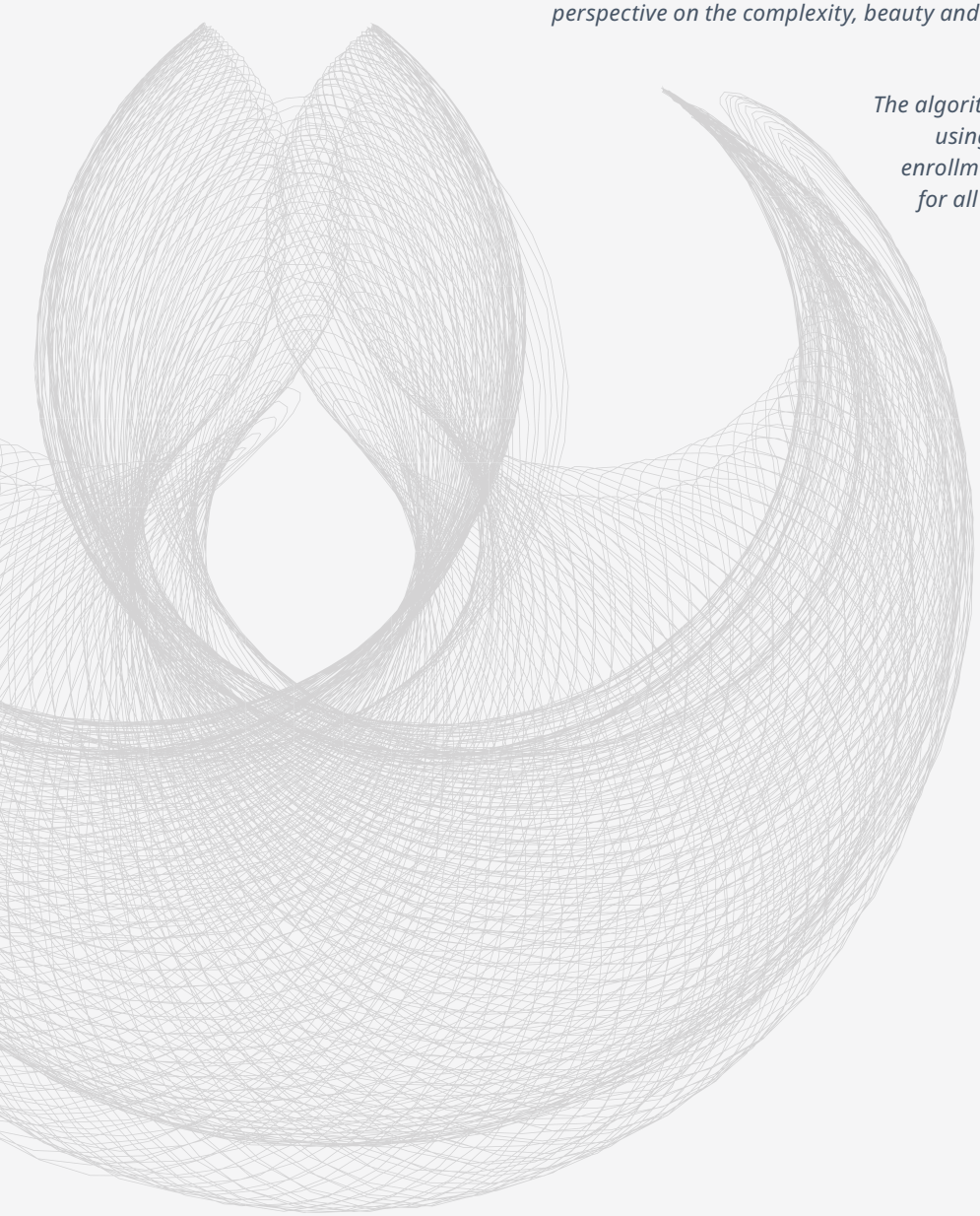
Guiding principles

The Institute operates from a set of guiding principles:

- Healthcare solutions of the future require fact based scientific evidence, expert analysis of information, technology, ingenuity and a focus on individuals.
- Rigorous analysis must be applied to vast amounts of timely, high quality and relevant data to provide value and move healthcare forward.
- Collaboration across all stakeholders in the public and private sectors is critical to advancing healthcare solutions.
- Insights gained from information and analysis should be made widely available to healthcare stakeholders.
- Protecting individual privacy is essential, so research will be based on the use of non-identified patient information and provider information will be aggregated.
- Information will be used responsibly to advance research, inform discourse, achieve better healthcare and improve the health of all people.

The IQVIA Institute for Human Data Science is committed to using human data science to provide timely, fact-based perspectives on the dynamics of health systems and human health around the world. The cover artwork is a visual representation of this mission. Using algorithms and data from the report itself, the final image presents a new perspective on the complexity, beauty and mathematics of human data science and the insights within the pages.

The algorithmic art featured on this report is generated using IQVIA Institute analysis of racial and ethnic enrollment percentages across key therapeutic areas for all ClinicalTrials.gov reported in Phase II and III trials with industry involvement and at least one U.S. site, and with trial completion dates between 2012 and 2021.



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