

Paradigms and perspectives

Addressing disparities in biologic drug development in the United States

Christopher Hvidas, PharmD,^a Margee Louisias, MD, MPH,^{b,c} Tanya M. Laidlaw, MD,^{b,c} and Ayobami Akenroye, MD, MPH^{b,d,e} Philadelphia, Pa; Boston, Mass; and Baltimore, Md

Key words: Allergy, disparities, clinical trials

Racial and ethnic minorities are underrepresented in clinical trials of mAbs (“biologics”) for allergic diseases, but this is not due to a paucity of minorities with allergic diseases.^{1,2} Contrariwise, racial/ethnic minorities bear a disproportionate burden of allergic diseases. Compared with White Americans, Blacks and Latinx of Puerto Rican origin have higher asthma prevalence and mortality.² These disparities extend to other allergic comorbidities, including allergic rhinitis, atopic dermatitis, and nasal polyposis.² Furthermore, asthma phenotype differs within racial and ethnic groups. For instance, minority populations are more likely to be sensitized to indoor allergens, and those with allergic phenotypes may respond better to some biologics.² Similarly, non-White patients with nasal polyposis are more likely to have severe disease refractory to surgery.³ Thus, results from trials based on White populations may not carry over to minority populations.

Minority underrepresentation in clinical trials is not unique to allergic diseases or trials of biologics; it dates back many decades.⁴ As an attempt to improve disparity, the National Institutes of Health Revitalization Act of 1993 mandated inclusion of women and minorities in clinical trials and funds studies focused on minority populations, such as the Consortium on Asthma among African-Ancestry Populations in the Americas. More recently, the US Food and Drug Administration released guidance on improving representation of minority populations in clinical trials. Despite these mandates and guides, poor representation of minority groups continue in most trials.

From the patient perspective, the reasons for minority underrepresentation include mistrust stemming from historical and lived exploitative research practices, logistic burden, and lack of awareness of or access to research.⁵ Additionally, racial and ethnic minorities may view informed consent as a process stripping their autonomy and absolving researchers from legal liabilities.⁴ However, evidence suggests that Black patients are as willing as White patients to participate in research, particularly if the benefits and harm of that research are clearly communicated.^{6,7} Moreover, evidence suggests that underrepresented groups may be overrepresented in phase I safety trials.⁸ This discrepancy between minority recruitment in phase I versus phase III trials suggests that minorities may not be inaccessible for clinical trials as assumed. Logistic issues such as time away from work, cost and feasibility of travel, child care, and general inconvenience, may select against racial/ethnic minority participants.^{7,9} Furthermore, clinicians tend to unjustifiably perceive minority populations to be less adherent to trial protocols.⁸

Given the refocus on trial diversity, multiple health care stakeholders are engaging in various efforts to improve representation. These include pharmaceutical companies training physicians from minority groups on conduct of research and creating networks linking patients and providers with ongoing research. However, the nature of temporary resource networks that are active only during the time of clinical trial prevent lasting change. The level of commitment also differs between companies and by therapeutic areas. Similarly, many large urban centers have community engagement teams. However, the improvements from these efforts have been local, with limited widespread effects. That existing regulations and recommendations have not led to significant improvements in minority enrollment suggests that there are no quick or easy fixes and that there has not been sufficient effort to push for quantifiable progress.

The current system of conducting clinical trials needs to be redesigned. Reinforcing current strengths and leveraging opportunities while eliminating threats and weaknesses are important to creating a just system, as Fig 1 comprehensively summarizes. Drug trials are concentrated in large urban centers with less diverse populations. Sponsor efforts to recruit enough minority participants may be resource-intensive, requiring adoption of innovative recruitment strategies, particularly if a study site's ability to engage, recruit, and retain minority participants is not assessed *a priori*.

Improvement strategies need to be multilevel, incremental, and synergistic across stakeholders. From the regulatory perspective, a carrot-and-stick approach may work. First, regulations need to be binding, and established standards for diversity in trials are needed. To ensure equitable and ethical practices, the US Food and Drug Administration could set a minimum proportion of racial/ethnic groups to be recruited on the basis of epidemiology of the disease. Consequently, populations likely to bear risk of

From ^athe Department of Pharmacy, Penn Presbyterian Medical Center, University of Pennsylvania Health System, Philadelphia; ^bthe Division of Allergy and Clinical Immunology, Brigham and Women's Hospital, Boston; ^cthe Department of Medicine, Harvard Medical School, Boston; ^dthe Division of Pediatric Allergy and Immunology, Johns Hopkins University School of Medicine, Baltimore; and ^ethe Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore.

Supported by the National Institutes of Health (NIH)/National Heart, Lung, and Blood Institute (NHLBI) (grant L30 HL143781 [to M.L.]), the NIH/National Institute of Allergy and Infectious Diseases (grant U19AI095219 [to T.M.L.]) and NHLBI (grant R01HL128241 [to T.M.L.]), the NIH/National Institute of Minority Health and Health Disparities K99/R00 MOSAIC program (grant K99MD015767 [to A.A.]), and the Johns Hopkins University Provost's Postdoctoral Award (to A.A.).

Disclosure of potential conflict of interest: T. M. Laidlaw has served on scientific advisory boards for GlaxoSmithKline, Sanofi-Genzyme, and Regeneron. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication June 9, 2021; revised August 11, 2021; accepted for publication September 8, 2021.

Corresponding author: Ayobami Akenroye, MD, MPH, Division of Pediatric Allergy, Immunology, and Rheumatology, Johns Hopkins University, 600 N Wolfe St, CMSC 1102, Baltimore, MD 21287. E-mail: aakenroye@bwh.harvard.edu.

J Allergy Clin Immunol 2021;■■■:■■■-■■■.
0091-6749/\$36.00

© 2021 American Academy of Allergy, Asthma & Immunology
<https://doi.org/10.1016/j.jaci.2021.09.006>

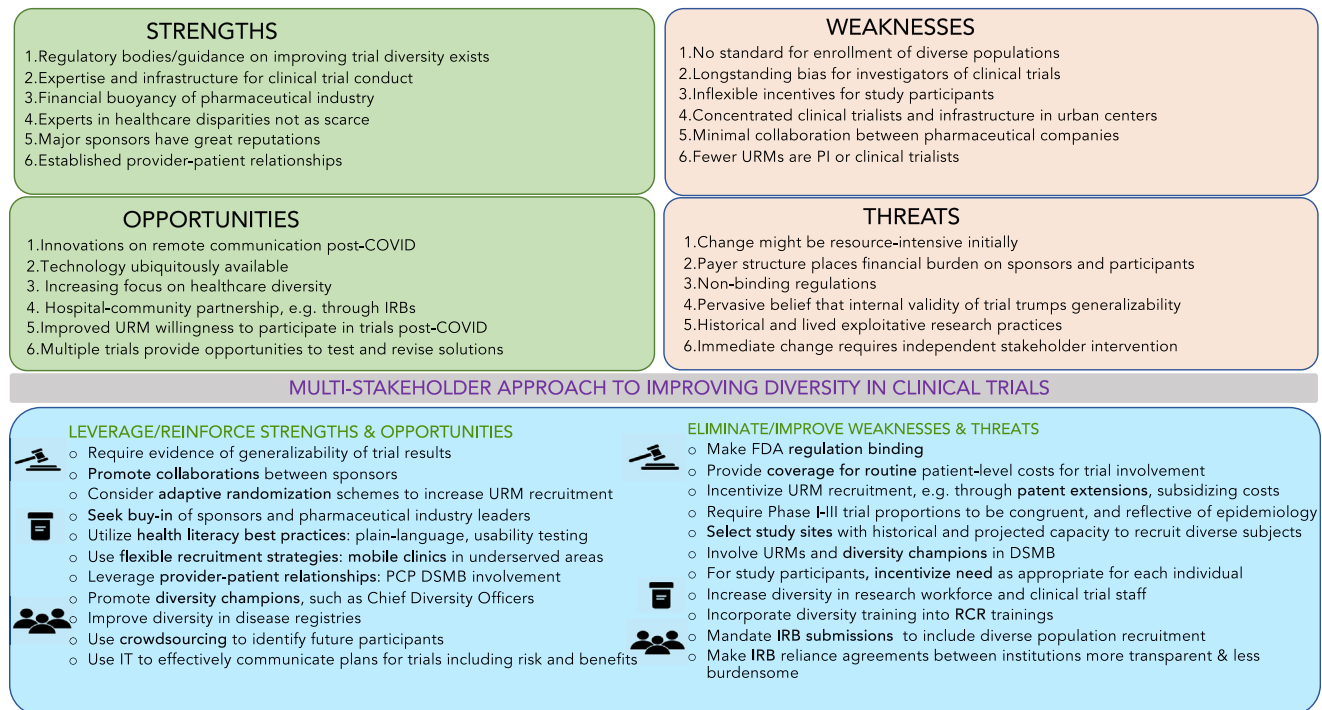


FIG 1. A strengths, weaknesses, opportunities, and threats analysis of important factors across all clinical trial stakeholders and recommendations to improve minority representation in trials. *DSMB*, Data safety monitoring board; *IRB*, institutional review board; *IT*, information technology; *PCP*, primary care provider; *PI*, primary investigator; *RCR*, responsible conduct of research; *URM*, underrepresented minorities.

phase I trials are also likely to benefit from phase III trials. Incentives such as expedited Biologics Licensing Applications review, patent extensions, and government subsidies of trial costs should be granted for studies representative of real-world populations.

Nonetheless, appropriate representation of diverse populations should be balanced against the need to expedite approval of novel therapies. For preexisting and completed studies, this issue could be solved through requirement of follow-on studies on conditions disproportionately affecting minority populations, similar to cardiovascular outcomes trials for antihyperglycemic studies. However, appropriate representation at every phase of the study should be the criterion standard. For payers, federally mandated expansion of coverage of routine costs associated with clinical trial involvement for all Medicaid enrollees starting in January 2022¹⁰ and continued coverage of these costs by Medicare and commercial insurers will be helpful.

Importantly, there is need to improve infrastructure for trials in underserved areas. Companies should prioritize study locations serving more diverse populations, train local providers on research conduct, work with local community outreach groups, create inclusive protocols with study questions applicable to the intended population, and develop contingency plans if diversity is not met. Innovative use of mobile clinics, remote communication, and telemedicine, as has been done during the COVID-19 pandemic, can be useful as companies consider diversifying trial recruitment. Mobile clinics, such as the Mobile Examination Center used for the National Health and Nutrition Examination Survey, can be used in remote areas and may contribute to the

local economy and overall population health. In addition, adaptive trial designs with flexible recruitment strategies provide an opportunity to ensure appropriate minority population representation.

Clinical trialists and health care organizations need to create an environment of trust, respect, and good rapport with minority communities that predates and outlasts a clinical trial. This starts with open communication; a well-trained team-based approach; and ongoing partnerships with families, schools, and other community-based organizations. Ensuring racial, ethnic, lingual, and cultural concordance between study teams and participants; increased minority representation in data and safety monitoring boards; and increased focus on diversity are all important parts of improving this issue. Incentives for study participation need to be flexible and based on need. Although biologic access is beyond the scope of this article, it is important to note that minority populations may be less likely to receive biologics in the real world, thus highlighting the importance of synergistic improvements across all health care stakeholders.

Despite bearing a disproportionate burden of allergic diseases, racial/ethnic minorities remain underrepresented in clinical trials of biologics. To fully reap the benefits of biologic therapies, however, trials should be conducted in representative populations. Advocacy of legislative and regulatory progress by patients, communities, providers, and leading health organizations is necessary. Immediate steps are dependent on self-awareness as stakeholders identify internal disparities and take incremental steps while binding legislative efforts are enacted to ensure lasting change.

REFERENCES

1. Akenroye A, Keet C. Underrepresentation of blacks, smokers, and obese patients in studies of monoclonal antibodies for asthma. *J Allergy Clin Immunol Pract* 2020;8:739-41.e6.
2. Davis CM, Apter AJ, Casillas A, Foggs MB, Louisias M, Morris EC, et al. Health disparities in allergic and immunologic conditions in racial and ethnic underserved populations: a work group report of the AAAAI Committee on the Underserved. *J Allergy Clin Immunol* 2021;147:1579-93.
3. Stevens WW, Peters AT, Hirsch AG, Nordberg CM, Schwartz BS, Mercer DG, et al. Clinical characteristics of patients with chronic rhinosinusitis with nasal polyps, asthma, and aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol Pract* 2017;5:1061-70.e3.
4. King TE Jr. Racial disparities in clinical trials. *N Engl J Med* 2002;346:1400-2.
5. Luebbert R, Perez A. Barriers to clinical research participation among African Americans. *J Transcult Nurs* 2016;27:456-63.
6. Wendler D, Kington R, Madans J, Van Wye G, Christ-Schmidt H, Pratt LA, et al. Are racial and ethnic minorities less willing to participate in health research? *PLoS Med* 2006;3:e19.
7. Brewer LC, Pasha M, Seele P, Penheiter S, White R, Willis F, et al. Overcoming historical barriers: enhancing positive perceptions of medical research among African Americans through a conference-based workshop. *J Gen Intern Med* 2021;36:2547-54.
8. Fisher JA, Kalbaugh CA. Challenging assumptions about minority participation in US clinical research. *Am J Public Health* 2011;101:2217-22.
9. Clark LT, Watkins L, Piña IL, Elmer M, Akinboboye O, Gorham M, et al. Increasing diversity in clinical trials: overcoming critical barriers. *Curr Probl Cardiol* 2019;44:148-72.
10. Takvorian SU, Guerra CE, Schpero WL. A hidden opportunity - Medicaid's role in supporting equitable access to clinical trials. *N Engl J Med* 2021;384:1975-8.