ScienceDirect

Contents lists available at sciencedirect.com
Journal homepage: www.elsevier.com/locate/jval

Comparative-Effectiveness Research/HTA

Evaluation of Diversity of Clinical Trials Informing Health Technology Assessments in the United States: A 5-Year Analysis of Institute for Clinical and Economic Review Assessments

Foluso Agboola, MBBS, MPH, Abigail C. Wright, PhD, MSc, Serina Herron-Smith, BA, Diya Mathur, BA, David Rind, MD, MSc

ABSTRACT

Objectives: This study aimed to evaluate the diversity of clinical trials informing assessments conducted by the Institute for Clinical and Economic Review.

Methods: This was a cross-sectional study of pivotal trials included in completed Institute for Clinical and Economic Review assessments over 5 years (2017-2021). Representation of racial/ethnic minority groups, females, and older adults was compared with the disease-specific and US population, using a relative representation cutoff of 0.8 for adequate representation.

Results: A total of 208 trials, evaluating 112 interventions for 31 unique conditions, were examined. Race/ethnicity data were inconsistently reported. The median participant-to-disease representative ratio (PDRR) for Blacks/African Americans (0.43 [interquartile range (IQR) 0.24-0.75]), American Indians/Alaska Natives (0.37 [IQR 0.09-0.77]), and Hispanics/Latinos (0.79 [IQR 0.30-1.22]) were below the adequate representation cutoff. In contrast, Whites (1.06 [IQR 0.92-1.2]), Asians (1.71 [IQR 0.50-3.75]), and Native Hawaiian/Other Pacific Islanders (1.61 [IQR 0.77-2.81]) were adequately represented. Findings were similar when compared with the US Census, except for Native Hawaiian/Pacific Islanders, which was substantially worse. Relative to all trials, a higher proportion of US-based trials adequately represented Blacks/African Americans (61% vs 23%, $P < .0001$) and Hispanics/Latinos (68% vs 50%; $P = .047$), but a lower proportion adequately represented Asians (15% vs 67%, $P < .0001$). Females were adequately represented in 74% of trials (PDRR: 1.02 [IQR 0.79-1.14]). Nevertheless, older adults were adequately represented in only 20% of trials (PDRR: 0.30 [IQR 0.13-0.64]).

Conclusions: The representation of racial/ethnic minorities and older adults was inadequate. Efforts are needed to enhance the diversity of clinical trials. Standardized and transparent evaluation of trial diversity should be part of the health technology assessment process.

Keywords: clinical trials, diversity, ethnicity, health technology assessment, older adults, race, sex.

VALUE HEALTH. 2023; 26(9):1345–1352

Introduction

There are concerns about the lack of diversity in clinical trial populations, which has implications for both generalizability and fairness, particularly because new therapies are regularly being introduced in the United States. In 1986, the National Institutes of Health established a policy encouraging researchers to include women and minorities in clinical research, and the US Congress made what had formerly been a policy into public law through a section in the National Institutes of Health Revitalization Act of 1993, as part of an effort to enhance the diversity of clinical trial populations. Similarly, over the last 3 decades, the US Food and Drug Administration (FDA) has created various guidelines for clinical trial sponsors to encourage diverse demographic enrollment.[1,2] Nevertheless, evaluations of clinical trials that support drug and vaccine approvals over the last decade have found that racial/ethnic minorities and women continue to be inadequately represented in clinical trials.[3-10] Other research have also noted that specific demographic information, particularly race and ethnicity, are not adequately captured in clinical trials,[11] further masking the lack of diversity.[12]

As a health technology assessment (HTA) organization that provides evidence-based information on new therapies to help inform pricing, coverage decisions, and patient-centered policies, Institute for Clinical and Economic Review (ICER) focuses on many of the most important therapies coming into the market, often representing the newest technologies with the greatest benefits. Unlike the FDA, which has regulatory authority on the approval of new therapies, ICER's work is intended to help inform pricing, coverage decisions, and patient-centered policies on the use of these therapies. We believed that evaluating the representativeness in a sample of ICER reviews would inform the discussion on

clinical trial diversity. Additionally, as a leading voice for independent HTA in the United States, ICER is considering methods to rate studies for representativeness in an effective and transparent manner. This study is an important first step in informing that process. Our aim was to evaluate representativeness in the pivotal clinical trials that served as the backbone of ICER's assessment over the past 5 years. Previous studies in this area have evaluated diversity based on a single demographic characteristic, such as racial group (eg, Black and White participant representation),[9] or in a specific disease area (eg, cardiovascular disease).[5,9] Furthermore, many of these studies have often defined diversity in clinical trials relative to the US population. In this study, we investigated how well information on sex, race, ethnicity, age, and socioeconomic factors of participants were reported and whether racial/ethnic minority groups, females, and older adults were adequately represented compared with disease-specific prevalence estimates and the US population. We further investigated how representation, particularly for race/ethnicity, differed when we evaluated the full set of clinical trials vs only US-based trials.

Methods

Design

This cross-sectional study examined the trials that informed ICER assessments between 2017 and 2021. Because ICER focuses mainly on drug assessments, for consistency, we excluded nondrug assessments from our evaluation. Trials that included only children (patients ≤18 years) were also excluded.

Data Sources and Extraction

We identified the trials (phase 2 and beyond) that informed ICER drug assessment between January 2017 and December 2021. Data were extracted from the article, supplemental materials, and the clinicaltrials.gov database for the following 5 categories: (1) recruitment details, (2) race, (3) ethnicity, (4) sex, and (5) age. Recruitment details included the following: the total sample size, whether the study was conducted in the United States (Y/N), whether the study was conducted exclusively in the United States (Y/N), the proportion of patients enrolled in the United States, the proportion of centers in the United States, and whether race was reported by country of enrollment (Y/N). Data on race included the following: whether race was reported (Y/N), percentage of the trial population who were White, Black/African American, Asian, American Indian/Alaska Native, Hawaiian/Pacific Islander, >1 race, or other. We used the FDA's recommended Office of Management and Budget racial/ethnic categories.[13] Data on ethnicity included the following: whether ethnicity was reported (Y/N), percentage of the trial population who were Hispanic/Latino, not Hispanic/Latino, or not reported/unknown. Relatedly, we also collected information on whether the trial included socioeconomic status (SES) measures (Y/N). For this study, SES could be measured by income, educational level, parents' income, or educational level. Data on sex included the following: whether sex was reported (Y/N), the percentage of the trial population who were female, whether the trial had exclusion criteria targeting females, and, if so, the details of those exclusion criteria. Data on age included the following: whether age was reported (Y/N), percentage of the trial population over 65 years of age, mean age and SD, age range, and age criteria. If data differed between reports on clinicaltrials.gov and the article, preference was given to the published article.

For disease-specific prevalence estimates, we searched the Global Burden of Disease (GBD) database to identify US-specific prevalence data for sex (female/male) and age (≥65 years). GBD is a comprehensive, publicly available, epidemiologic data set supported by the World Health Organization.[14] GBD database provides an array of estimates for health conditions around the world, including prevalence and incidence estimates. The GBD database provides separate estimates for each country and US state. In this article, we obtained estimates from the United States of America in 2019. Race/ethnicity data (and sex and age data when unavailable in the GBD database) were obtained from the Centers for Disease Control and Prevention website[15] or through academic or nonprofit organization sources that are regularly used by clinicians and patients (eg, Cystic Fibrosis Foundation, CancerRates.info). If data were unavailable through those sources, a comprehensive literature search was conducted to obtain peer-reviewed journal articles that estimated the prevalence of US disease by sex, age, race, and ethnicity. Finally, we used the 2021 US Census data for comparison to the US population because it aligned with the year of the last ICER assessment evaluated, and we assumed that US population data were unlikely to have changed significantly across the 5 years.

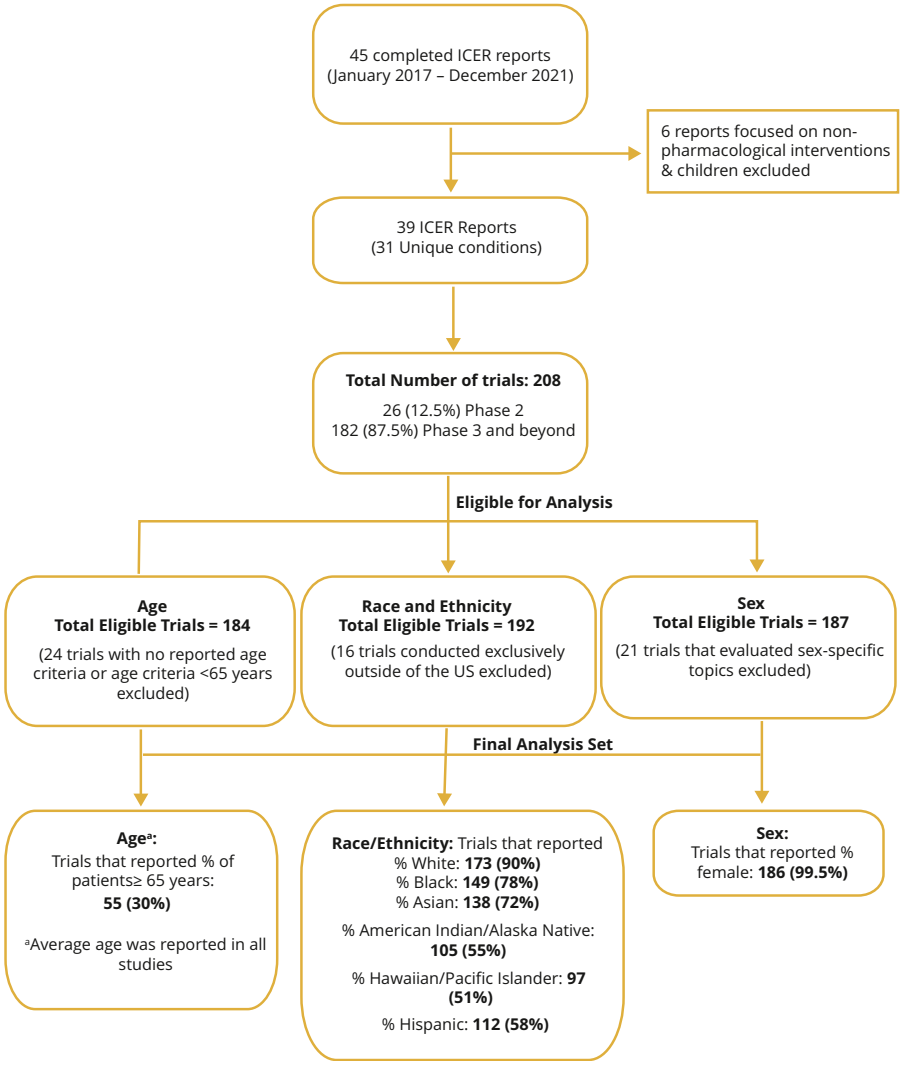
Outcomes

The primary outcomes evaluated were the following: (1) reporting of race, ethnicity, sex, age, and SES across all trials; (2) representation of racial/ethnic minority groups, female, and older individuals.

Statistical Analysis

Descriptive statistics were provided for the reporting of demographic characteristics. The number of trials with missing data for each category was reported. We evaluated the representation of race, ethnicity, sex, and age in the trials relative to both the proportion of those groups in the disease population and the general US population using a metric of "participation-to-disease representative ratio" (PDRR) and "participation-to-population representative ratio" (PPRR). Traditionally, PPRR has been used to estimate representativeness in trials. Because there are known differences in the prevalence of diseases across demographic groups, we evaluated PDRR as an estimation of representativeness based on disease-specific prevalence data. We presented median estimates and associated interquartile range (IQR). A metric of "participation-to-prevalence ratio" was previously used by investigators,[16,17] who noted that a ratio between 0.8 and 1.2 indicated adequate representation relative to disease population, and <0.8 or >1.2 represented under or overrepresentation. We used a criterion of <0.8 to represent underrepresentation. We limited our calculation to only PPRR in situations that we did not have reliable disease-specific prevalence data. If trial-specific demographic characteristics were not reported or were unreliable (eg, race categories were not separated), no comparison was made. Age-specific or sex-specific trials were excluded from sex/age PDRR/PPRR calculations. Similarly, if a trial was conducted exclusively outside of the United States, we excluded the trial from all the race/ethnicity PDRR/PPRR calculations. These trials were excluded from our analysis because all trial participants were recruited from places that are likely demographically distinct from the United States and are unlikely to represent the racial and ethnic diversity of the US population. To assess differences in PPRR or PDRR for trials that recruited patients exclusively in the United States compared with trials that recruited patients globally (both inside and outside the United States), we recalculated the PDRR and PPRR for the US-based trials only as a secondary analysis. Finally, we presented the results of PDRR and PPRR by condition. Analyses were completed using Microsoft Excel.

Figure 1. Flow chart of clinical trials included in this study.



Results

General Characteristics and Reporting

There were 45 completed ICER reports between 2017 and 2021, of which 6 were excluded because they covered non-pharmacologic interventions or included only trials of children (patients ≤18 years) (Fig. 1). The 39 reports examined 31 unique conditions, including 112 interventions and 208 Pivotal trials with 183 086 patients. Of the 208 trials, 182 (87.5%) were Phase 3 and beyond, whereas the remaining 26 (12.5%) were Phase 2. Most trials were multinational, with 157 (75%) trials conducted in the United States and other countries, 35 (17%) exclusively US-based, and 16 (8%) trials conducted outside of the United States. All trials reported participants' average age, and all but 1 trial reported sex. Nevertheless, race/ethnicity characteristics were not consistently reported across trials, with 92 (50%) trials providing information on all 5 racial categories and 82 (42%) reporting on all racial and ethnic categories. Specifically, 173 (90%) trials reported White, 149 (78%) reported Black/African American, 105 (55%) reported American Indian/Alaska Native alone, 138 (72%) reported Asian, 97 (51%) reported Native Hawaiian/Pacific Islander, 112 (58%) reported Hispanic/Latinos, and 19 trials (9%) did not provide any information on race/ethnicity. None of the trials reported information on SES.

Race and Ethnicity

Table 1 presents PDRR and PPRR results for all racial/ethnic categories. The number of trials included in the analysis for each racial/ethnic category differed because of variability in reporting and the lack of reliable disease-specific prevalence estimates for some categories. Among the 173 trials that reported White, adequate representation as assessed by PDRR was achieved in 159 trials (92%), with a median PDRR of 1.06 (IQR 0.92-1.2). In contrast, Black/African Americans (analytic group: 149 trials) achieved adequate representation in only 35 trials (23%), with a median PDRR of 0.43 (IQR 0.24-0.75). Similarly, American Indians/Alaska

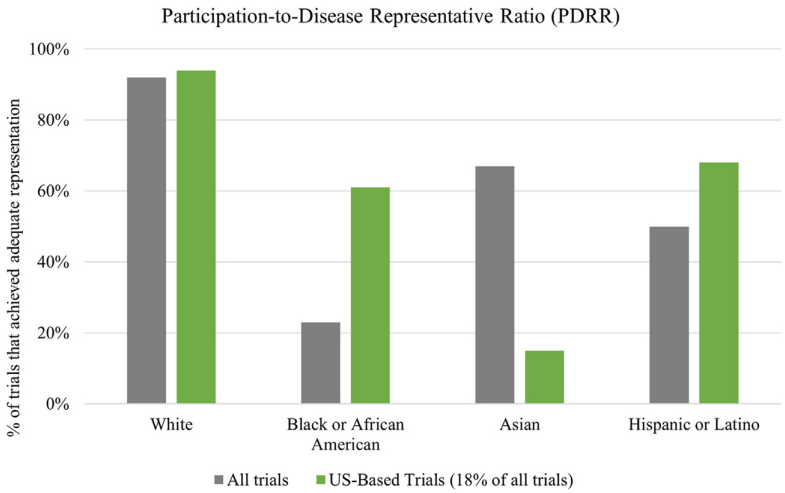
Table 1. Clinical trial representation by race, ethnicity, and sex.

PDRR			PPRR		
	Number of trials with PDRR ≥0.8 (%)	Median PDRR (IQR)		Number of trials with PPRR ≥0.8 (%)	Median PDRR (IQR)
Race (total number of trials)*			Race (total number of trials)†		
White (n = 173)	159 (92)	1.06 (0.92-1.20)	White (n = 173)	158 (91)	1.05 (0.93-1.18)
Black or African American (n = 149)	35 (23)	0.43 (0.24-0.75)	Black or African American (n = 149)	37 (25)	0.43 (0.19-0.75)
American Indian and Alaska Native alone (n = 71)	17 (24)	0.37 (0.09-0.77)	American Indian and Alaska Native alone (n = 105)	22 (21)	0.23 [0.07-0.77]
Asian (n = 117)	78 (67)	1.71 (0.50-3.75)	Asian (n = 138)	74 (54)	1.01 (0.26-2.54)
Native Hawaiian and Other Pacific Islander alone (n = 20)	14 (70)	1.61 (0.77-2.81)	Native Hawaiian and Other Pacific Islander alone (n = 97)	44 (45)	0.50 (0-1.81)
Ethnicity (total number of trials)*			Ethnicity (Total Number of Trials)†		
Hispanic (n = 107)	53 (50)	0.79 (0.30-1.22)	Hispanic (n = 112)	38 (34)	0.61 (0.24-0.93)
Sex (total number of trials)*			Sex (total number of trials)†		
Female (n = 186)	138 (74)	1.02 (0.79-1.14)	Female (n = 186)	141 (76)	1.04 (0.81-1.38)
Age (total number of trials)*			Age (total number of trials)†		
≥65 years (n = 51)	10 (20)	0.30 (0.13-0.64)	≥65 years (n = 58)	28 (48)	0.52 (0.22-1.86)

IQR indicates interquartile range; PDRR, participation-to-disease representative ratio; PPRR, participation-to-population representative ratio.
*Number of trials for each demographic analysis is informed by the number of trials that reported the specific demographic characteristic and where we have a reliable prevalence estimate by demographic for the condition being studied.
†Number of trials for analysis is informed by the trials that reported the specific demographic characteristic.

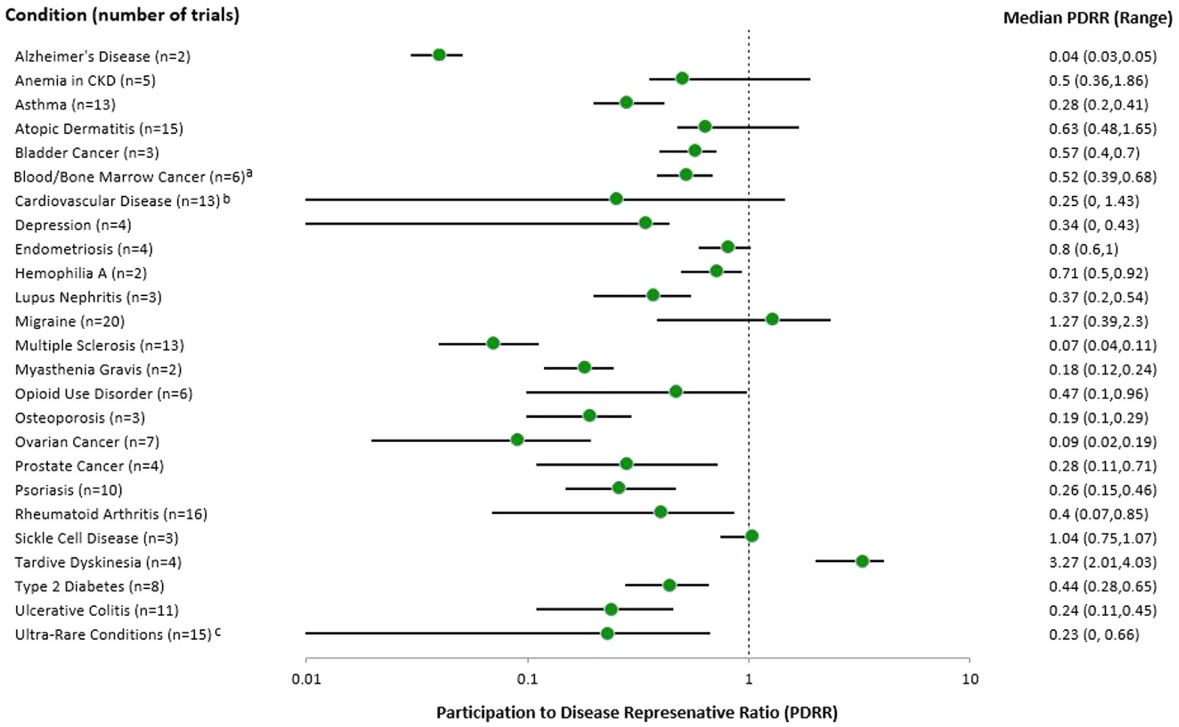
Natives (analytic group: 71 trials) achieved adequate representation in 17 trials (24%), with a median PDRR of 0.37 (IQR 0.09-0.77), Hispanics/Latinos (analytic group: 107 trials) in 53 trials (50%), with a median PDRR of 0.79 (IQR 0.30-1.22), Native Hawaiian/Pacific Islanders (analytic group: 20 trials) in 14 trials (70%), with a median PDRR of 1.61 (IQR 0.77-2.81), and Asians (analytic groups: 117 trials) in 78 trials (67%), with a median PDRR of 1.71 (0.50-3.75). The analytic group for Native Hawaiian/Pacific Islanders was very small (20 trials), considerably less than the 97 trials that reported information on this group. In many cases, this was due to

Figure 2. Percentage of trials that achieved adequate PDRR (all trials vs US-based trials). Bar chart displaying percentage of trials that achieved adequate representation based on PDRR. Gray bars represent all trials and green bars represent US-based trials only that made up 18% of all trials.



PDRR indicates participation-to-disease representative ratio.

Figure 3. Participation-to-disease ratio of Black or African American participants by condition. Forest plot displaying median PDRR of Black or African American participants for trials within each condition that was examined. The green circles represent the median PDRR and the black horizontal bars represent the range for each condition. [a]Includes trials of treatments for leukemia/lymphoma and multiple myeloma. PDRR for each condition was calculated with disease-specific prevalence estimates. [b]Includes trials of treatments for high cholesterol and prevention of major adverse cardiovascular events and treatments for hypertrophic cardiomyopathy. [c]Includes trials of treatment for hATTR amyloidosis, mutation-specific cystic fibrosis, biallelic RPE65-mediated retinal disease, and hereditary angioedema. PDRR for each condition was calculated with disease-specific prevalence estimate.



hATTR indicates hereditary transthyretin-related; PDRR, participation-to-disease representative ratio.

the lack of reliable disease-specific prevalence estimates. The representation assessed by the population estimate (PPRR) likely gave a more reliable evaluation for the Native Hawaiians/Pacific Islanders (analytic group: 97 trials: Median PPRR: 0.50). PPRR findings for the other racial/ethnic groups were similar to the PDRR findings (Table 1).

Of the 35 exclusively US-based trials, data on race/ethnicity were reported for 33. Similar to the primary analysis, the analytic group for each racial and ethnic category differed, ranging from 11 to 33 trials across the categories. Given the limitations of small samples, we conducted the PDRR analyses for racial/ethnic categories with at least 20 trials: White, Black/African American, Asian, and Hispanic/Latino. Figure 2 presents the results comparing the US-based trials with all trials. The proportion of trials with adequate representation for Whites remained similar compared with the primary analysis (92% vs 94%; $P = .68$). A significantly higher proportion of the US-based trials achieved adequate representation for Blacks/African Americans (61% vs 23%, $P < .0001$) and Hispanics/Latinos (68% vs 50%; $P = .047$), but a significantly lower proportion of the US-based trials achieved adequate representation for Asians (15% vs 67%, $P < .0001$).

We presented disease-specific representative ratios across all 31 conditions in Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.05.014. Figure 3 highlights the median PDRR of Black/African American participants across the 31 conditions (excludes trials conducted exclusively outside of the United States). Black/African American participants were underrepresented (PDRR < 0.8) in all conditions examined, except for tardive dyskinesia (PDRR: 3.25 [IQR 2.73-3.69]), migraine (PDRR: 1.27 [IQR 0.86-1.72]), sickle cell disease (PDRR: 1.04 [IQR 0.89-1.05]), and endometriosis (PDRR: 0.83 [IQR 0.75-0.93]).

Sex

Of the 186 trials (representing 26 conditions) evaluated for female representativeness, adequate representation as assessed by PDRR was achieved in 138 trials (74%), with a median PDRR of 1.02 (IQR 0.79-1.14). Adequate representation as assessed by PPRR was achieved in 141 trials (76%), with a median PPRR of 1.04 (IQR 0.81-1.38). Results remained similar when we limited our analysis to US-based studies. Disease-specific information is presented in Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.05.014. Of the 26 conditions examined, female participants achieved adequate representation in 20. Female participants were underrepresented in cardiovascular disease (25% of trial participants, PDRR: 0.49), psoriasis (30% of trial participants, PDRR: 0.59), bladder cancer (18% of trial participants, PDRR: 0.62), opioid use disorder (36.3% of trial participants, PDRR: 0.73), atopic dermatitis (42% of trial participants, PDRR: 0.78), and hypertrophic cardiomyopathy (40.6% of trial participants, PDRR: 0.79).

Age

All trials reported the mean/median age of participants. Of the 184 trials that included those aged ≥65 years, only 55 trials (30%) reported the number of patients aged ≥65 years. We had disease-specific prevalence estimates for only 51 of the 58 trials. Therefore, our evaluation of PDRR was limited to these trials. Patients aged ≥65 years achieved adequate representation in only 10 (20%) out of the 51 trials, with a median PDRR of 0.30 (IQR 0.13-0.64). When evaluated using the population estimate (PPRR), patients aged ≥65 years achieved adequate representation in 28 (48%) out of 58 trials, with a median PPRR of 0.52 (IQR 0.22-1.86). Given the limited number of trials per condition, we did not attempt to estimate disease-specific representative ratios.

Discussion

In this analysis of the pivotal clinical trials used for ICER assessments over 5 years, we found that race and ethnicity data were not consistently reported, and no trial provided information on the SES. In addition, racial and ethnic minority groups and older adults were underrepresented, with median representative ratios well below the defined adequate representation cutoff. Females appeared to be adequately represented when reviewing all trials but were underrepresented in certain conditions.

In recent years, more initiatives by research and regulatory agents have been aimed at increasing clinical trial diversity.[1,2,18] Despite these initiatives and advancements by clinical trial developers, trial diversity, remains less than ideal. Our analyses showed that only about 40% of trials provided information on all racial and ethnic categories, and 9% of studies did not provide any information on race or ethnicity. Recent studies have highlighted the poor reporting of demographic characteristics, with industry-funded studies associated with less race/ethnicity reporting than government-funded trials.[19] Similar to other recent studies, our analysis also showed that racial/ethnic minorities are underrepresented compared with disease-specific and US population estimates.[3,9] Our disease-specific analysis highlighted that racial and ethnic minorities were underrepresented across most conditions examined, with Black/African Americans underrepresented in 27 of the 31 conditions. Because racial categories combine social and biological effects in complex ways, the validity of race in interpreting the generalizability of a study is often understandably questioned. In the absence of a prior hypothesis or evidence to suggest otherwise, the appropriate scientific approach in interpreting evidence from a trial would be to accept that the evidence is generalizable to all racial/ethnic groups. Nevertheless, for certain conditions in our analysis, such as atopic dermatitis, prostate cancer, chronic kidney disease, lupus nephritis, osteoporosis, and asthma, there is prior evidence from other clinical trials and observational studies to suggest drug response may differ based on racial/ethnic factors.[20-25] Unfortunately, racial/ethnic minorities were not adequately represented in these trials to allow for further probing of these prior hypotheses and evaluation of differences in treatment response.

In contrast to race/ethnicity reporting, sex was reported in all but 1 trial. Consistent with the reports that representation of women has improved in clinical research over the past decade,[7] the median representative ratios for women across all trials were >1. Nevertheless, women's representation still varied by disease type. Women were underrepresented in trials of psoriasis, atopic dermatitis, opioid use disorder, cardiovascular disease, bladder cancer, and hypertrophic cardiomyopathy. Our findings on the underrepresentation of women in these conditions are consistent with previous studies that have evaluated diversity specifically in these disease areas.[26-28] Although there are potential explanations for having fewer women in the trials of these conditions, further investigation may be informative, given the strong representation of women in other disease areas.

Finally, analyzing the representativeness of older adults was challenging. Although all trials reported the average age of participants, there was very limited information on those aged ≥65 years. Among the 55 trials that reported this information, older adults were underrepresented compared with the disease-specific and US population estimates. This finding was not surprising because 36% of clinical trials that were reviewed had upper-age limits or exclusion criteria that implicitly exclude older adults. There are many complex and challenging barriers, including ethical considerations, to the inclusion of older adults in clinical trials.[29-31] Although the use of upper-age restrictions has been decreasing over time,[32] the underrepresentation of older adults, a group that carries a greater burden of chronic disease and consumes more prescription drugs than other age groups, can have important consequences, such as creating uncertainties about the efficacy, safety, and generalizability of treatments in this population.

There are important differences between our study and previous studies worth highlighting. First, our evaluation focused on clinical trials that serve as the key source of information for HTA. These trials form the basis for the approval of new drugs and serve as the foundation of ICER's work to translate evidence into decisions about pricing and coverage for new drugs. Second, previous studies have evaluated clinical trial diversity without evaluating the impact of non-US-based trials on the interpretation of the results or focused exclusively on only US-based trials to avoid this problem. In our primary analysis, we chose not to restrict to US-based trials, although multinational trials include patients demographically distinct from the United States. Instead, we conducted an additional analysis with US-based studies. Our rationale for this approach is that these multinational trials inform regulatory, policy, and clinical decisions in the United States. Evaluating the differences between trials that were exclusively US-based versus all trials helped show important trends in the representation of racial/ethnic minorities, such as a higher representation of Blacks/African Americans and Hispanics/Latinos in the US-based trials. Because clinical trial sponsors consider recruiting patients globally, this may have implications for health equity in HTA, in which it is sometimes felt to be appropriate to grant priority to services that would help achieve more equal health outcomes for groups that may have been historically disadvantaged.[33] Given the changing US population and the current trend of global trials, the disparity between the US population and clinical trials may worsen if proactive steps are not taken to mitigate this.[34] Third, many previous studies evaluated adequate representation by comparing the demographic characteristics to the US Census. Although this represents one way of evaluating representation, the comparison to disease-specific prevalence more closely reflects the FDA's stated goal for clinical trials to better reflect the population most likely to use the therapy.

Limitations

There are limitations to our study. Some studies did not follow the FDA-recommended racial/ethnic categories, thus limiting the use of such data in our study. These categories themselves are somewhat arbitrary and combine widely diverse groups (eg, "Asians") in single buckets. Groups and researchers not following FDA guidance, including other US federal agencies, such as Centers for Disease Control and Prevention, need not adopts these same

categories; thus, for some conditions, the prevalence estimates from these sources had racial/ethnic categories that did not match the reported racial/ethnic categories. In part because of this, we could not always identify prevalence data for some racial groups in particular conditions, which caused us to exclude certain studies from the PDRR estimates for these groups. In this case, we focused on PPRR estimates. Thus, although we propose that PDRR provides a more accurate estimation of representativeness in clinical trials, considerations should be given to evaluate clinical trial diversity based on PPRR estimate and to interpret the finding accordingly in cases which epidemiological prevalence data are not yet available. As noted, we had missing information on race/ethnicity and the proportion of older adults for several trials. Missing data are a potential source of bias. Although the direction of the bias is unclear, the higher rate of missing data for the racial and ethnic minority groups (22%-49%) compared with Whites (10%) may be an indication of even worse representation for these groups. Missing data, particularly for racial and ethnic minority groups, may further mask the lack of diversity in clinical trials. Finally, for disease-specific estimates, we had only a few trials for certain conditions; thus, it would be difficult to draw conclusions and generalize from the representative ratios generated for these conditions.

Conclusions

This cross-sectional study of the pivotal clinical trials informing HTA found gaps in the reporting of demographic characteristics of participants but highlights that racial and ethnic minorities and older adults were underrepresented in the majority of the trials examined. These findings suggest that further efforts are needed to enhance the diversity of clinical trials, and solving this problem requires effort by all stakeholders. Although investigators and clinical trial developers are at the front line of recruiting diverse participants, regulators and HTA bodies have a role in enhancing transparency and accountability by developing standardized approaches to evaluating clinical trial diversity. The FDA Drug Trials snapshot is part of the overall effort by the FDA to make information on clinical trial diversity more transparent. As a leading voice for independent HTA in the United States, ICER has proposed evaluating the demographic diversity of clinical trials included in HTA and providing a rating for each trial as a way to elevate the conversation on clinical trial diversity and enhance transparency and accountability.[35] Standardized approaches to evaluating clinical trial diversity, with established thresholds for defining "representativeness," will help strengthen these efforts further and help track improvement over time.

Supplemental Materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2023.05.014.

Article and Author Information

Accepted for Publication: May 15, 2023

Published Online: June 13, 2023

doi: https://doi.org/10.1016/j.jval.2023.05.014

Author Affiliations: Institute for Clinical and Economic Review (ICER), Boston, MA, USA (Agboola, Wright, Herron-Smith, Rind); Geisel School of Medicine at Dartmouth College, Hanover, NH, USA (Mathur).

Correspondence: Foluso Agboola, MBBS, MPH, Institute for Clinical and Economic Review, 14 Beacon Str, Boston MA 02108, USA. Email: fagboola@icer.org

Author Contributions: *Concept and design:* Agboola, Wright, Rind
Acquisition of data: Agboola, Wright, Herron-Smith, Mathur
Analysis and interpretation of data: Agboola, Wright, Rind
Drafting of the article: Agboola, Wright, Herron-Smith, Mathur
Critical revision of the article for important intellectual content: Agboola, Wright, Rind
Statistical analysis: Agboola, Wright
Administrative, technical, or logistic support: Wright, Herron-Smith, Mathur
Supervision: Agboola, Rind

Conflict of Interest Disclosures: Drs Agboola, Wright, and Rind, and Ms Herron-Smith are employed by the Institute for Clinical and Economic Review (ICER), an independent organization that evaluates the evidence on the value of healthcare interventions. ICER reported receiving grants from Arnold Ventures, Blue Cross Blue Shield of MA, California Healthcare Foundation, The Commonwealth Fund, grants and the Peterson Center on Healthcare during the conduct of this study. ICER's annual policy summit is supported by dues from AbbVie, Aetna, America's Health Insurance Plans, Anthem, Alnylam, AstraZeneca, Biogen, Blue Shield of CA, Boehringer-Ingelheim, Cambia Health Services, CVS, Editas, Evolve Pharmacy, Express Scripts, Genentech/Roche, GlaxoSmithKline, Harvard Pilgrim, Health Care Service Corporation, HealthFirst, Health Partners, Humana, Johnson & Johnson (Janssen), Kaiser Permanente, LEO Pharma, Mallinckrodt, Merck, Novartis, National Pharmaceutical Council, Pfizer, Premera, Prime Therapeutics, Regeneron, Sanofi, Spark Therapeutics, uniQure, and United Healthcare. No other disclosures were reported.

Funding/Support: This study was supported by a grant from the Commonwealth Fund.

Role of Funders/Sponsors: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the article; or decision to submit the article for publication.

Acknowledgment: Emily Nhan provided support for data abstraction.

REFERENCES

1. Diversity plans to improve enrollment of participants from underrepresented racial and ethnic populations in clinical trials guidance for industry; availability. US Food and Drug Administration. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/diversity-plans-improve-enrollment-participants-underrepresented-racial-and-ethnic-populations. Accessed September 29, 2022.
2. Enhancing the diversity of clinical trial populations—eligibility criteria, enrollment practices, and trial designs guidance for industry. US Food and Drug Administration. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enhancing-diversity-clinical-trial-populations-eligibility-criteria-enrollment-practices-and-trial. Accessed September 29, 2022.
3. Flores LE, Frontera WR, Andrasik MP, et al. Assessment of the inclusion of racial/ethnic minority, female, and older individuals in vaccine clinical trials. *JAMA Netw Open*. 2021;4(2):e2037640.
4. Loree JM, Anand S, Dasari A, et al. Disparity of race reporting and representation in clinical trials leading to cancer drug approvals from 2008 to 2018. *JAMA Oncol*. 2019;5(10):e191870.
5. Khan MS, Shahid I, Siddiqi TJ, et al. Ten-year trends in enrollment of women and minorities in pivotal trials supporting recent US Food and Drug Administration approval of novel cardiometabolic drugs. *J Am Heart Assoc*. 2020;9(11):e015594.
6. Geller SE, Koch AR, Roesch P, Filut A, Hallgren E, Carnes M. The more things change, the more they stay the same: a study to evaluate compliance with inclusion and assessment of women and minorities in randomized controlled trials. *Acad Med*. 2018;93(4):630–635.
7. Jenei K, Meyers DE, Prasad V. The inclusion of women in global oncology drug trials over the past 20 years. *JAMA Oncol*. 2021;7(10):1569–1570.
8. Geller SE, Koch A, Pellettieri B, Carnes M. Inclusion, analysis, and reporting of sex and race/ethnicity in clinical trials: have we made progress? *J Womens Health (Larchmt)*. 2011;20(3):315–320.
9. Green AK, Trivedi N, Hsu JJ, Yu NL, Bach PB, Chimonas S. Despite the FDA's five-year plan, black patients remain inadequately represented in clinical trials for drugs. *Health Aff (Millwood)*. 2022;41(3):368–374.
10. Chen MS, Lara PN, Dang JTH, Paterniti DA, Kelly K. Twenty years post-NIH Revitalization Act: renewing the case for enhancing minority

participation in cancer clinical trials. *Cancer*. 2014;120(suppl 7): 1091–1096.
11. Corbie-Smith G, St George DM, Moody-Ayers S, Ransohoff DF. Adequacy of reporting race/ethnicity in clinical trials in areas of health disparities. *J Clin Epidemiol*. 2003;56(5):416–420.
12. Flanagin A, Frey T, Christiansen SL, AMA Manual of Style Committee. Updated guidance on the reporting of race and ethnicity in medical and science journals. *JAMA*. 2021;326(7):621–627.
13. Revisions to the standards for the classification of federal data on race and ethnicity. Office of Management and Budget. https://obamawhitehouse.archives.gov/omb/fedreg_1997standards#:~:text=The%20revised%20standards%20will%20have,%22Not%20Hispanic%20or%20Latino.%22. Accessed September 29, 2022.
14. Global health data exchange. Global Burden of Disease Collaborative Network. https://vizhub.healthdata.org/gbd-results/. Accessed March 14, 2022.
15. Data & statistics. Centers for Disease Control and Prevention. https://www.cdc.gov/datastatistics/index.html. Accessed March 14, 2022.
16. Poon R, Khanijow K, Umarjee S, et al. Participation of women and sex analyses in late-phase clinical trials of new molecular entity drugs and biologics approved by the FDA in 2007-2009. *J Womens Health*. 2013;22(7):604–616.
17. Eshera N, Itana H, Zhang L, Soon G, Fadiran EO. Demographics of clinical trials participants in pivotal clinical trials for new molecular entity drugs and biologics approved by FDA from 2010 to 2012. *Am J Ther*. 2015;22(6):435–455.
18. Collection of race and ethnicity data in clinical trials. Guidance for industry and Food and Drug Administration staff. US Department of Health and Human Services. https://www.fda.gov/media/75453/download. Accessed September 30, 2022.
19. Turner BE, Steinberg JR, Weeks BT, Rodriquez F, Cullen MR. Race/ethnicity reporting and representation in US clinical trials: a cohort study. *Lancet Reg Health Am*. 2022;11:100252.
20. Wechsler ME, Castro M, Lehman E, et al. Impact of race on asthma treatment failures in the asthma clinical research network. *Am J Respir Crit Care Med*. 2011;184(11):1247–1253.
21. Isenberg D, Appel GB, Contreras G, et al. Influence of race/ethnicity on response to lupus nephritis treatment: the ALMS study. *Rheumatology*. 2010;49(1):128–140.
22. Noel SE, Santos MP, Wright NC. Racial and ethnic disparities in bone health and outcomes in the United States. *J Bone Miner Res*. 2021;36(10):1881–1905.
23. Bitting RL, Goodman M, George DJ. Racial disparity in response to prostate cancer systemic therapies. *Curr Oncol Rep*. 2020;22(9):96.
24. George DJ, Halabi S, Heath EI, et al. A prospective trial of abiraterone acetate plus prednisone in Black and White men with metastatic castrate-resistant prostate cancer. *Cancer*. 2021;127(16):2954–2965.
25. Daya M, KC B. African American ancestry contribution to asthma and atopic dermatitis. *Ann Allergy Asthma Immunol*. 2019;122(5):456–462.
26. Javier-DesLoges J, Nelson TJ, Murphy JD, et al. An evaluation of trends in the representation of patients by age, sex, and diverse race/ethnic groups in bladder and kidney cancer clinical trials. *Urol Oncol*. 2022;40(5):199.e15–199.e21.
27. Chen V, Akhtar S, Zheng C, Kumaresan V, Nouri K. Assessment of changes in diversity in dermatology clinical trials between 2010-2015 and 2015-2020: a systematic review. *JAMA Dermatol*. 2022;158(3):288–292.
28. Montemitro C, Cavallotto C, Giovannetti G, et al. Analysis of female enrollment in clinical trials for alcohol and substance use disorders: is it time for sex-informed pharmacotherapy? *Contemp Clin Trials*. 2022;118:106784.
29. Sedrak MS, Freedman RA, Cohen HJ, et al. Older adult participation in cancer clinical trials: a systematic review of barriers and interventions. *CA Cancer J Clin*. 2021;71(1):78–92.
30. Townsley CA, Selby R, Siu LL. Systematic review of barriers to the recruitment of older patients with cancer onto clinical trials. *J Clin Oncol*. 2005;23(13):3112–3124.
31. Altawalbeh SM, Alkhateeb FM, Attarabeen OF. Ethical issues in consenting older adults: academic researchers and community perspectives. *J Pharm Health Serv Res*. 2020;11(1):25–32.
32. Ludmir EB, Subbiah IM, Mainwaring W, et al. Decreasing incidence of upper age restriction enrollment criteria among cancer clinical trials. *J Geriatr Oncol*. 2020;11(3):451–454.
33. Gormley N, Fashoyin-Aje L, Locke T, et al. Recommendations on eliminating racial disparities in multiple myeloma therapies: a step toward achieving equity in healthcare. *Blood Cancer Discov*. 2021;2(2):119–124.
34. Nazha B, Mishra M, Pentz R, Owonikoko TK. Enrollment of racial minorities in clinical trials: old problem assumes new urgency in the age of immunotherapy. *Am Soc Clin Oncol Educ Book*. 2019;39:3–10.
35. Agboola F, Whittington MD, Pearson SD. Advancing health technology assessment methods that support health equity. Institute for Clinical and Economic Review. https://icer.org/wp-content/uploads/2022/07/ICER_Advancing-Health-Technology-Assessment-Methods-that-Support-Health-Equity_03152023.pdf. Accessed April 4, 2023.