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Commentary

Accountability in clinical trial diversity: The buck stops where?

Lauren D. Nephew

Division of Gastroenterology/Hepatology, Department of Medicine, Indiana University School of Medicine, 702 Rotary Building, Suite 225, Indianapolis, IN 46202, United States

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If the Pfizer and Moderna Coronavirus Disease (COVID-19) studies taught us one thing, it is that clinical trials can better reflect the diverse demographics of the population. Why then, do not most other Phase 3 clinical trials account for the diversity of the population who will most likely use the drug? Most do not, because there is no accountability. In developing the COVID-19 vaccine, industry and its partners were well aware of their mandate: develop a vaccine quickly that would be acceptable and legitimate to the public. A vaccine deemed acceptable and legitimate to the United States (US) public had to be tested in a population that reflected the demographics of the population infected by the virus. By putting clinical trial sites in urban areas, leveraging previously developed relationships with community partners, and ensuring accessible enrollment, Pfizer and Moderna's Phase 3 clinical trials respectively enrolled 9.3% and 10.2% Black, 28.0% and 20.5% Hispanic, and 4.3% and 4.6% Asian participants (Table 1) [1–3]. While this does not fully approximate the Black and Asian populations in the US, and certainly does not reflect the disproportionate numbers of minorities infected with the virus, the numbers come closer than many previous Phase 3 clinical trials.

To better understand which populations provide the drug safety and efficacy information used by the US Food and Drug Administration (FDA), Knepper et al. reviewed the approvals made by the agency at five time points from 1997 to 2014[4]. During the study period, the number of countries contributing to the clinical trial data that the FDA uses to approve drugs nearly doubled from 32 to 57. Yet, the racial and ethnic make-up of the trials remained flat. The median percentage of Black participants ranged from 1.8 to 3.5% and Asian participants ranged from 0 to 7%. For reference, 75% of the global population lives in Asia or Africa [4].

In an effort to change this trend, in November 2020, the FDA issued a report "*Enhancing the Diversity of Clinical Trial Populations-Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry*" [5]. The 21-page report provides guidance on areas such as broadening eligibility criteria to increase diversity in enrollment and efforts to make trial participation less burdensome to enhance inclusiveness. The report provides important guidance strategies to help industry and its partners take important steps towards improving clinical trial diversity. Regrettably, this and all FDA guidance documents can only make recommendations. This report is quite clear in its introduction that "*the use of the word should in Agency guidance means that something is suggested or recommended, but not required*" [5].

This noncommittal stance leaves us to question whose role is it to ensure diversity in clinical trials? Who is responsible for holding industry and its partners accountable? Where does the buck stop? Approximately one-fifth of new drugs approved by the FDA demonstrated differences in exposure and/or response across racial and ethnic groups [6]. This is likely the result of a complex interplay between differential environmental exposures and genetics, but nevertheless the differences are present. The COVID-19 trials demonstrate that industry can prioritize diversity. However, can we depend on this becoming the norm? I would argue that precedent tells us we cannot.

Table 1
Participant diversity in COVID-19 phase 3 clinical trials compared to the United States population.

	Total US Population Age 16+	Pfizer Phase 3	Moderna Phase 3
Total	258 million*	37,706	30,351
Race (%)			
White	60.1	82.9	79.2
Black	12.2	9.3	10.2
Asian	5.6	4.3	4.6
Native American or Alaska Native	0.7	0.5	0.8
Native Hawaiian or Pacific Islander	0.2	0.2	0.2
Multiracial	2.8	2.3	2.1
Other/Missing		0.6	3.0
Ethnicity (%)			
Hispanic or Latinix	18.5	28.0	20.5

* Race and ethnicity considered together in the KFF Census Bureau's American Community Survey.

E-mail address: lnephew@iu.edu

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There are multiple opportunities along the scientific trial pathway including private and academic institutional review board (IRB) approval/renewal, FDA approval, and scientific review and publication, where trials that failed to enroll a representative cohort could be held to account. IRBs could require a proposal to enroll vulnerable subjects be outlined at the start of a project and failures be mitigated with a written action plan. Industry could provide supplemental funding to investigators to cover these proposals that will likely increase trial costs. The FDA could require a minimal bar of diversity be met in Phase 3 trials before issuing an approval. A change in policy such as this would require the FDA to champion and issue a proposed rule for review by government agencies and signficant public support. However, with the increased public attention on clinical trials in this COVID-19 vaccine era as well as growing calls for diversity in all arenas, the time to consider this is now. Finally, journals could uphold this diversity bar prior to publication and require authors who fail to enroll suitable study populations describe this limitation in their manuscript. All involved parties, working together, can ensure representation and scientific integrity.

As a scientific community, we cannot continue to legitimize work that is not universally applicable when it has been clearly demonstrated that diversity is an attainable standard. When industry and its partners are held to account, I believe we will start seeing the diverse clinical trial populations our patients deserve.

Declaration of Competing Interest

The author has no conflicts of interests or disclosures to report.

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