

White Paper

Practical Strategies for Ensuring a Diverse Patient Population in Clinical Trials



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Introduction

The clock is ticking on the requirement for pharmaceutical companies to include diversity action plans (DAPs) for pivotal studies in their clinical trials. A few deadlines have slipped since the Food and Drug Omnibus Reform Act (FDORA) was signed into law in April 2022 but the deadline for comments on the FDA's draft guidance on DAPs passed on Sept. 26, 2024. The guidance is mandated to be final on June 26, 2025, and the act should go into effect 180 days later. Citeline experts regard these reforms as necessary and in the industry's interests for many reasons.

“Medications can work differently in different populations. If we're not able to test medications across all races, ethnicities, genders, and ages, then we don't know how they work in these populations,” says

Jessica Washington-Moore, Senior Director of Implementation at Citeline. “If we know that these medications are safe and effective in certain populations, we can provide the right level of care and increase access to underrepresented communities.”

Claire Riches, Head of Clinical Solutions at Citeline, says: “Fundamentally, the long-term benefit is having data from a real-world population. Historically, the clinical trial population in the US in pivotal Phase II to III trials, and indeed globally, was sanitized, skewing towards middle-aged white people with access to healthcare and probably a better-than-average prognosis. As a result, studies often missed the signals that they would have seen in a full patient population and outcomes suffered.”



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What the FDA wants

The stated objective of the act is “to improve enrollment of participants from underrepresented racial and ethnic populations in clinical trials.” Companies will be required to submit enrollment goals disaggregated by ethnicity, race, sex, and age group in DAPs, as well as the rationale for their enrollment goals. These are expected to include:

- Background information necessary to understand the disease, including prevalence and incidence estimates
- Data on other population-level or individual characteristics that could impact clinical outcomes
- If multiple studies have different goals, how this contributes to the overall goal
- Available data regarding differences in pharmacokinetics (PK), pharmacodynamics (PD), safety, or effectiveness

The FDA has also listed examples of measures companies might take to meet their enrollment goals. These include, but are not necessarily limited to:

- Sustained community engagement
- Cultural competency training for clinical investigators
- Language assistance for persons with limited English proficiency
- Transportation assistance
- Avoiding unnecessary study-related procedures, imaging, and laboratory tests
- Reimbursement for costs incurred
- Dependent care
- Flexible hours for study participation
- Limiting clinical study exclusion criteria

- Considering the accessibility needs of persons with disabilities
- Using sites that serve a demographically diverse population
- Study decentralization

In addition, the FDA wants to see sponsors’ plan to monitor the goals, including any measures that may be undertaken should the sponsor determine that the study is not on track. The DAP should not be more than 10 pages long, excluding references. It should be submitted with the protocol for the drug’s pivotal study, which the FDA recommends being at the end-of-Phase-II meeting or whenever the pivotal protocol is being discussed. The agency has 60 days to respond to waiver requests, so these must be submitted at least 60 days before DAP submission is required and early enough to allow a DAP to be prepared if the request is rejected.



Mistrust & other barriers

There are, of course, reasons beyond mere convenience why clinical trials in the US have historically skewed away from minority patients: For one, educated, suburban whites were easier to reach. Some communities have a built-in mistrust of the pharmaceutical industry and prescribing physicians, notably among the Black population because of historic scandals like the Tuskegee Institute's highly unethical studies, for which the government was still paying compensation until quite recently.

"The whole health equity bigger picture is to instill trust in populations who don't normally take up treatments that are available to them," Riches says. "We're also looking at things like the diverse makeup of our investigators, making sure they are a similarly diverse split of individuals as the patients, because there's more of a trust between female patients and female doctors and definitely within ethnic groups as well."

Accessibility is another major issue in clinical trials. Childcare needs, work patterns, and the cost and difficulty of reaching testing sites have all tended to deter certain groups from participating.

Matt Holms, VP of Patient Engagement & Recruitment at Citeline, adds that the rise of precision medicine is another reason why diversity is crucial. Particularly in oncology, many trials are specific to a biomarker that may have a higher prevalence within some demographics. Understanding how these different treatments work better in some groups than others is "extremely important" to their success, he says.

Washington-Moore adds that the challenge is not so much having a certain percentage of every race or ethnicity in a study but ensuring that the sample in a clinical trial is representative of the real-world prevalence of that particular disease.

The FDA guidance focuses initially on race, ethnicity, gender, sex, and age, but the agency wants to look at further social determinants of health, such as economic and educational status, comorbidities, geographic locations, and access to transport. These all have potential impacts on patients' access to drugs and compliance with medication. Although this level of detail is not yet mandatory, Riches is certain it will be within a few years as more data become available.

"Pharma companies are going to have to make concerted efforts to bring certain groups into clinical trials," she says. That means, among many other things, targeting areas of a city where a particular patient population is more prevalent, organizing different types of advocacy efforts, and advertising in different ways where these patients are found. "That may lead to longer recruitment periods because those group are underrepresented and don't uptake trials."

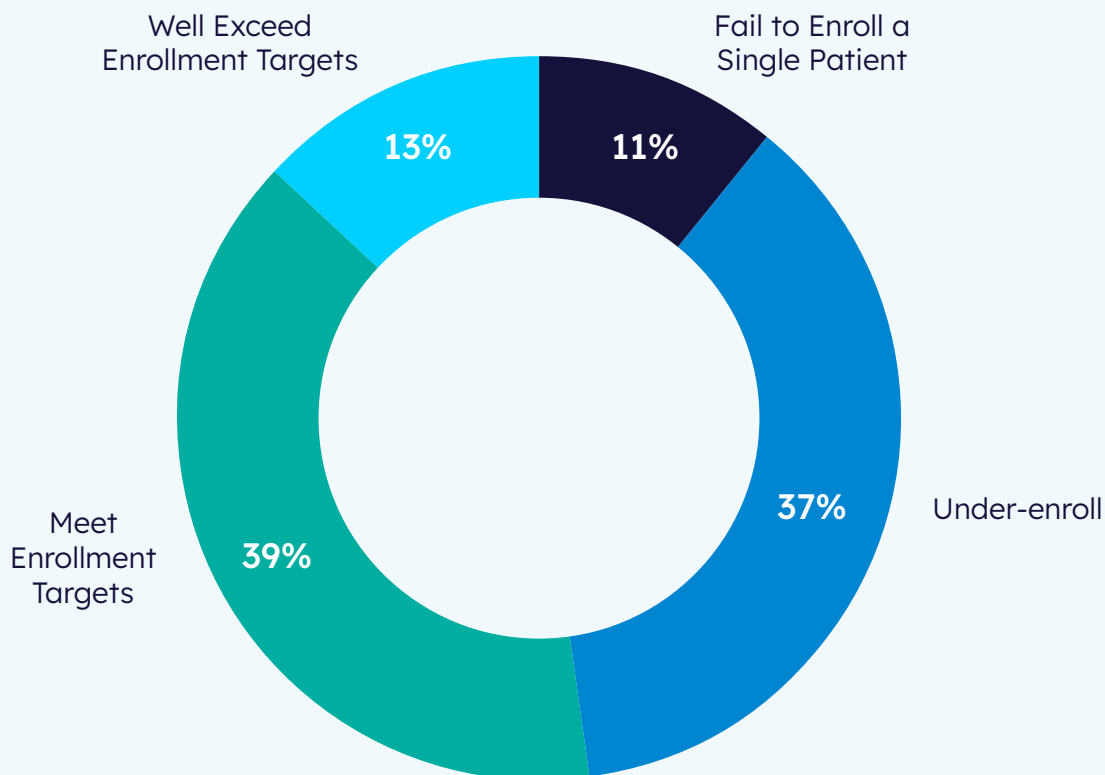
Recruitment headaches

Recruitment has always been a complex challenge and one of the main factors in determining how long a study runs, which is directly tied to how much it costs to run a trial. “Now that we’ve added this layer of mandating certain races and ethnicities and making sure that we’re meeting our diversity goals, that is adding to the timelines and the cost,” Washington-Moore says.

Clinical trials, moreover, are already becoming longer, more complex, and more expensive.

Holms cites statistics, from Tufts Center for the Study of Drug Development (CSDD), showing that the average trial duration across all drug development phases has increased by 35% over the last decade and about 85% of most trials require a major amendment. The number of endpoints, procedures, and sites used per study have all increased as well. Despite many sponsors’ efforts to “pick the best sites,” the more consistent outcome is that only half the sites meet or exceed enrollment targets (Figure 1).

Figure 1: Sites vary considerably in the success of their patient recruitment



Source: Tufts CSDD, 2021

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“Recruitment has become harder due to more complex protocol designs, along with a supply-and-demand imbalance where there simply are not enough research sites, which are commonly under-resourced, for sponsors to find the necessary volume of patients within their desired timelines,” says Holms.

“Randomization and completion rates have gone down drastically compared to pre-pandemic rates across broad-based indications like cardiovascular/metabolic, oncology, central nervous system [CNS]/neurosciences and inflammatory diseases.” (Figure 2)

Figure 2: Randomization & completion rates for clinical trials by indication

Phase II/III Trials	Randomization Rates		Completion Rates	
	2019	2023	2019	2023
Cardiovascular/Metabolic	84%	66%	93%	61%
CNS/Neurosciences	25%	16%	74%	66%
Inflammatory Diseases	75%	68%	81%	54%
Oncology	63%	56%	69%	22%

Source: Tufts CSDD, 2021

In Riches’ view, one positive outcome from the pandemic was improved perceptions of the pharmaceutical industry as (most) people are crediting it with developing vaccines rapidly and effectively ending the pandemic. In addition, the urgent need to develop vaccines and get them to market meant that regulatory and ethical pathways were expedited and financial and other barriers were removed from trial

participants.

“Can you imagine if every trial had that same level of participant interest and expedited processes?” she asks. “It shouldn’t take a pandemic. There should be a trust level such that we can remove barriers and things like placebo, and we’ll be in a much better position.”



Using technology for outreach

Some companies are addressing the distrust some people have head-on. They visit local churches and connect with leaders to help build that trust in communities of color. However, grassroots outreach is expensive and time-consuming. This is where technologies like artificial intelligence (AI) come in. Used intelligently, they can help to reduce timelines and costs without cutting corners on safety or quality.

Riches says there is a fine balance to be struck in terms of access to data, finding patients, and understanding their journey. “Patients, on the whole, are not aware of clinical trials,” she says. “If they’re diagnosed, most people, and indeed physicians, don’t know how to go about finding a trial, enrolling, and participating. It’s hard enough for folks who understand the industry to find trials.”

The ability to access patients’ journeys through data, for example, can make it possible to eliminate the use of placebos in trial and reduce the numbers required significantly, by creating a synthetic arm. This creates a virtuous circle because patients will be more likely to join the trial, they can be recruited faster, and data analysis can be done more swiftly.

Post-COVID, sites, physicians, and other healthcare professional (HCP) networks are stretched thin. Many have left the industry or retired, leading to a shortage of experienced investigative HCPs to run clinical trials. Consequently, companies tend to keep going back to the same investigators.

“It’s now time to look at a new generation of investigator, where they are, and how technology connects people,” says Riches. Time-poor patients no longer need to go to sites for an assessment. Instead, they can be

communicated with by apps and participate on their own terms.

“We can also start widening networks and pinpointing patients through data. We can say ‘There are 5,000 patients in this territory who have your specific biomarker, and these are their treating HCPs. That HCP might not be a principal investigator [PI] on a trial, but we can reach out to that physician and say ‘You have a patient with this particular biomarker and there’s a trial running 12 miles down the road. Would you be interested in referring your patient for a new treatment? We need to meet patients and HCPs at the right time and right place during their healthcare journey.’”

Moreover, drugs increasingly must meet an unmet medical need — being either for an indication lacking any treatment or more effective and/or safer than market drugs — to win approval. In this situation, taking part in a clinical trial can be a more attractive option for patients than standard of care, particularly those failing on the normal standard of care.



Regulatory change

Riches is certain of two things. The diversity requirements that are not yet mandatory will become mandatory and for all trials, not just pivotal Phase II and III trials; and the European Medicines Agency (EMA) will follow the FDA lead as it usually does and will enact its own diversity requirements. Companies in this often-slow-moving industry are now realizing that diversity in clinical trials is a must and that they have to prioritize this in their strategies.

Moreover, the FDA has made it crystal clear that

it will want to know where the data for DAPs are sourced. These will have to come from reputable sources, not just one paper. The agency will also check the plans for a clear patient recruitment strategy.

As a result, pharma companies will have to think earlier and differently about how they recruit these patients and give ongoing updates. Waivers are highly unlikely to be granted, except for an extremely rare disease where there is a massive unmet need.

Strategies to address roadblocks

PIs can use various strategies to address these roadblocks to diversity in patient enrollment: strategic site selection, targeted outreach, flexible trial design, involving patients more throughout the process, and utilizing technology to enhance recruitment and retention, to name the most obvious. For Washington-Moore, who previously worked at a large site management organization, intelligent site selection is crucial, and sites must reside in the communities they are trying to engage with.

She also encountered language issues for trials delayed in recruiting Spanish-speaking participants when sponsors did not prioritize approval of Spanish-language materials. Her most successful sites were those that made trials most accessible for participants. Offering travel stipends, expanding clinic hours, and offering childcare were easy ways to make trial participation easier for participants lacking transportation and/or childcare.

“The industry is definitely moving towards a more decentralized approach to trials

where we’re seeing technologies that allow participation from home,” Washington-Moore says. “Technology is enabling patients to conduct visits at home instead of having to travel to a site. That also bears on the childcare issue: You don’t have to get childcare because you’re already at home. That has definitely helped with the diversity problem in clinical trials.”

(Decentralized trials are not a silver bullet, of course. There are many isolated, particularly older, people who are either unwilling to use an app, however user-friendly, and/or enjoy their weekly trip to an investigative site as a rare chance for interaction with other people.)

In addition, site management organizations (SMOs) and sponsors are spending time and money seeking patients’ opinions via patient advocacy groups on what they need from clinical trials, what motivates them, and what they dislike. “I think this is finally starting to trickle into the trial design,” Washington-Moore says.

Outlook

There is a “four-way road” ahead, in Riches’ view, with regulatory bodies, the pharma industry, patients, and data companies all working together to improve every aspect of clinical trials, including diversity. To succeed, “it has got to be super synergistic.” She regards the FDA guidance as “a good step in the right direction.”

“It’s going to make us focus on making sure the right patient population is recruited. Is that going to slow down recruitment? Probably, but in a way, I think that nudge and that consequent slowdown of recruitment is going

to make the pharma industry look in a different way about how it runs trials and making them more attractive to a broader patient population.

“I think it will rethink designs, recruitment tactics, which sites will be asked to participate, and how we access patients. The ultimate goal is a world that has better health equity, so that anybody, regardless of who they are, how they’re educated, the color of their skin, their age, their ethnicity, their socioeconomic status, their geography, has the same level of access to a particular drug.”

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