EDITORIALS

Striving for Diversity in Research Studies

The Editors

Physicians often find it challenging to apply the lessons of large research studies to their clinical practice, especially when the research participants do not reflect the racial identity, ethnicity, age, or sex and gender of the physicians' patients. Strict eligibility criteria for enrollment in a study may exclude relevant participants. The study population may not include groups representing large fractions of those who might be candidates for the trial intervention. This can leave clinicians in a quandary about whether and how to apply the research findings to their own patients, for whom the risk–benefit profile may differ.

Of these trial design lapses, racial and ethnic gaps are particularly disturbing. For years, the *Journal* has published studies that simply do not include enough participants from the racial and ethnic groups that are disproportionately affected by the illnesses being studied to support any conclusions about their treatment. In the United States, for example, Black Americans have high rates of hypertension and chronic kidney disease, Hispanic Americans have the highest prevalence of nonalcoholic fatty liver disease, Native Americans are disproportionately likely to have metabolic syndrome, and Asian Americans are at particular risk for hepatitis B infection and subsequent cirrhosis, but these groups are frequently underrepresented in clinical trials and cohort studies.

There are several possible reasons for this lack of representation in research studies. Simple logistic obstacles, such as an inflexible work schedule or the lack of convenient and affordable transportation to a research center, can act as impediments. Some potential participants may fear being exploited or harmed by the medical establishment, given a history of mistreatment in which the Tuskegee experiment in untreated syphilis in Black men is only the tip of the iceberg.

Another major contributor is the dearth of investigators and study staff who are themselves members of minority groups. Involvement of such persons in conducting the study may increase the confidence of potential minority research participants and community leaders, who can be key to engaging broader participation and accommodating the needs of their communities. Mentoring such investigators, who could then work with underserved communities, would both enhance the recruitment of representative participants and improve communication so that it contextualizes the research questions and the potential benefits of participation in the study appropriately.

For too long, we have tolerated conditions that actively exclude groups from critical resources in health care delivery, research, and education. This exclusion has tragic consequences and undermines confidence in the institutions and the people who are conducting biomedical research. And clinicians cannot know how to optimally prevent and treat disease in members of communities that have not been studied.

Solving this problem will require changes throughout the research enterprise. We need to have a collective conversation about what constitutes acceptable and reasonable representativeness in clinical research. Every funder should mandate appropriate representation. Clinical trialists should devise better methods of recruitment from traditionally underrepresented groups. And medical schools and training programs must

Table 1. Sample Supplementary Table on the Representativeness of Study Participants.

Category	Example
Disease, problem, or condition under investigation	Heart failure with reduced ejection fraction (HFrEF)
Special considerations related to	
Sex and gender	HFrEF affects men more than women (ratio of 2:1 or 3:1).
Age	Prevalence increases steeply with age; women with HFrEF are older than men with HFrEF.
Race or ethnic group	HFrEF affects Black persons disproportionately in the United States.
Geography	Age and cause vary among countries — patients in Latin America and Asia are younger and more often have noncoronary causes than patients in Europe and North America. Much less is known about heart failure in Africa than in other regions of the world.
Other considerations	In the United States, HFrEF develops at a younger age and more often has a noncoronary cause in Black patients than in White patients.Throughout the world, mortality and hospitalization rates vary widely within and between countries.
Overall representativeness of this trial	The participants in the present trial demonstrated the expected ratio of men to women. Biologic sex was reported by the participants; on the intake survey, they were asked, "What was your sex assigned at birth?" Options were female, male, and intersex. Gender was also reported by participants; they were asked, "What is your gender identity?" Options were woman, man, nonbinary, and prefer not to say. Patients with HFrEF are younger outside North America and Western Europe; thus, the age distribution in the study population is different from that encountered in some countries. The proportion of Black patients who underwent randomization overall was small (4.8%), but among patients enrolled in North America, 18.9% were Black, a somewhat larger proportion than the total population distribution of Black people in the United States. Causes of heart failure and other features such as coexisting conditions and kidney function were consistent with epidemiologic and registry data where these were available from participating countries. No patient was enrolled in Africa.

commit to the long-term work required to make sure more members of underrepresented groups become leaders in medical research.

As a medical journal, we cannot fix all these problems. But we can take concrete steps. Our research papers often, but not always, comment on gender, race, and ethnicity within the study sample. But as of January 1, 2022, we will require, as a new step, that authors of research studies prepare a supplementary table that provides background information on the disease, problem, or condition and the representativeness of the study group, to be posted with the article at the time of publication online. An example of the kind of information authors should provide is shown in Table 1.

We will seek the same clarity and transparency in these descriptions of the selection and representativeness of study participants that we seek in any important methodologic feature of research. We believe this requirement will foster greater thought and effort in the recruitment of appropriately representative participants in studies.

We recognize that this step toward transparency is a small one and that it will not overcome many limitations in the application of study results. Studies conducted in one country, for example, may have limited applicability to other countries in which income levels, races, ethnicities, and cultural practices differ. This is one reason we continue to encourage global health research. We have, for some time, taken representation into account in evaluating the suitability of manuscripts for publication in the *Journal*; ultimately, we will require a more diverse study population for trials conducted in countries with underrepresented groups affected by the condition being studied. And we hope to work with funders, researchers, and other journals to appropriately diversify trial participation, increase

the number of persons from underrepresented groups among researchers, and design studies that meet the clinical needs of those most burdened by disease.

Our mission as a journal is to communicate to physicians and other public health and allied health professionals the latest research and the most authoritative thinking to help them care for their patients. From this perspective, diversity in research isn't simply a matter of social justice. It's a critical part of learning how to improve the health of every person.

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Covid-19 Vaccine Effectiveness and the Test-Negative Design

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Observational studies are emerging as fundamental sources of information about vaccine effectiveness outside the controlled environment of randomized trials, and they are being used to generate evidence of effectiveness against outcomes that are underpowered in trials, such as hospitalization or intensive care unit (ICU) admission, or for narrow subgroups.[1] These studies can monitor the waning of vaccine effectiveness or measure the performance of vaccines against novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants when large randomized, controlled trials are not feasible.[2]

Thompson et al.[3] now describe in the *Journal* the application of a retrospective test-negative design to estimate coronavirus disease 2019 (Covid-19) vaccine effectiveness in adults 50 years of age or older. A multisite network contributed data on 41,552 admissions to 187 hospitals and 21,522 visits to 221 emergency departments or urgent care clinics. These data were derived from patients who had accessed medical care for Covid-19–like illness and had had molecular testing for SARS-CoV-2. In the test-negative design, the case patients were those who tested positive for SARS-CoV-2, and the control patients were those who tested negative. Vaccine effectiveness was estimated by comparing the odds of vaccination between cases and controls. Table 1 shows how data from such studies may be used to calculate vaccine effectiveness.

The test-negative design may be used to estimate vaccine effectiveness against medically attended, laboratory-confirmed SARS-CoV-2 infection among patients who would seek — and have access to — medical care.[4] Thompson et al. estimated effectiveness with respect to three distinct outcomes: an emergency department or

Table 1. Calculation of Unadjusted Vaccine Effectiveness among Patients with Covid-19–like Illness in a Study with a Test-Negative Design.*

Vaccination Status	Patients Who Sought Medical Care		Patients Who Did Not Seek Medical Care	
	Positive SARS-CoV-2 Test	Negative SARS-CoV-2 Test	Positive SARS-CoV-2 Test	Negative SARS-CoV-2 Test
Vaccinated	Stratum A, 600 patients	Stratum B, 20,000 patients	Stratum C	Stratum D
Not vaccinated	Stratum E, 4000 patients	Stratum F, 16,000 patients	Stratum G	Stratum H

* Shown are the strata of a full population before sampling and the numbers of patients in a hypothetical sample. This test-negative design involves data from patients who sought medical care for coronavirus disease 2019 (Covid-19)–like illness and had a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test result. The remaining information on the patients who did not seek medical care is not observed. Unadjusted vaccine effectiveness (VE) is estimated as 1 minus the odds ratio for vaccine effectiveness among patients who sought medical care for Covid-19–like illness and had a SARS-CoV-2 test result, calculated as VE=1−(A/E) divided by (B/F), or 1−(600÷4000)÷(20,000÷16,000)=88%. In order for the VE odds ratio to be a valid measure of effectiveness in the full population, it must be assumed that VE is the same for patients who sought medical care for Covid-19–like illness and those who did not. This implies equivalence between the odds ratios (A/E) divided by (B/F) and (C/G) divided by (D/H). To adjust for confounders that are observed, an adjusted odds ratio, estimated with case weighting or regression, is used in place of the unadjusted odds ratio. Adapted from Jackson and Nelson.[4]