Recommendations on Eliminating Racial Disparities in Multiple Myeloma Therapies: A Step toward Achieving Equity in Healthcare

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Summary: African Americans are at higher risk of multiple myeloma (MM) yet are underrepresented in clinical trials and reap fewer benefits from novel therapies of the disease. To improve representation of African Americans in MM clinical trials, researchers, healthcare providers, patients, industry partners, and regulators at an FDA-AACR workshop developed recommendations to all stakeholders. The outlined principles offer a road map to addressing disparities broadly in clinical trials.

INTRODUCTION

Multiple myeloma (MM) is characterized by excess plasma cells in the bone marrow associated with monoclonal protein in the blood and/or urine. Clinical sequelae include hypercalcemia, renal dysfunction, anemia, bone disease, increased risk of infection, and neuropathy. There has been remarkable progress in the treatment of myeloma with the advent first of high-dose therapy and autologous stem cell transplantation, and then with novel agents including immunomodulatory drugs, proteasome inhibitors, monoclonal antibodies, a histone deacetylase inhibitor, a nuclear transport inhibitor, and an antibody–drug conjugate. More therapies are in development, which will even further improve patient outcome.

Yet, a retrospective analysis of data from the nine original NCI Surveillance, Epidemiology, and End Results registries suggests that African Americans are not benefiting from advances in MM treatments (1). For white Americans diagnosed with MM between 1973 and 2005, 5-year relative survival rates (the ratio of observed to expected survival for a specific group) increased significantly from 26.3% to 35.0% (P < 0.005), while increasing from only 31.0% to 34.1% for African Americans.

Over 30,000 new MM cases are diagnosed in the United States each year, and over 12,500 deaths will result from myeloma (2). MM is more common in men than in women and among African Americans compared with whites. Indeed, incidence rates in African Americans are more than double those seen in whites (15.9 vs. 7.5 cases per 100,000), a trend that also extends to mortality (5.6 vs. 2.4 MM deaths per 100,000 for African Americans compared with whites; ref. 3). Patients with high African ancestry are more likely than those with high European ancestry to have translocations involving the immunoglobulin heavy-chain gene on chromosome 14, specifically t(11;14), t(14;16), or t(14;20) (ref. 4; the latter two confer high-risk disease). Conversely, African Americans are less likely than whites to have a deletion of TP53/17p, which is a hallmark of high-risk disease and associated with shortened survival (5). These observations highlight that there may be fundamental differences in disease biology between African Americans and whites.

Among nine large MM clinical trials conducted by NCI Cooperative Groups, enrollment of African Americans was 13% from 2002 to 2011, a decrease from the 16.5% enrollment in the previous 10-year period (2). Importantly, most racial and ethnic minority patients participated in clinical trials that did not involve novel agents. Among trials included in new drug application and biological license application submissions for MM indications between 2003 and 2017, a mere 4.5% (range, 0.5–19.9) were African Americans, and this subgroup comprised only 1.8% of the study population in international trials (6). Considering that African Americans account for 13% of the U.S. population and 20% of individuals who are diagnosed with MM (6), their under-representation in MM clinical trials raises concerns regarding the applicability of study results to this subgroup. Due to underlying genetic and biological differences between African Americans and whites with MM, it is possible that clinical trials may not adequately characterize either the safety or efficacy of approved drugs in these patients. Importantly, FDA reviewers need diverse clinical trial data to inform the...
RECOMMENDATIONS FOR PREAPPROVAL CLINICAL TRIALS

1. **Broden eligibility criteria** for clinical trials whenever possible and appropriate. Additionally, trial sponsors should consider expansion cohorts with broader eligibility criteria within registrational trials to assess feasibility/tolerability and to collect more data in racial and ethnic subpopulations.

2. Trial sponsors should complete a specific, prospective diversity study plan, which:
   a. sets concrete targets for trial enrollment based on disease epidemiology, which:
      i. aim to meet the predetermined diversity target within the trial,
      ii. include plans for meeting the target in the post-approval setting in case this goal is not met in the preapproval trials, and
      iii. if plans include the use of real-world data, sponsors should prespecify what analyses will incorporate those data, accounting for the lack of randomization to control for unknown confounders.
   b. prespecifics analyses and endpoints to be assessed in racial subgroups:
      i. models the effects of having more or fewer patients than expected for a given subgroup
      ii. explores potential alternative endpoints that may be more easily interpreted in racial subgroups
   c. outlines strategies to enroll, accrue, and retain an appropriately diverse population in the trial, including approaches to overcome cultural barriers
   d. shares examples of strategies used by those conducting trials that helped meet target enrollment in subpopulations

3. **Appoint a diversity officer** to phase II and III clinical trials to assist with trial design and recruitment

4. **Trial design should** encompass disease subtypes and features most commonly seen in African Americans.
   a. Include biological variables relevant for racial differences in multiple myeloma outcome differences, e.g., venetoclax in t(11;14), high Bcl-2 patients.
   b. Thoroughly monitor safety signals detected in African American patients.
   c. Collect and analyze pharmacokinetic and pharmacodynamic data, pursuing signals in racial subgroups to the extent that is reasonable.
   d. Gather data on outcomes in racial subgroups early on and throughout the drug development process, when feasible, to inform later investigations.
   e. Collect genomic data in compliance with updated International Council for Harmonization (ICH) guidelines to better understand the disease and safety and efficacy of drugs in different patient subpopulations, and to establish bases for differences in outcomes.
   f. Race/ethnicity data should be collected prospectively whenever possible. However, trial sites outside the United States may have confidentiality laws that do not allow reporting on or collecting race/ethnicity data.

5. Recommend that FDA review divisions ensure study plans are in place and ask sponsors to monitor targets.

Product’s use in a U.S. patient population, and caregivers need this information to make informed treatment decisions. To address these issues, the FDA collaborated with the American Association for Cancer Research (AACR) to conduct the Workshop to Examine Under-representation of African Americans in Multiple Myeloma Clinical Trials. Working groups (WG; Supplementary Table S1) comprised of researchers, physicians, patients, statisticians, and regulators considered issues including the genetics and biology underlying racial and ethnic differences in MM; enrollment characteristics and outcomes of African American patients in MM trials and real-world data sources; the limitations of currently available data on racial and ethnic minorities with MM; and approaches to increase our knowledge of the safety and effectiveness of myeloma therapeutics in racial and ethnic minorities. With these considerations, WGs developed recommendations for improving and understanding data on outcomes and effectiveness of MM therapies in African Americans. As detailed in Supplementary Fig. S1, the recommendations were shared with representatives from industry WG (Supplementary Table S1) and presented to the public workshop participants to gain input on feasibility and the likelihood of acceptance. After incorporating their feedback, the WG co-chairs consolidated the recommendations into those presented herein.

It is important to note that the recommendations were made and are presented in the context of improving the representation of African American patients in clinical trials of MM therapeutics, but these recommendations could be extrapolated to the inclusion of other subpopulations and underrepresented groups in clinical trials in general.

PREAPPROVAL CLINICAL TRIALS

Measures to increase clinical trial representativeness should be incorporated in the earliest stages of trial design to ensure that trials are representative; such steps may include setting appropriate eligibility criteria and selecting trial sites with...
RECOMMENDATIONS FOR POSTAPPROVAL CLINICAL TRIALS

1. **Conduct prespecified analyses** in the postapproval setting to identify differences among subpopulations defined by race and ethnicity when there is a safety signal or question about efficacy.
   a. Sponsors should submit specific, prospective plans with detailed strategies for enrolling and tracking accrual of African American patients in numbers reflective of disease prevalence.
   b. Exploratory analyses should be described in the trial protocol.
   c. If data on African Americans within registrational trials are insufficient, pilot studies or expansion cohorts may be utilized to interrogate potential racial or ethnic differences, including differences in pharmacokinetics and pharmacodynamics.

2. **Pool data** across pharmaceutical industry and/or cooperative group studies to aggregate sufficient data to perform safety and efficacy analyses for racial and ethnic subpopulations.

3. **Increase diversity**: Stakeholders should devise strategies to overcome clinical, social, and socioeconomic impediments to trial access.
   a. Modernize eligibility criteria for clinical trials whenever possible and appropriate.
   b. When eligibility criteria for registrational trials are more conservative, postmarketing studies of those agents should have liberalized eligibility criteria, so populations who use the agents in the real world are better represented.
   c. Engage with patient advocacy groups to build trust and encourage participation in trials and registry studies. Having patients share their trial experiences with others considering clinical trials can help alleviate fears or concerns about joining a trial.
   d. Forge partnerships through outreach to include social groups not traditionally approached for trial enrollment (e.g., churches, sororities/fraternities), medical societies, and pharmaceutical companies.
   e. Develop precompetitive programs that make resources available to support clinical trial infrastructure in treatment locations that are race/ethnicity rich but have not traditionally been part of the clinical trial ecosystem.

4. **Incentivize inclusiveness**:
   a. Nongovernment stakeholder groups should discuss approaches with Congress for providing incentives to conduct clinical trials prioritizing inclusion of relevant racial groups, as is done for orphan drug or pediatric indications.
   b. Recommend that FDA review divisions ensure plans are in place and ask sponsors to monitor accrual targets.

representation in mind. Furthermore, incorporating diversity officers into the study team during the initial trial design and conduct phases is an intentional step toward ensuring more representative trials and should be encouraged, especially for larger trials. When trials succeed in meeting enrollment targets, it is important to share best practices.

The WG’s recommendations aim to convey support for policies that set such requirements in place for trial sponsors and clinical trial sites. Although the WG members recognized that the FDA cannot unilaterally require such plans, all stakeholders within the community, including principal investigators, funding agencies, trial sponsors, ethical committee boards, public policy makers, clinical societies, and medical journals, should work to make sure that these recommendations become the expected norm rather than an afterthought. The WG encourages the use of strategies that do not significantly delay the trial process. When trials succeed in meeting diversity targets, it is important to share lessons learned with the community so future trials can improve enrollment strategies.

POSTAPPROVAL CLINICAL TRIALS

If insufficient data on the safety and efficacy of MM therapeutics in African American patients are generated during first-in-human and registrational trials, there are additional, statistically sound means by which they can be acquired. Although having adequately powered results for population subgroups may not be feasible, it is nevertheless essential that certain principles of generalizability be addressed. Clinical trials of new agents conducted without regulatory intent at any point on the drug development pathway can further inform their clinical use and can also provide data for pooled analysis. Information pertaining to safety signals among African Americans can be compared with other subgroups. Emerging signals that may suggest different efficacy in African Americans compared with other subgroups can be described and evaluated further if needed. The following recommendations were developed to guide efforts and seek commitment by all stakeholders to achieve this fundamental level of generalizability to better inform myeloma therapeutics among African Americans.

REAL-WORLD DATA STUDIES

Randomized clinical trials represent the gold standard for evidence in clinical research because the random assignment of treatment balances groups of patients by both observed and unobserved variables that can influence study outcomes, such that randomized trials generate an unbiased assessment of the effect of treatment for the study...
**RECOMMENDATIONS FOR REAL-WORLD STUDIES**

1. If the conduct of a randomized trial is not feasible, practical, or timely, prospective studies should be conducted, or the use of existing real-world data should be used for further assessment that can contribute to the understanding of the causal inference in convincing fashion.
   a. Use real-world data (from studies such as INSIGHT MM, Connect MM, or others) to study efficacy and tolerability in specific subpopulations, which could, in turn, generate hypotheses for clinical trials enriched for that subpopulation.
      i. When using real-world evidence to interrogate safety and efficacy, be very specific about the questions being asked and the sufficiency of the underlying data.
      ii. Define real-world endpoints for multiple myeloma.
      iii. Describe an ideal registry and determine the minimum data elements to ask and answer pertinent questions.
   2. Discuss, determine, and disseminate a common reporting framework for multiple myeloma clinical trials that all stakeholders accept as the minimum amount of data that should be collected and abstracted, which includes:
      i. minimum data elements,
      ii. reporting format that includes race and ethnicity, and
      iii. harmonized line of treatment definitions.
   3. If evidence from meta-analyses or real-world data indicates the need to investigate a critical hypothesis about how a cancer drug may work differently in a patient subpopulation, further evaluation should be undertaken, preferably by means of a randomized trial.

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**DISCUSSION**

**Academic Perspective**

The academic community recognizes the need for innovative approaches to enroll African Americans living in rural and urban settings, both to raise awareness of myeloma and to offer access to trial participation in their community. Identification of cultural and social barriers is critical for both clinical trial enrollment and retention, and will inform interventions to achieve health equity. In the preapproval setting, collaborative efforts should be directed to expand eligibility criteria and promote clinical trial designs that allow for inclusion of more representative patient populations. If timelines for registration trials is an issue, expansion cohorts can be utilized with liberalized eligibility criteria to obtain clinical outcome data in racial and ethnic subpopulations. Similar expansion cohorts in the postapproval setting were recommended to interrogate potential racial or ethnic differences. Exploring potential genetic variables that affect differences in outcomes was recommended, including clinical trials of venetoclax in t(11;14) myeloma enriched in African American patients (4), prospective trials evaluating differential therapeutic responses to monoclonal antibodies by race (10), as well as trials establishing safety of anti-myeloma agents in African American patients.

The members emphasized the need for a diversity officer for each trial, as well as an objective prespecified system to define and assess attainment of diversity accrual goals of clinical trials. If the conduct of a prospective randomized trial with expansion cohorts is not feasible or timely, meta-analyses or real-world data, such as from patient registries, may be used to provide further data to investigate a specific hypothesis about how the anti-myeloma agents may work differently in a patient subpopulation. Given the heterogeneity of endpoints for real-world MM studies, the academic community acknowledged the need for harmonizing the data elements and endpoints to describe an ideal registry to probe for pertinent questions.

**Regulatory Perspective**

The FDA is responsible for protecting and promoting the public health of the U.S. patient population, including by ensuring the safety and efficacy of new therapeutics. There has been tremendous progress in the area of MM, with 11 new therapeutics approved by the FDA since 2006. These therapeutics represent novel therapeutic approaches and classes of agents, such as immunomodulatory agents, proteasome inhibitors, histone deacetylase inhibitors, SINE export inhibitors, monoclonal antibodies, and antibody–drug conjugates. These new therapeutics have significantly improved outcomes for patients during this time period (11).

Despite these therapeutic advancements and the resultant improvement in outcomes, less is known about whether these results are generalizable to African Americans, who are disproportionately affected by MM. During the review of a new therapeutic, the FDA evaluates the product’s safety and effectiveness as demonstrated in adequate and well-controlled clinical trials. Although there may be differences between the clinical trial population and the population...
that will ultimately receive the therapeutic after approval, a more representative clinical trial population allows for the trial results to be generalizable to the broader patient population. The underrepresentation of important subgroups (e.g., African Americans in MM) in the clinical trials supporting an application may result in insufficient information upon which to characterize the safety and effectiveness of the product in that population. The FDA expects that prior to approval, trial sponsors should have adequate information to inform the safe and effective use of their product in a population of patients that is representative of those that will ultimately receive the product if it is granted approval. However, the need for robust information must be balanced with the need to provide access to new therapeutics in an expeditious fashion. If there is insufficient information or there are concerns that are presented by the data available at the time of approval, the FDA may request or require additional studies be performed in the postapproval setting.

The recommendations overlap with several ongoing efforts at the FDA to address the underrepresentation of clinically important subgroups in clinical trials. The FDA has long identified eligibility criteria as a significant barrier to clinical trial participation, particularly for racial and ethnic minorities who may be disproportionately affected by comorbid conditions. Another area of overlap is in the importance of implementing a prospective plan early in drug development to ensure diverse patient accrual in clinical trials in sufficient numbers to permit an assessment of safety and efficacy by clinically important demographic subgroups.

**Patient Perspective**

As myeloma patients and advocates, we support the FDA–AACR recommendations to improve the representation of African Americans in MM clinical trials. We emphasize the need to meet patients with myeloma where they are, which includes their level of education, trust, understanding of the medical process, as well as engagement appetite or ability. Education should be widely disseminated through various mediums, such as support groups, social media, virtual discussion boards, churches, village elders, celebrities, and such. We strongly support the recommendation of a diversity officer to define strategies that support African American participation in clinical trials, envisioning the role of the diversity officer as helping to interrupt the biases, either personally or through systematic implementation of processes and procedures. In addition, this officer can help identify and understand the regional differences and barriers for minority enrollment and create best practices. We have a responsibility as patients and patient advocates to educate ourselves, local hematologists, and our patient cohorts, about the importance of clinical trials, how clinical trials are designed, and how they lead to drug approvals. It is also important that the patient is a part of the clinical trial design team within and outside the industry. Requiring teams to explore innovative strategies that include African American patients in trial development and design will hold researchers and industry accountable to conduct more inclusive and patient-centric trials. Finally, the FDA should mandate trials to remain open until a statistically predefined number of minorities are enrolled.

**Industry Perspective**

From an industry perspective, the actions needed to help address underrepresentation of minorities in clinical trials can be parsed into three categories: (i) promote diversity at clinical sites for both the research staff and the patient population they serve; (ii) collaborate with relevant stakeholders to identify feasible and effective interventions dedicated to enhancing enrollment and retention of minority patients in clinical trials; and (iii) throughout the course of clinical development and in alignment with health authorities, establish enrollment goals that are representative of the disease epidemiology.

Although only indirectly modifiable by industry, diversity in clinical research staff could be supported by prioritizing recruitment of sites meeting certain diversity criteria or by sponsoring diversity and inclusion training programs and requiring such qualifications for trials investigators. Geographic areas with high density of minority populations overlap, to a meaningful extent, with lower availability of oncology practices and lower socioeconomic status (12). Therefore, recruiting and retaining patients at such sites would involve either providing adequate support to ensure optimal trial compliance in the traditional trial setting or developing innovative approaches of trial conduct such as decentralized trials. It is also critical for industry sponsors to work in concert with all vested parties, such as research and academic institutions, patient advocacy groups, and community outreach organizations, to identify and address barriers to participation of minority patients in clinical trials. Supporting culturally competent education programs and communication are paramount to ensure patient receptivity to, awareness of, and trust in clinical trials. Such programs and communication tools should be periodically evaluated for effectiveness and modified as needed. To achieve the preset enrollment goals, the sponsors should ensure careful oversight during the study recruitment period, and in the event the target is not reached, the sponsor should consider contingency plans such as postmarketing studies to ensure critical clinical parameters are evaluated in minority populations.

**CONCLUSION**

The importance of diverse representation cannot be underscored enough and is critical to ensure that safe and effective products are available to the U.S. patient population. Here we have laid out concrete steps that clinical trial sponsors and other stakeholders can and should take to improve the representativeness of African Americans in studies examining MM indications. The current discrepancy between the percentage of patients diagnosed with MM who are African American and the percentage enrolled in MM clinical trials is troubling on many levels but can be addressed on multiple fronts. African Americans with MM are one example of an underrepresented and underserved population that is disproportionately affected by disease. By and large, the recommendations shared here can be generalized or applied to other groups and diseases to improve both their representation in the drug development process and our understanding of drugs’ performance in the population in which they will be used following regulatory approval. Indeed, it is the hope of everyone who contributed to this initiative that these
recommendations will lead to a more inclusive, “real-world” drug development paradigm.

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