DIVERSITY OF PARTICIPANTS IN CLINICAL TRIALS INITIATIVE

FDA DIVERSITY PLAN EARLY INSIGHTS AND CONSIDERATIONS

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Accelerating Answers.

Contents

1.0 Introduction: Purpose of stakeholder insight interviews

Historically, clinical trials have lacked racial and ethnic diversity in their participant populations, and this has led to disparities in the data collected about people from specific communities and in the level of contribution some racial and ethnic minority groups have been able to make to research. For a trial to provide results with greater real-word applicability, it is necessary to consider how well historically underrepresented populations[1] in clinical trials truly reflect the racial and ethnic diversity of the population expected to use the medical product if approved.

Given the importance of increasing enrollment from historically underrepresented racial and ethnic populations, the U.S. Food and Drug Administration (FDA) has called upon the entire drug development industry to do more to improve racial and ethnic diversity in clinical trials.

In its April 2022 Draft Guidance, the FDA recommends that sponsors develop and submit a Diversity Plan to help ensure the adequate participation of relevant and underrepresented populations and analyses of data collected from clinically relevant populations. The FDA Draft Guidance (April 2022) further builds from previously released FDA guidance (November 2020 & October 2016)[2], the Diverse and Equitable Participation in Clinical Trials (DEPICT) Act[3] passed and approved by Congress earlier last year (2022), and International Council for Harmonisation (ICH) guidelines[4].

As the FDA Draft Guidance is finalized, sponsor companies and other industry stakeholders seek added clarity on this critical issue. TransCelerate BioPharma realized this was an opportunity to learn from one another and to overcome these challenges by collaboratively sharing lessons learned as companies begin to develop and implement Diversity Plans and the strategies anchoring their content. In response, TransCelerate's Diversity team conducted 8-member company interviews specifically aimed to understand four key elements:

1. Identify emerging best practices related to the program and study level development and implementation of FDA Diversity Plans
2. Summarize FDA diversity plan considerations across multiple dimensions of diversity including, but not limited to, race, ethnicity, sex, and age
3. Identify common challenges development teams have come across in the implementation of FDA Diversity Plans
4. Identify gaps for further collaboration within the industry for the FDA and other stakeholders

The "FDA Diversity Plan Early Insights and Considerations" document collates insights gathered from the member company interviews. These considerations can help to inform operational strategies and identify how practical implementation may progress as industry thinking matures in this area. Below is the collection of considerations and key themes seen across the interviews.

2.0 Impact of Guidance: Increased urgency related to implementing end-to-end Diversity, Equity, and Inclusion in Clinical Trials (DEICT) strategies in a more organized, coordinated way

Even though the majority of companies have been working on DEICT strategies, whether it is at a program or study-level, the approach taken has not always been applied throughout a drug's overall clinical development plan or been consistent across disease areas. Additionally, some companies may not have had well-defined processes such as developing end-to-end, data-driven and scientifically grounded strategies to increase diversity in clinical trials.

While the FDA had issued several guidance documents related to inclusive research in the past (U.S. Regulatory Landscape: Diversity in Clinical Trials), the expectations laid out in the draft guidance on diversity plans have led some companies to take a more proactive approach to the development of DEICT strategies. This proactive approach includes earlier planning in the compound development process, deeper cross-functional collaboration and coordination, and the creation of standardized templates and SOPs to guide consistency across the company. In parallel to the FDA publications and Draft Guidance (April 2022), several post marketing commitments (PMCs) and post marketing requirements (PMRs) have been issued by FDA in relation to DEICT, especially over the last 2-3 years, further highlighting the need for companies to proactively and more consistently implement end-to-end DEICT strategies.

In addition, while the focus of the FDA Draft Guidance (April 2022) is mostly race and ethnicity, it also led some companies to evaluate the need for more diversity based on other demographics parameters (e.g., age, gender identity, socioeconomic status etc.). That is in line with more recent public talks from FDA officials on how they define inclusive research and should certainly be considered by companies as they develop their own template and SOPs.

3.0 Challenges, Successes & Opportunities

A. Driving internal, cross-functional alignment early on in the development of DEICT strategies is critical

As with any new process or priority, alignment across functions on overall diversity goals as well as roles and responsibilities in developing and executing on these goals is pivotal to success. Discussions to gather cross-functional input/insights should occur during the early design and planning stages of a clinical trial or broader clinical development program. This will support thoughtful consideration about the role that various functions should play in developing DEICT strategies. Ideally, this cross-functional collaboration should lead to discussion and alignment on a disease-level DEICT strategy that can be replicated and refined across clinical development programs and individual trials in a company's disease-specific portfolio.

A proactive approach will also enable early identification of ongoing processes where diverse and inclusive practices could be embedded, allowing for more comprehensive planning. Companies have developed processes to ensure implementation of the diversity strategy, including adoption of a

diversity plan template and creation of a steering committee to drive and monitor completion of FDA diversity plans. In this way, greater accuracy in resource assumptions/ estimates and more targeted risk mitigation plans may be delivered.

B. Developing processes to drive the efficient completion of written diversity plans

Some member companies with less experience in the development of end-to-end diversity strategies have struggled to define a process for the creation of diversity plans. During the early stages of the development of DEICT strategies, companies may consider developing a standard diversity plan template and internal guidance, based on the FDA Draft Guidance, that might evolve as experience grows. That template and guidance would help teams know who should be involved in the development, review, and finalization of a diversity plan.

Internal collaborators/partners that would be critical to the development of diversity strategies could include, but are certainly not limited to, Clinical, Regulatory, Medical Affairs, Early Development, Data Science, Biostats, Epidemiology, Trial Management, Feasibility, Pharmacovigilance, Patient Insights/Engagement, and Diversity & Inclusion teams.

There may be added value, while initiating a process or streamlining current process, to consider forming a steering committee or working group to ensure focus areas are agreed upon and embedded consistently across program and business areas within a company. This, for example, could be an extension of a central DEICT office or center of excellence, or a new forum.

C. Leveraging more data-driven and scientific approaches to the development of DEICT strategy

As companies drive internal alignment and develop new processes to facilitate the development of FDA diversity plans, there has been a growing awareness that diversity can no longer be treated as "nice to have," but must be understood as critical to understanding the safety and efficacy of medical products across all impacted patient populations. This awareness is rooted in a growing understanding that there may be meaningful population-level differences in treatment response across racial, ethnic, and other diverse patient populations. Despite this growing awareness, companies face some challenges in accessing robust, reliable data (e.g., epidemiological data, real world data, etc.) that are needed in order to define incidence and prevalence of the disease being studied. These data will help to develop strategies to explore and account for potential heterogeneous treatment effect across racially and ethnically diverse patient populations.

i. Opportunities and Challenges in Sourcing Reliable Data to Support Enrollment Benchmarking

Prior to the expectation to prospectively develop the Diversity Plans called for by the FDA, companies mostly relied upon the comparable trial demographics (e.g., FDA Drug Trials Snapshots if available) or US Census data to develop benchmarks for the enrollment of underrepresented racial and ethnic patient populations. As a result of new FDA Draft Guidance (April 2022) explicitly detailing the expectations on Diversity Plans, companies interviewed are focused on leveraging more data-driven approaches to help define their diversity enrollment goals. Some approaches may include, using real-world claims data, medical literature, US census data, epidemiological data, etc. to develop their clinical trial diversity strategy.

Although member companies interview responses were largely consistent in the need to seek more data-driven approaches to the development of data-driven benchmarking for the enrollment of underrepresented racial and ethnic patient populations, member companies expressed facing multiple challenges related to sourcing reliable robust data. Member companies noted that lack of reliable data, particularly epidemiological data, posed a major challenge to the development of data-driven, scientifically robust diversity plans, specifically for rare indications, genetic alterations, and specific stages of disease.

The availability of epidemiological data can vary by indication, line of treatment, or genetic target. For example, in some disease areas e.g., oncology or chronic conditions, patients may receive several lines of treatment, and establishing a representative patient population and therefore a suitable enrollment target may prove challenging.

This central challenge may be further compounded within clinical studies, where patients choose to record 'UNK' (unknown) for 'Race' or 'Ethnicity'. In some cases, the reasons may be because there is not a suitable variable to select or there may be a reluctance on the part of the patient to have their demographic information recorded. Education and awareness are needed to support better recording of data variables to provide more complete demographic datasets for our clinical trials.

ii. Lessons Learned

At the time of writing, the FDA Draft Guidance (April 2022) has been available for a relatively short time. Therefore, experience developing, submitting, and implementing FDA Diversity Plans is limited. Although the FDA Draft Guidance (April 2022) has yet to be finalized, it has already had a major impact on member companies' overall approach to the development of DEICT strategies. Specific examples of major lessons learned in the early development and implementation phase of FDA Diversity Plans are listed below:

1. **Development of FDA Diversity Plans cannot be treated as a "check-the-box" exercise. Member Companies that participated in the interviews noted that DEICT has at times been treated as ancillary to the goals, objectives, and scientific rigor of clinical development programs**. The FDA Draft Guidance (April 2022) further reinforced a growing understanding in industry that DEICT is central to the scientific integrity of clinical development programs.

2. **Successful development and implementation of comprehensive Diversity Plans requires iterative engagement, alignment, and coordination across functions.** Early and frequent cross-functional engagement is key to the success of Diversity Plans. Some of this engagement may be complicated by individuals and functions who lack education related to DEICT and are overwhelmed by the possibility that implementing enhanced DEICT strategies may threaten already strained study timelines and budgets.

3. **Diversity Plans should be viewed as a dynamic, living document that should be updated and refined throughout the lifecycle of a clinical development program.** Member Companies noted that their perspective on the impact of a specific diseases on underrepresented racial and ethnic patient population and approaches needed to mitigate barriers to DEICT may change over time. Therefore, sponsors should look for opportunities to continually refine and improve their

approach to developing and implementing diversity plans to better respond to the needs of underrepresented patient populations.

4. **The FDA Draft Guidance (April 2022) provides a good foundation for sponsors to evolve more integrated approaches to increasing health equity for patient populations across the globe.** Although it is limited to considerations related to the participation of underrepresented US racial and ethnic minority patient populations, sponsors can leverage US-focused diversity plans as a springboard to develop more holistic health equity strategies for global patient populations impacted by their disease areas of interest.

D. Broadening our understanding of diversity

i. Other underrepresented patient populations of interest

The FDA Draft Guidance (April 2022) provides recommendations to sponsors on the approach for developing race and ethnicity diversity plans. These plans are expected to focus on enrolling representative numbers of participants from **underrepresented racial and ethnic populations in the United States**, such as Black or African American, Hispanic/Latino, Indigenous and Native American, Asian, Native Hawaiian and Other Pacific Islanders, in clinical trials. Individuals from these populations have been frequently underrepresented in clinical research despite having a disproportionate disease burden for certain diseases, relative to their proportional representation in the general population. For purposes of satisfying the expectations set out in the FDA Draft Guidance (April 2022), the epidemiology of the disease being studied should be the driver for the development of the FDA Diversity Plan. In addition to race and ethnicity, there may be other dimensions of diversity that may need to be considered based on disease being studied.

Other Dimensions of Diversity to be considered:

- Age (elderly and pediatric populations)
- Sex
- Sexual Orientation/Gender Identity
- Social Determinants of Health
- Veteran status
- Specificity around the Hispanic/Latino ethnicity
- Co-morbidities/ organ dysfunction (that may be commonly seen in the disease under study)
- Pregnant/ Lactating patients
- Disabilities

There may be a paucity of publicly available data for other dimensions in certain diseases. It is also important that data for these other dimensions be collected during the operation of clinical trials bearing in mind that there will be an impact on the development of case report forms.

ii. Global consideration

The FDA Draft Guidance (April 2022) focuses on diversity enrollment in the US, which is recognized to be a “melting pot” of races and ethnicities. To be in compliance with FDA Draft Guidance (April 2022) and to meet the defined enrollment goals, companies may have to increase US site contribution which will have implications in site selection in other regions. Race and ethnicity data may be collected differently or not at all in some countries as a result of local laws and regulations. In addition, terminology used to

describe race and ethnicity in the literature is variable and inconsistent. During the design of multi-regional clinical trials, sponsors should understand how data collected from ex-US countries can impact the enrollment targets set in the diversity plan and that country and site selection should be supported by population science[5].

Broader implementation of legislation beyond the US is anticipated (e.g., with information requested from Health Canada and consultation with UK, MHRA directly related to collecting disaggregated demography data and achieving greater diversity in clinical trials respectively), therefore it may be useful to evaluate implementation of diversity in clinical trials in the US to understand how this may be applied in other countries.

4.0 Conclusion

Some patient groups have historically been excluded from clinical trials which may have led to a disparity between a clinical trial population compared to the representative patient population for the disease under study.

Addressing this disparity in response to Draft Guidance issued by the FDA (April 2022), the pharmaceutical industry can learn from emerging best practices as companies develop more experience in implementing Diversity programs at the program and study level. The response requires a multi-disciplinary approach, as solutions evolve over time collaboration between both internal and external partners is essential.

A data driven approach is critical to the success of achieving greater clinical trial diversity. FDA Diversity plans must reference data ideally reflecting US epidemiology. Sponsors should consider multiple sources of data in order to determine an enrollment target e.g., US epidemiology data, RWE data, US census data. Companies may consider referring to enrollment data from past clinical trials and FDA snapshot data to understand previous challenges and identify opportunities. This may then improve representation in clinical trials through targeted implementation of interventions to enroll a representative patient population.

Challenges remain in developing an acceptable threshold for recruitment targets in US patient populations compared to the representative population. Potential areas where industry can lead in commitments to demonstrating diversity in participant populations would be to consider ways to broaden and update data collection and reporting for demography to:

- cater to broader and deeper race/ethnicity categories (e.g., patients with multi racial/ethnic categories)
- provide additional differentiation within general race categories, allowing for more granular options to define heritage (e.g. Asian/Chinese/Indian/Filipino)
- update standards for socio-economic groups.

Anticipated future reporting / areas for consideration; pharmaceutical companies could consider increasing transparency e.g., based on race, ethnicity demographics. Sponsors could consider reporting recruitment of patients in pivotal trials based on race / ethnicity in transparency reporting. This could be based on categorization provided at the Federal level – Office of Management of the Budget (OMB)[6], and industry organizations such as Transcelerate, based on conclusions in the Clinical Study Report. This is an opportunity for cross industry collaboration. Greater transparency could foster improved community of practice amongst industry and broader collaboration with stakeholders in healthcare. It is important to note that while interventions implemented by the pharmaceutical industry are critical in

improving representation in the clinical research landscape, the industry is a stakeholder in a broader ecosystem delivering healthcare to patients. Commitment is required across the healthcare continuum with collaboration welcomed with sites and staff. Communication and education in the importance of Diversity, Equity and Inclusion in clinical research is needed to support broader stakeholder collaboration.

At the time of this writing, we recognize the Food and Drug Omnibus Reform Act (FDORA) has been signed into law, and includes among other things, a new FDA requirement for sponsors to submit a diversity plan for all Phase 3 clinical trials or pivotal studies for new drugs. This reinforces the theme we have heard from member companies that diversity in clinical trials can no longer be treated as a "nice to have," but is now a research imperative that companies must critically consider and prospectively plan ahead for in their development strategies.

5.0 Planned Future Engagement

Sponsor insights related to the development and implementation of FDA diversity plans will continue to evolve. TransCelerate sees the need for continued stakeholder feedback across the clinical trials enterprise in mid-2023 and we plan to explore the following:

1. Review how the release of the finalized FDA Draft Guidance (April 2022) / regulation will impact development of the Diversity Plan and alter approaches to recruitment of underserved / underrepresented patients,
2. Feedback received from the FDA on submitted diversity plans,
3. Challenges experienced with the implementation of program-level and study-level diversity plans,
4. Efforts to leverage FDA US diversity plans to guide DEICT efforts in ex-US global regions,
5. Review how sponsors are balancing the diversity mandate when considering emerging policy/ regulation from other countries.

These engagement events are intended to support ongoing cross industry and cross sector dialogue and collaboration aimed at transforming the clinical trial research enterprise to encompass the needs of all patients.

[1] Within the context of this document, we define historically underrepresented patient populations as patient populations that have lacked equitable access to healthcare and clinical research due to long-standing biases and structural inequalities.

[2] See the 2016 and 2020 Guidance released by the FDA for additional context

[3] See DEPICT Act for additional context

[4] See ICH E6(R2) and ICH E8(R1), and TransCelerate's U.S. Regulatory Landscape: Diversity in Clinical Trials solution for additional context

[5] See ICH E-5 and E-17 for additional context

[6] OMB racial and ethnic categories are currently under review and may potentially be expanded, see this link for additional details