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Improving Equity in Oncology Clinical Trials: Challenges and Strategies for Setting Diversity Enrollment Goals

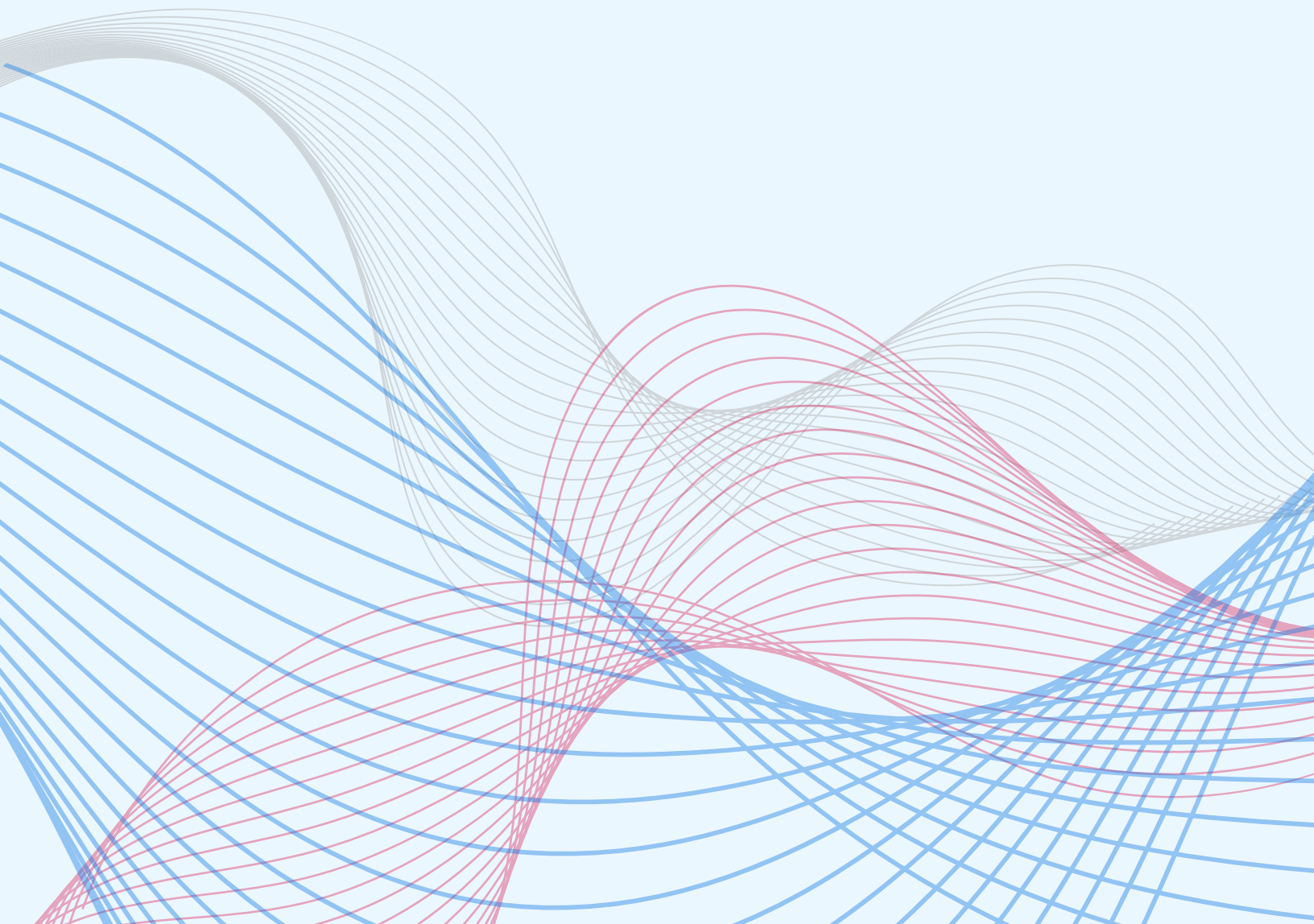2024 Discussion Document

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Acknowledgements

Executive Summary

Roughly 8% of adult patients with cancer participate in clinical trials, and among these participants, there has historically been a lack of diversity.[1] This underrepresentation impacts the generalizability of trial results and perpetuates health inequities. Recognizing this, the U.S. Food and Drug Administration (FDA) announced guidance documents and initiatives, including Project Equity, to encourage efforts to improve representativeness in oncology drug development. The recent Food and Drug Omnibus Reform Act (FDORA) further solidified this effort by requiring Diversity Action Plans for Phase III clinical trials, which must consider race, ethnicity, age, and sex/gender.

A survey by Friends of Cancer Research evaluated how 23 drug sponsors are implementing FDA guidance and FDORA mandates. Findings show that key steps include characterizing the population of patients with a particular disease, identifying and analyzing diverse data sources, and setting enrollment goals. This discussion document details two proposals to address challenges in data availability and integration:

1. **Central Repository for Biomarker Data in U.S./Canada:** Create a centralized, nationally representative repository for cancer biomarker data, inclusive of race and ethnicity data.

2. **Collaborative Data Consolidation Efforts:** Consolidate and harmonize data sources to bridge gaps in data coverage and establish standards for collecting and reporting race and ethnicity variables.

In addition to establishing enrollment goals, diversity plans must incorporate patient-directed measures, community engagement, workforce-directed measures, and trial design considerations to achieve these goals. Measures include:

- Building trust and partnerships in diverse communities.

- Lowering barriers to participation by addressing financial burdens and removing restrictive eligibility criteria.

- Intentional site selection focusing on health centers serving diverse populations.

Sponsors should implement mechanisms to track progress towards achieving enrollment goals, enabling them to reassess and adapt strategies, as necessary. This discussion document emphasizes that to achieve the shared goal of more inclusive and representative patient populations in clinical trials, a multifaceted approach involving robust data analysis, strategic planning, community engagement, and inclusive trial practices is required.

Introduction & Background

It is estimated that around 8% of adult patients with cancer participate in clinical trials in the United States (U.S.).[1-3] Further, of those patients participating in clinical trials, there is often a lack of diversity and representativeness of the overall patient population with the disease.[4] Patients from certain racial and ethnic populations are frequently underrepresented in oncology clinical trials, and clinical research more broadly, despite these patients experiencing a disproportionate burden of disease for several cancer types, such as breast, prostate, and multiple myeloma.[5,6] This lack of inclusion and representativeness in current clinical trials may hinder the generalizability of results to the intended patient population, contribute to existing health inequities, and limit the potential to personalize treatment to meet the unique needs of various patient populations. Actions to improve inclusion of patients from underrepresented racial and ethnic groups in clinical trials are necessary to achieve the broader goals of providing equitable healthcare and reducing health disparities.[7] The U.S. Food and Drug Administration (FDA) recognizes the need for improved representativeness in clinical trials as evidenced by the release of guidance documents, policies, public meetings, and other initiatives such as Project Equity. These efforts provide recommended standards for race and ethnicity data collection and reporting in clinical trials, provide considerations for broadening eligibility criteria to be more inclusive, and describe measures that can lower barriers to participation.[8-14]

In April 2022, the FDA released a new draft guidance document titled "Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials," recommending trial sponsors develop Race and Ethnicity Diversity Plans for most investigational medical products.[14] The guidance states these Diversity Plans should include representative enrollment goals for historically underrepresented racial and ethnic populations in the U.S., including Black or African American, Hispanic/Latinx, Indigenous and Native American, Asian, Native Hawaiian and Other Pacific Islander populations, and strategies for enrolling and retaining these patients on clinical trials.

In December 2022, Congress passed the Food and Drug Omnibus Reform Act (FDORA), which includes several provisions to enhance diversity and representativeness in clinical trials.[15] Among these, the law codified components of the April 2022 guidance and expanded requirements to consider age and sex/gender in Diversity Action Plans for Phase III or other pivotal clinical trials for investigational medical products, which will be represented in an updated guidance document from the FDA. As outlined in the law, drug sponsors must submit Diversity Action Plans to the FDA by the time they submit the study protocol for any Phase III or other pivotal drug study, excluding bioavailability or bioequivalence studies and include enrollment goals, rationale supporting these goals, and a strategy for achieving these goals.

Considering these recommendations and requirements, drug sponsors have mobilized their teams to implement measures that support the development, submission, and implementation of diversity planning as part of the clinical development process.[16] Friends of Cancer Research (*Friends*)

surveyed 27 drug sponsors, as well as data aggregators, to assess specific approaches used to implement the recommendations and requirements outlined in the April 2022 draft guidance and FDORA and identify strategies for enhancing adoption of FDA recommendations. The following questions were posed:

1. How are sponsors applying FDA guidance and recent FDORA mandates to set diversity enrollment goals for oncology clinical studies? (e.g., U.S. enrollees and/or international)?
2. What key factors do sponsors consider when identifying data sources (e.g., the Surveillance, Epidemiology, and End Results [SEER] data, EHRs, past clinical trials, registries, etc.) for establishing benchmarks for population diversity (i.e., by race, ethnicity, sex, age group)? What are known strengths and limitations associated with different data sources?
3. What types of data are difficult or not feasible to obtain from data sources? What approaches are used to access information/data that may not be readily accessible/available (e.g., information on biomarker-defined subgroups)? What are the limitations of this information and what approaches can be taken to overcome them?

In addition to responses to these questions, the goal was to better understand measures to achieve enrollment goals.

Applying FDA Guidance

Since the release of the April 2022 draft guidance (and prior to its release in some instances), and in anticipation of the FDORA Diversity Action Plan requirement coming into effect, sponsors have been proactively implementing steps to achieve greater diversity in trials and voluntarily submitting diversity plans to the FDA. Between April 2022 and April 2023, 42 sponsors submitted 76 diversity plans across 40 oncologic indications to the Center for Drug Evaluation and Research's (CDER) oncology divisions.[17] Although the currently available guidance focuses on diversity plans for enrolling underrepresented racial and ethnic groups, sponsors indicated they are also incorporating considerations such as age and sex/gender, and social determinants of health (SDoH) to ensure enrollment goals represent the disease burden across patient populations. As the community works toward implementing concepts in the guidance document and law, it is important to align on the goals and intentions of these requirements, which can include 1) ensuring a sufficient number of patients enroll and are retained from underrepresented racial and ethnic groups to determine whether demographic factors impact safety and efficacy; 2) having global studies that represent disease epidemiology and are generalizable to the intended use population in the U.S.; and 3) enrolling as many underrepresented U.S. patients into clinical trials as possible to provide equitable opportunities to participate in oncology clinical research and thereby reduce disparities in oncology health outcomes across diverse, U.S. patient groups with cancer. The specific intention of including more diverse patients in a clinical trial will have implications on the trial design, enrollment goal setting, and statistical analysis plan.

Data Analysis and Goal Setting

One of the key steps towards achieving more representative enrollment in clinical trials is characterizing the population affected by a particular disease, including who it affects, where these patients live, and understanding treatment and testing patterns. However, there is no standardized source for these data or aligned methodology for capturing them, and therefore, goal setting can be a complicated task because it may require synthesis of data from disparate sources. Various data sources that include information on U.S. population-level demographic variables and disease incidence and prevalence need to be identified and analyzed. Using these data, sponsors set enrollment goals for U.S. enrollment in global studies and provide the rationale for these goals.

Setting enrollment goals for achieving diversity is part of broader U.S. initiatives to have more diverse patients represented in clinical trials and clarify expectations around the proportion of patients who should be enrolled from the U.S. This includes understanding what constitutes a clinical trial population that is representative of the epidemiology and demographics of U.S. patients for whom a therapy is intended to be used. Many sponsors run global development programs and conduct clinical trials spanning multiple countries including the U.S. Therefore, sponsors may monitor enrollment outside of the U.S. and identify ways to tailor enrollment from these countries to supplement U.S. enrollment goals.

However, there is often a lack of robust, decentralized data sources to obtain similar information about diversity outside of the U.S., which is largely due to incomplete collection, varying definitions of race and ethnicity, and laws that prevent collecting this information in some countries.[18] Additionally, lived experiences among similar racial and ethnic groups often vary from one country to another. As a result, it is not clear whether or how enrollment of diverse patients from outside the U.S. would be considered when determining whether diversity requirements are fulfilled, and importantly, it also does not address the issue of unequal access to or participation in clinical trials within the U.S.

Data Sources Used for Enrollment Goal Setting

Sponsors use a variety of data sources to inform clinical trial enrollment goals. Data sources are selected based on several key factors, including the availability, completeness, and granularity of variables in the data source; the timing of data collection; the representativeness of the data source; accessibility of the data; and the expected reliability and acceptability of the data source by the FDA.

Data of interest include clinical factors such as histology, stage, co-morbidities, and relevant biomarkers, demographic and non-demographic variables such as age, sex assigned at birth, race, ethnicity, and SDoH such as income, education level, healthcare utilization, and insurance status. Table 1 outlines a range of examples for select data sources used by sponsors to set enrollment goals, which generally fall into four categories:

1. **Epidemiological Data Sources** are publicly accessible and useful for understanding disease incidence, prevalence, survival, mortality, and other clinical information stratified by variables such as age, race and ethnicity, and geographic area. However, sources like these lack

granularity about clinical variables such as biomarker status and prior therapies. In addition, disease progression data can be lacking and there can be time lags in data reporting of one to several years for certain data elements leading to potential misalignment with other data sources. *Examples include the SEER Database and Centers for Disease Control and Prevention (CDC) Databases.*

2. **Past Clinical Trial Data & Literature** provide helpful estimates for benchmarking based on prior clinical trial enrollment or evidence from retrospective database studies, prospective observational studies, and multicenter studies. There may also be patient-level data on clinical outcomes and clinical variables of interest. However, these data sources may not represent the current standard of care and historically lack representation of patients from diverse racial and ethnic groups. Additionally, race, ethnicity, and other socio-demographic data tend to be poorly and inconsistently documented across published clinical trials. *Examples include sponsor-specific data/records from past clinical trials, literature reviews, and meta-analyses of past clinical trials.*

3. **Real-world Data (RWD) Sources** contain patient-level data and capture a range of treatment information and other clinical data. RWD sources also have a variety of ways in which to capture and define race and ethnicity. These data sources often lack SDoH information and have variability in available demographic information, though some efforts have been made to leverage other data points to establish SDoH variables.[19] Additionally, these data sources may not always represent the general population. There can also be inconsistency in the quality and completeness of data across patients and RWD sources, and thus, the quality and robustness of the data source will need to be evaluated. *Examples include Electronic Health Records (EHRs), healthcare medical claims data, and disease-specific registries.*

4. **Genomic Databases/Repositories** are the most readily available source of biomarker data, but they have inconsistent categorization of race and ethnicity data and include largely patients served by large academic medical centers and patients of European descent. *Examples include The Cancer Genome Atlas (TCGA) Program, American Association for Cancer Research (AACR) Project GENIE, and other clinical-genomic databases.*

Table 1. Select Examples of Data Sources Used to Inform Enrollment Goals.

Type	Specific Examples	Usages	Strengths	Limitations
Publicly Available Epidemiological Data	SEER Data, Centers for Disease Control and Prevention (CDC) National Program of Cancer Registries (NPCR)	Understanding disease prevalence, incidence, and demographic estimates	Representative of the civilian U.S. population, low missing data on demographics, publicly available/easily accessible	Limited data on rare indications, some data may not be up-to-date given timing/cadence of data collection and publishing of results, incomplete race and ethnicity data, and if included are limited to existing race and ethnicity categories, and these sources may also not include specific biomarker data and treatment history
Real-World Data (RWD)	Healthcare medical claims data (e.g., CMS, private insurers), Electronic Health Records (EHRs) data (e.g., Flatiron Health, Tempus, Cerner Health), other clinical provider databases	Identifying geographies and areas for high-incidence diseases, evaluating treatment effectiveness and safety	Patient-level data, captures treatment and genomic information, demographic data, near real-time	Capture of insured populations with healthcare access, missing data on race and ethnicity in some cases, variable data quality/completeness, variable reporting on biomarker data
Literature Searches	PubMed, clinicaltrials.gov	Informing historical disease characteristics, benchmarking goals	Provides insights into historical disease characteristics	May not provide current and representative data, selection bias in clinical trial data, biomarker data variability
Government Sources and Surveys	U.S. Census Data, National Health Information Survey (NHIS), National Health and Nutrition Examination Survey (NHANES), Medical Expenditure Panel Survey (MEPS)	Estimating the total population at risk, assessing disease burden in health-specific surveys, demographics, and treatment patterns	Large sample size, relevant for benchmarking population-level diversity, low missingness for race/ethnicity data	Some data may not be up-to-date given timing/cadence of data collection and publishing of results, no specific cancer staging, tumor size, etc.

Type	Specific Examples	Usages	Strengths	Limitations
Registries	Disease-specific advocacy group registries	Aggregating data from a targeted patient population (disease-specific), offering network, and disease-specific demographics	Can provide specific demographic data, helpful for certain rare hereditary cancers/diseases	Availability may vary (i.e., disease and/or population specific), not universally accessible, potential for bias in who participates, may not include all demographic information, small size
Past Clinical Trial Data	Clinical trial data, Meta-analyses combining data from past clinical trials including non-interventional (or observational) studies	Estimating placebo rates, understanding historical enrollment rates by demographic group, benchmarking, estimating biomarker prevalence prior to treatment	Comprehensive data from multiple trials, robust estimations, outcomes data	Limited to data from previous trials that may lack representation of diverse racial and ethnic groups, may not reflect current disease landscape, selection bias in clinical trial data, race/ethnicity reporting can vary
Genomic Databases	AACR Project GENIE, TCGA, other clinical-genomic databases (e.g., Flatiron Health-FMI database, Tempus)	Understanding biomarker prevalence	Most readily available source of genomic information	Limited institutions contributing (e.g., academic medical centers), potential for bias in patients included, inconsistent categorization of race and ethnicity. Historic lack of testing in minority populations

Data Challenges

Sponsors must leverage multiple heterogeneous data sources to set enrollment goals, which can be resource intensive and complex. As described in **Table 1,** different data sources have different uses, strengths, and weaknesses. Combining multiple sources can help to collect all necessary data; however, when using this approach to inform representative enrollment goals and develop strategies to provide more equitable opportunities for participation in clinical trials to meet these goals, it can be difficult to synthesize data across sources, particularly where data may be overlapping or are inconsistent. In addition to the resources required and methodology needed for aggregating data across sources, several gaps were identified in the existing data, including several variables of interest that are challenging to obtain even when combining data:

- **Availability of clinical variables across data sources** – With the increasing number of approvals for targeted therapies that rely on biomarker testing to select eligible patients, there is a need to improve approaches and sources for assessing biomarker frequency stratified by race and ethnicity.[20] In the absence of sufficient biomarker data by demographic group, especially for novel biomarkers, one approach is to assume that the frequency of the biomarker is equal across racial and ethnic groups thereby setting enrollment goals based on the overall prevalence of the cancer, irrespective of biomarker status. Assumptions like this may be difficult to test or validate with a high degree of confidence, within a particular clinical context. These assumptions can also lead to underestimating disease burden in underrepresented patients, and in turn, underestimating enrollment targets. Thus, it is difficult to project whether a group may be underrepresented in a trial due to gaps in data for certain populations. Other clinical variables that are difficult to obtain in some data sources include the stage of cancer, tumor histology, line of therapy, and prior therapies.

- **Availability of non-clinical or non-medical variables** – SDoH variables such as income, education level, built environments, and social and community contexts are often not routinely collected or reported likely due to a lack of standards for how this information should be collected.[21] Some national data or U.S. Census data may have information related to SDoH, but these data are not specific to cancers of interest. However, these data can provide essential information for assessing barriers to, and facilitators of, patients' participation in a clinical trial and how lived experiences influence health outcomes. In addition, a lack of standards and reporting limit availability of data on the inclusion of sexual orientation and gender identity and people with disabilities in clinical trials.[22]

- **Variable definitions for race and ethnicity data** – The lack of appropriate and consistent definitions for race and ethnicity impacts data collection, analysis, and reporting. The granularity in which race and ethnicity data are collected also can vary. More granular reporting of Asian populations (e.g., Korean, Japanese, and Chinese), and Hispanic and Latinx populations (e.g., Spanish vs. Central/South American, Mexican, Argentinian, etc.) may be necessary in some instances, and proposals are in place to implement a separate Middle

Eastern or North African (MENA) race category to better distinguish individuals of MENA descent who are frequently reported within the White race category. Currently, the Office of Management and Budget (OMB) is reviewing proposals to update existing race and ethnicity categories.[23] These efforts are important because broad categories such as White, Asian, Black, Hispanic, and non-Hispanic are frequently used, and there may be instances where individuals may not identify with any of these broadly characterized groups or some individuals may be multiracial. This in turn can result in inaccurate data, thereby skewing the ability to establish and measure enrollment goals.

- **Ex-U.S. data** – Obtaining robust data from outside the U.S. presents another challenge. Definitions for race and ethnicity not only vary in the U.S. but also vary globally, and there can be legal restrictions in reporting and sharing this type of patient-level data in certain countries. This poses challenges when clinical trials conducted with the intent to support U.S. submissions include ex-U.S. sites that lack race and ethnicity data. The lack of unified race and ethnicity data outside the U.S. makes it difficult to set enrollment goals for ex-U.S. populations and to estimate the number of patients from underrepresented racial and ethnic populations that could be enrolled outside the U.S. to help meet enrollment goals outlined by sponsors in their diversity action plans. Though, even with more unified race and ethnicity data availability outside the U.S., how these data would apply to achieving enrollment goals in diversity plans in support of U.S. regulatory submissions is unclear. Additionally, while sponsors set current enrollment goals with a U.S. focus, there is also a need to enroll clinical trial populations representative of the entire population who will benefit from use of the drug, particularly targeting patients in countries outside of the U.S. where there is an intent to apply for approval or market the drug. Sponsors will also need to consider variations in lived experiences among racial and ethnic groups in different countries if leveraging ex-U.S. populations to meet U.S. enrollment goals.

Addressing Data Challenges

More work is needed to address these noted data challenges and several forward-leaning proposals have been identified to address different aspects of data integration. Specifically, statistical considerations will also need be considered for combining data sources to strengthen and minimize limitations of any one data source.[24] Additionally, clarity around the level of acceptable uncertainty in estimating the characteristics of the intended patient population with respect to setting enrollment goals and how the relevance/reliability of the data used to set enrollment goals will be considered.

Proposal 1: Central Repository for Biomarker Data in U.S./Canada
One approach to addressing the availability of clinical variables, particularly for biomarker data, is to create a centralized repository that is nationally representative for multiple cancer types, includes race and ethnicity data, and is broadly accessible. The BROAD Institute's Repository for prostate cancer serves as one example.[25] These efforts aim to identify sources of variability across race and ethnicity groups, improve reporting standards, and promote alignment on definitions for race and ethnicity. This initiative may also highlight inequities in

biomarker testing, and thus, highlight the need for resources and strategies to close the gap in biomarker testing across race and ethnicity groups.[20]

Proposal 2: Collaborative Data Consolidation Efforts

To address the challenge of needing to combine multiple data sources, efforts are needed to consolidate and harmonize curated data sources. Collaborative data consolidation bridges gaps in data coverage, providing a more comprehensive and accessible dataset for informed enrollment goal decisions. To assist with consolidating multiple data sources, standards will be necessary.

Government agencies are currently seeking proposals to establish standards for collecting and reporting race and ethnicity variables to enhance primary data collection.[23] The SEER program recently implemented changes to race and Hispanic ethnicity towards five mutually exclusive categories: Non-Hispanic White, Non-Hispanic Black, Non-Hispanic Asian/Pacific/Islander, Non-Hispanic American Indian/Alaska Native, and Hispanic.[26] Additionally, legislative and policy efforts may be necessary to enhance how race is assigned by the U.S. Census and reduce the misclassification of race in cancer data. By working collectively, stakeholders can share the responsibility of data collection and integration, making it a more efficient and cost-effective endeavor.

Additionally, broad initiatives to improve reporting standards and promote alignment of definitions for race and ethnicity are needed. This can include using Clinical Data Interchange Standards Consortium (CDISC) standards as a framework for the structured exchange of clinical and non-clinical research data to ensure that race and ethnicity data are collected and reported in a consistent manner across different studies and data sources. Efforts to create and pilot updated eCRFs can help to ensure that race and ethnicity data are consistent and comparable across different countries and regions. This not only helps in achieving uniformity but also facilitates setting more precise enrollment goals and ensures that the representation of diverse racial and ethnic groups is accurate.

Sponsors recognize the need for efficient data integration to inform enrollment goals and have responded by investing in data integration solutions, establishing partnerships with data providers, and developing standardized data collection protocols. Several strategies may help alleviate data challenges. The use of standard electronic case report forms (eCRF) within the U.S. to capture patient demographic information consistently across all clinical trials can help ensure a more holistic view of representativeness across a sponsor's clinical development programs as well as across different sponsors. Additionally, providing definitions and guidance on race and ethnicity categories in eCRF instructions can help improve the accuracy of data. Epidemiologists should be part of diversity planning strategic discussions and several important questions are noted to consider:

- Is the occurrence of disease higher/lower in specific underrepresented racial and ethnic populations?
- How does the age distribution of disease vary across racial and ethnic groups?

- Do disease characteristics including biomarkers differ across racial and ethnic groups such that we need to show efficacy in each?

- What is the burden of disease across underrepresented racial and ethnic populations, including access to biomarker testing and treatment and morbidity/mortality?

- Do trial inclusion/exclusion criteria disproportionately impact enrollment of certain racial and ethnic populations and/or geographic locations?

Given the increasing number of precision medicine trials, biomarker data is becoming increasingly important. Summarizing published and/or other available evidence per geographical region, number of patients screened for the biomarker, type of biomarker tests, and other parameters can allow for more accurate estimates of the target trial population. Such a comprehensive review of data helps in determining how closely the study conditions mirror real-world settings (external validity) and the degree to which the study findings are free from biases (internal validity).

Measures to Achieve Enrollment Goals

In addition to setting enrollment goals, diversity plans will need to outline measures for achieving these goals. FDA's assessment of experience with diversity plans in the first-year after the April 2022 guidance identified strategies sponsors currently employ to achieve enrollment goals, including patient-directed measures (84% of plans), community engagement (82%), clinical research workforce-directed measures, and trial design considerations such as use of decentralized elements (21%), and eligibility criteria considerations (21%).[17] Survey responses highlight measures being taken and outline some of the approaches that should be leveraged to recruit, enroll, and retain diverse patient populations:

Building Trust and Partnerships in Diverse Communities

Sponsors should actively and continually work to cultivate new partnerships and sustain relationships within diverse communities by partnering with community health centers serving diverse populations, diverse providers, and other community organizations and patient advocacy groups. These relationships can help build patient and provider trust in clinical trials, promote participation, and gather valuable patient and provider feedback crucial for informing clinical development programs. Engagement includes partnering with sites experienced in recruiting diverse patients to understand successful approaches and leveraging these learnings to train and support other clinical trial sites on the importance of including patients from underrepresented groups in clinical trials. Partnerships with diverse sites and providers can also help to facilitate dialogue regarding the specific needs of site staff to support effective recruitment and retention of patients. Depending on the needs identified by site staff, participating sites can be supported with tailored plans and resources including accessible patient-facing materials in various languages, transportation services for trial participants, and trainings on communicating clinical trial opportunities and processes.

Sponsors should also consider how to effectively communicate clinical trial conduct and outcomes with patients. Regular and accessible updates on trial processes, progress, and results at the conclusion of the study (e.g., lay summaries of data) can help to build trust by enhancing transparency, and help to empower patients by providing information to support self-advocacy. Additionally, Sponsors should seek the input of health care providers and patient navigators from underrepresented populations in all aspects of trial conduct and planning including collaborative development resources and educational materials and trial design.

Engagement with diverse communities outside of the healthcare setting is also necessary to build trust. Active participation in community events addressing SDoH and collaborative efforts with community- and faith-based organizations on relevant public policy endeavors are critical components of forming these sustained partnerships. Collaboration with community outreach organizations and patient advocacy groups focused on narrowing health equity gaps is also important. In addition, efforts should be made to develop tailored media and advertising, provide translation services and multilingual materials to bridge language barriers to ensure there is accessible information being disseminated about available clinical trials. It is critical that all patients are provided the necessary information and asked to participate in clinical trials.

A deeper understanding of local dynamics within a community, as well as the power dynamics between the community and research/healthcare system, can help to clarify how these factors influence healthcare utilization and clinical trial enrollment and retention. A clearer understanding of these dynamics can inform strategies to address these factors head on to enhance inclusion and participation and facilitate a sustained engagement and commitment to diverse communities.

Lowering Barriers to Participation

To enhance enrollment and retention, sponsors should actively assess and address barriers that hinder patient recruitment in clinical trials. Understanding these obstacles can facilitate access for participants interested in clinical trials. For instance, sponsors should consider the financial burden on patients enrolled onto trials, offering pre-loaded reimbursements for transportation, accommodations, meals, and potential compensations for loss of earnings incurred due to trial participation. In addition, financial burden (beyond travel expenses and other out of pocket costs) continues to be a hurdle for many clinical trial participants, and can disproportionately affect some therapeutic areas, such as those requiring very frequent, lengthy, or complex assessments, indications that require extended research timelines, and/or treatment areas where even the standard of care is not adequately covered for patients who have insurance or are participants in government healthcare programs, such as Medicaid.[27] FDA should work with HHS and other agencies to ensure that these roadblocks are addressed in a way that allows sponsors to provide the support needed to help ensure that clinical research is a realistic option across different communities.

Sponsors should also evaluate protocols to identify areas for lowering barriers to enrollment, such as removing overly restrictive eligibility criteria, when scientifically justified.[28,29] Additionally,

decentralizing aspects of a trial through the use of mobile units, telemedicine, and/or distributing medicine through the mail can enhance accessibility. Other trial design aspects should be considered to streamline protocols and reduce operational burden for both patients and investigators. This process should include patient advocates and advocacy groups to regularly evaluate protocol complexity and pinpoint areas where reducing the burden could encourage greater participation. Industry should share best practices, and in particular, strategies that have a positive impact on diversity in enrollment to learn from one another.

Intentional Site Selection

In addition to setting enrollment goals, sponsors should be intentional in their site selection by identifying health centers and providers in community settings that serve catchment areas with diverse patient populations and have diverse representativeness in trial personnel. Intentional site selection is critical to ensure diverse communities have access to clinical trials, which can lead to enrollment and retention of representative patient populations. Traditional site selection has focused on historical site performance metrics (e.g., GCP/protocol compliance, data quality, ability to efficiently recruit, enroll, and retain patients). However, as part of efforts to enroll more representative populations, it is important to incorporate diversity considerations in site selection processes. For example, site surveys and questionnaires, such as the Diversity Site Assessment Tool (DSAT) developed by the Society for Clinical Research Sites, can be used to evaluate site readiness in recruiting, enrolling, and retaining patients from underrepresented populations.[30] These assessments should encompass evaluating whether care incorporates cultural humility/safety, availability of language services, site staff diversity, and patient-centric services. Given that practices caring for underrepresented populations may be less likely to participate in clinical trials, dedicated training programs should be offered to onboard and enhance the capabilities of sites without previous experience engaging with clinical research, ensuring readiness to effectively participate in clinical studies. These programs to bolster site readiness are necessary to achieve the longer-term goal of cultivating a network of sites equipped to engage diverse patient populations effectively.

Real-time Tracking of Enrollment Progress

Implementing real-time tracking mechanisms to monitor enrollment progress can help assess progress toward the achievement of enrollment goals and identify potential areas for improvement. This approach allows sponsors to proactively understand actual versus projected enrollment status, especially in enrolling individuals from historically or currently underrepresented racial and ethnic groups, enabling them to reassess and adapt strategies, as necessary. Implementing a comprehensive dashboard integrating site performance data, local diversity metrics, incidence data, and risk factors could be one approach for providing a holistic view of trial progress. Analysis of screen failure reasons offers insights into the effectiveness of tactics employed and facilitates potential or appropriate adaptations. Overall, frequent evaluation of diversity plan progress can allow for adjustments as needed.

Conclusion

Improving the representativeness of diverse racial and ethnic groups in clinical trials while also considering other diversity dimensions such age, sex/gender, and SDoH is necessary to address health disparities and ensure equitable healthcare access. The lack of inclusivity in current clinical trials can impact the generalizability of findings and enable continued disparities in health outcomes. Efforts by the U.S. FDA underscored by draft guidance documents and the passage of key provisions in FDORA signal a substantial commitment to enhancing diversity and representativeness in clinical trials.

However, as sponsors navigate the implementation of these recommendations, systemic challenges, particularly regarding availability of comprehensive data sources, need to be addressed and best practices established for achieving enrollment goals. Between April 2022 and April 2023, 82% of diversity plans submitted to CDER included enrollment goals and many included various measures for achieving these goals. FDA provides feedback to sponsors who submit plans to support effective implementation, which indicates the need for additional guidance in several areas to support diversity planning: 90% of feedback focused on enrollment goals, 29% of feedback was on strategies for enhancing accrual to meet the goals, and 29% on trial enrollment monitoring, with some feedback focusing on multiple topics.[17] To achieve more inclusive trials, a multifaceted approach is needed that encompasses robust data analysis, strategic planning, community engagement, clinical trial designs, and thoughtful site selection (**Figure 1**). While this effort will require significant investment and resources, by addressing data challenges, partnering with communities, and implementing inclusive trial practices, the community will realize a more equitable and representative clinical trials system.
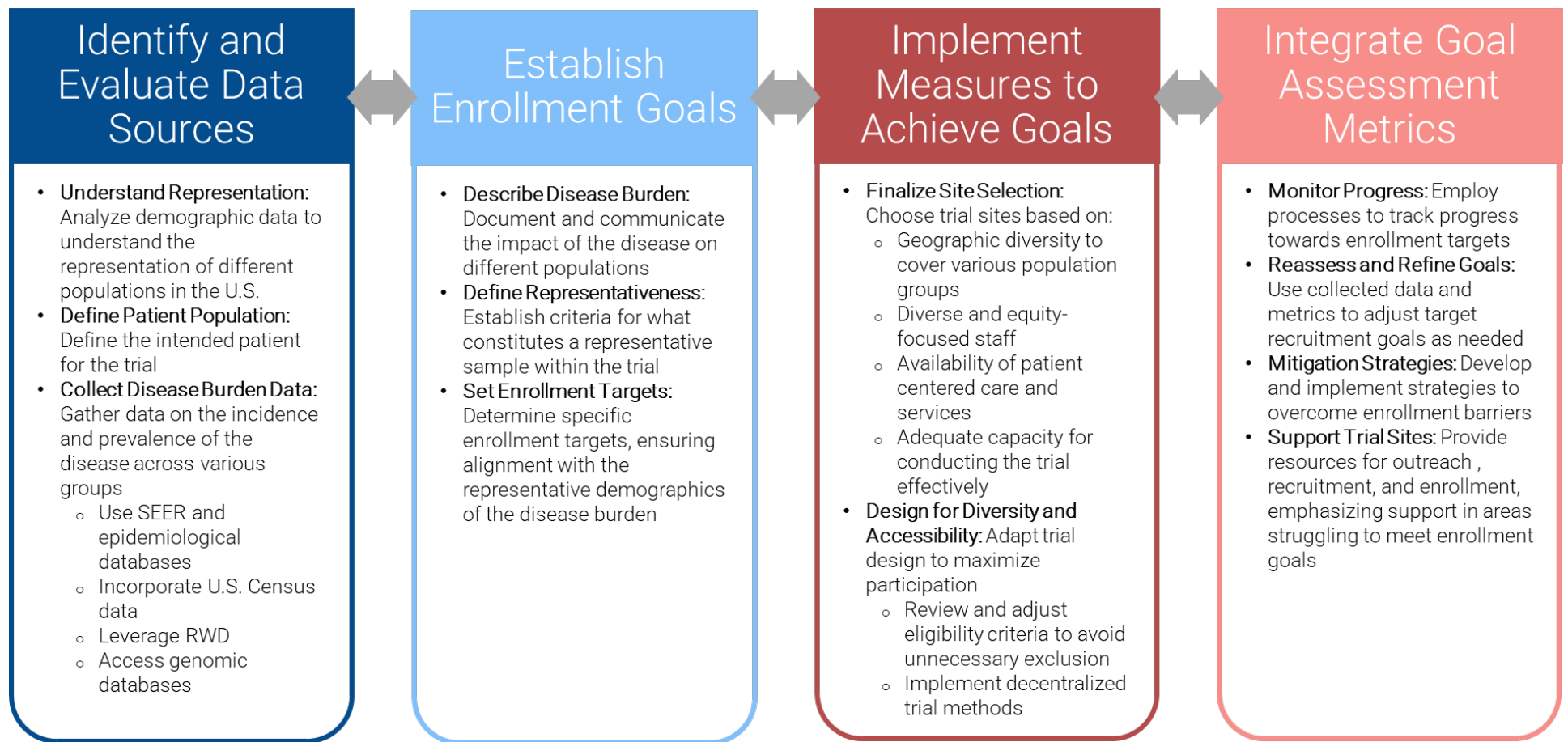
Identify and Evaluate Data Sources

- **Understand Representation:** Analyze demographic data to understand the representation of different populations in the U.S.
- **Define Patient Population:** Define the intended patient for the trial
- **Collect Disease Burden Data:** Gather data on the incidence and prevalence of the disease across various groups
  - Use SEER and epidemiological databases
  - Incorporate U.S. Census data
  - Leverage RWD
  - Access genomic databases

Establish Enrollment Goals

- **Describe Disease Burden:** Document and communicate the impact of the disease on different populations
- **Define Representativeness:** Establish criteria for what constitutes a representative sample within the trial
- **Set Enrollment Targets:** Determine specific enrollment targets, ensuring alignment with the representative demographics of the disease burden

Implement Measures to Achieve Goals

- **Finalize Site Selection:** Choose trial sites based on:
  - Geographic diversity to cover various population groups
  - Diverse and equity-focused staff
  - Availability of patient centered care and services
  - Adequate capacity for conducting the trial effectively
- **Design for Diversity and Accessibility:** Adapt trial design to maximize participation
  - Review and adjust eligibility criteria to avoid unnecessary exclusion
  - Implement decentralized trial methods

Integrate Goal Assessment Metrics

- **Monitor Progress:** Employ processes to track progress towards enrollment targets
- **Reassess and Refine Goals:** Use collected data and metrics to adjust target recruitment goals as needed
- **Mitigation Strategies:** Develop and implement strategies to overcome enrollment barriers
- **Support Trial Sites:** Provide resources for outreach , recruitment, and enrollment, emphasizing support in areas struggling to meet enrollment goals

Figure 1. A Multifaceted Approach for Establishing and Achieving Enrollment Goals.

A strategic framework for enhancing enrollment of diverse patient populations in clinical trials involves identifying and evaluating data sources, establishing enrollment goals, implementing measures to achieve goals, and integrating goal assessment metrics. This process should involve a feedback loop where one is monitoring progress and reassessing and refining goals to allow for adjustments as needed.

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