VIEWPOINT

Promoting Inclusion of Members of Racial and Ethnic Minority Groups in Cancer Drug Development

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Members of racial and ethnic minority groups in the US are frequently underrepresented in clinical trials submitted to the US Food and Drug Administration (FDA) to support approval of anticancer therapeutics.[1,2] The FDA has long held the view that trials should represent the populations for which the therapeutic is intended to ensure external validity of results. The FDA recommendations to improve trial diversity address the collection and analysis of data on racial and ethnic minority groups, describe considerations for broadening eligibility, and encourage discussions with the appropriate division at the FDA regarding enrollment plans.[3,4] External stakeholders have also recommended that pharmaceutical companies develop a plan that outlines measures to ensure diverse clinical trial participation.[5] In oncology, a greater reliance on small studies, intermediate and early end points, and innovative trial designs to expedite drug development and approval underscore the need to prospectively define such a plan.

Clinical trials provide the primary mechanism for collecting data to characterize the safety, effectiveness, and dosage of a therapeutic agent. Although the primary consideration in the design of a trial intended to support regulatory decisions is to characterize the cause-and-effect relationship between an investigational treatment and the outcomes of interest, it is also important to consider factors, such as clinical and demographic characteristics, that support extrapolation of study results to the general population. Race is a sociopolitical construct. Categories used to collect and analyze data on race in the US may have limited global applicability. In addition, the association of race with genetic ancestry, which may be more relevant for assessing population differences in pathophysiologic process or response to drugs, is unclear. Notwithstanding these limitations, race may enrich for variables that directly impact outcomes. For example, exploratory subgroup analyses of clinical trials of Asian patients with lung cancer who received gefitinib showed higher response rates compared with White patients.[6] Initially, the mechanisms explaining these differences were not understood, but further investigation in Asian female patients showed that this subgroup was enriched for a high prevalence of certain activating variations of the epidermal growth factor receptor. This example illustrates that the benefits of enrolling a diverse population in trials may help refine the understanding of drug effects across the entire population. Diverse representation in trials helps inform benefits and risks in these subgroups. In addition, because clinical trials may be a component of care for diseases, such as cancer, they offer timely access to potentially innovative therapies to all patients.

Framework for a Diversity Plan

A diversity plan that outlines the strategy to collect and analyze data to elucidate how race and ethnicity are associated with patient outcomes could facilitate and streamline appropriate trial enrollment. This diversity plan could leverage available data generated during the entire development life cycle of the therapeutic agent (ie, the early clinical setting preapproval and in the postapproval setting) and consider the use of externally sourced data and information. The diversity plan could be revised on the basis of emerging data or information. Ultimately, a diversity plan will be most successful if developed and discussed with the FDA before the initiation of trials that are intended to provide the primary basis for approval (eg, at the end of the dose-finding studies). Although it is optimal to characterize safety, efficacy, and dosage in a highly representative population before approval, this may not be feasible; therefore, obtaining these data postapproval may be appropriate.[7] In addition, when the dose-finding study is intended as the pivotal trial, and phase 2 and 3 trials are planned postapproval, or when the clinical studies will be conducted predominantly or entirely outside the US, there should be early consideration of how data on racial and ethnic minority groups will be generated.

Critical components of a diversity plan include an overview of the disease with respect to racial and ethnic minority groups and specific racial and ethnic categories, the planned drug development strategy, target enrollment by demographic subgroup, measures to increase enrollment of members of racial and ethnic minority groups, and, if applicable, justification for deferral of evaluation until after approval (**Table**). Defining enrollment targets for racial and ethnic minority patients is critical to achieving adequate representation in a given clinical setting. Ideally, these targets should be based in part on the hypothesis that is the subject of the investigation. For example, in evaluating how race is associated with outcomes, a priori information that indicates differential safety risks or drug exposure (or the potential thereof) across racial subgroups may inform the design and objectives of the trial. Unfortunately, historical underrepresentation of members of racial and ethnic minority groups in clinical research has led to a paucity of data to inform trial design with respect to enrollment by race and ethnicity. In these cases, it may be appropriate for enrollment targets to reflect the epidemiologic characteristics of the disease. There are limitations with this approach, particularly when the disease is rare, and small single-group trials provide the evidence of safety and effectiveness. However, consistent enrollment of historically underrepresented subgroups provides opportunities for pooling data to investigate out-

Table. Proposed Elements of a Diversity Plan for Cancer Drug Trials

Domain	Components
Overview of the disease or condition	Summarize available information on the incidence and prevalence of the disease or condition in the overall population and in racial and ethnic minority subgroups, if known.
	Describe available data on the pathophysiologic process of the disease, methods of diagnosis, and currently available treatments and/or prevention strategies in members of racial and ethnic minority groups.
	Discuss the current understanding of and available evidence supporting similarities and/or differences between the general population and racial and ethnic minority subgroups.
Drug development strategy	Describe the planned studies, outlining the following:
	Study design, population, end points, and expected geographic location of studies
	Clinical pharmacological assessment (eg, pharmacokinetic and pharmacodynamic data and/or information about the drug relevant to racial and ethnic minority subgroups)
Target enrollment of members of racial and ethnic minority groups	Define and provide justification for the planned accrual of patients representing diverse racial and ethnic minority groups.
	Define the targeted enrollment of members of racial and ethnic minority groups (eg, based on the epidemiologic characteristics of the disease or a priori information regarding differences associated with race and ethnicity).
Measures to enroll a diverse population	Describe measures that will be implemented to enroll and retain racial and ethnic minority patients in trials and planned use of data from trials to characterize safety, efficacy, and dosage in racial and ethnic minority patients.
	Describe trial accrual and retention strategy in terms of the following:
	Site location and access (eg, language, transportation)
	Community engagement (eg, community advisory boards and navigators, patient advocacy groups)
	Reducing burdens due to trial design and conduct (eg, number or frequency of study-related procedures, use of local laboratory or imaging, telemedicine)
	Describe metrics to ensure achievement of racial and ethnic minority patient accrual goals and specify measures to be implemented during the conduct of the trials if planned enrollment targets are not met.
Justification for deferral to postapproval	Describe factors precluding obtaining data in pivotal trials.
	Describe the proposed postapproval trials that will provide the data on racial and ethnic minority patients.
	Provide a timeline for initiating and completing studies.

comes in these subgroups. For drugs developed to target a rare molecular aberration in a tumor, there may be limited data to characterize the distribution of the biomarker across racial and ethnic minority subgroups. In these cases, alternate data sources could be leveraged (eg, real-world data, published literature) to define enrollment targets or define enrollment targets based on incidence of the disease in the overall population.

The clinical pharmacological assessment facilitates exposure-response analyses that inform safe and effective dosing regimens across the intended patient population. Pharmacokinetic and pharmacodynamic assessment from a diverse population should occur in parallel with assessment of other covariates known to affect drug pharmacokinetics and pharmacodynamics. These data should be of sufficient quantity and quality. Where applicable, available information on pharmacogenomics should be leveraged to assess the likely influence of race and/or ethnicity on outcomes.

Conclusions

Members of racial and ethnic minority groups have historically been underrepresented in cancer drug trials, even though they tend to be disproportionately represented among individuals who develop the disease. Given the serious and life-threatening nature of cancer, expedited drug development and approval is a highly desirable goal that must be balanced with achieving broader representation in trials and promoting equitable access to potentially life-changing drugs. A prospectively defined strategy that leverages the entire life cycle may help generate data to characterize safety and efficacy in historically underrepresented subgroups.

ARTICLE INFORMATION

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