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Racial, Ethnic, and Gender Diversity in United States Ophthalmology Clinical Trials

Fateme Montazeri, MD, MPH,[1] *Michael Wang, BS,*[2] *Abhijith Atkuru, MS,*[3] *Marcela Maria Estrada, MD,*[1] *Yin Allison Liu, MD, PhD,*[1,4] *Parisa Emami-Naeini, MD, MPH*[1]

Purpose: To investigate the representation of various gender, racial, and ethnic groups in ophthalmology clinical trials conducted in the United States (US) between 1997 and 2022.

Design: Retrospective cross-sectional study.

Participants: We included all participants in completed phase II/III, III, and IV ophthalmology clinical trials reported on the ClincialTrials.gov database.

Methods: The proportional enrollment of each racial/ethnic and gender group in the clinical trials was calculated and compared with the US population. We also investigated the impact of various clinical trial features on the rate of reporting demographic information and enrollment of minorities.

Main Outcome Measures: Proportional enrollment of each gender and race/ethnicity group compared with the US Census.

Results: Of the total clinical trials included in the study, less than half (43.6%) provided information on the racial or ethnic backgrounds of their participants. The majority of the enrollees in trials were female (median: 57.5%, interquartile range [IQR]: 47.2%−65.8%). Among the trials that reported race and/or ethnicity data, White populations were overrepresented (median: 76.6%, IQR: 69.0%−84.0%, $P = 0.001$), and minorities, including Asian, Hispanic, and "other" groups, were underrepresented compared with the 2010 US Census ($P < 0.001$). Enrollment of Black individuals was found to be comparable to the US population estimates (median: 12.4%, IQR: 6.2%−20.8%, $P = 0.44$). The trial phase, the number of study participants, the primary clinical condition, and the year the trial started all affected demographic reporting and minority enrollments.

Conclusions: Our findings highlight the need for increased efforts to promote diversity and inclusivity in ophthalmology clinical trials. Ensuring equitable inclusion of different gender, racial, and ethnic groups in the trials is essential for minimizing disparities and producing unbiased scientific findings generalizable to the entire population.

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Gender, racial, and ethnic disparities continue to remain among the most pervasive health inequities.[1] Different racial and ethnic groups experience varying levels of health outcomes, with some groups disproportionately affected by certain diseases and health conditions.[2] This is caused by a complex interplay of factors such as genetics, environment, lifestyle, and access to health care.[2] Minority groups have less access to high-quality medical and health care services, which is also reflected in clinical trial enrollment.[3] Clinical trials provide a crucial source of evidence-based information for patient care and treatment. Underrepresentation of minority groups in these trials can result in a lack of data on the efficacy and safety of treatments for these populations.[4] This can lead to bias in research and innovation toward therapies that have not been appropriately studied for their impact on minorities, creating data gaps that may further exacerbate existing health disparities.[5]

In recent years, there has been a growing recognition of the importance of diversity in medical research. This has led to efforts to increase the participation of minority groups in clinical trials.[6] In 1993, the National Institutes of Health (NIH) Revitalization Act was passed, which mandated the inclusion of minorities in NIH-funded studies.[7] The 2007 passage of the Food and Drug Administration (FDA) Amendments Act and the confirmation of the Final Rule in 2017 expanded the requirements for reporting race and ethnicity data on clinical trial participants.[6,8,9] While these regulations have helped to increase the representation of minorities, studies have shown that these efforts have not been entirely successful in reaching their intended goals.[10] A study by Kaakour et al recently highlighted the

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disparities in the racial/ethnic composition of participants in diabetic macular edema and retinal vein occlusion trials compared with the demographics of the United States (US) population.[9] A similar representation gap has been recognized in diabetic macular edema trials, even when compared with the group of patients who receive therapies for the condition.[11] Other studies have identified an underrepresentation of minorities in the studies that resulted in FDA approval of ophthalmic therapeutics.[12,13] Moreover, it has been shown that a significant portion of ophthalmology manuscripts published in 2019 did not contain information regarding race and/or ethnicity, and most US clinical trials did not disclose the participants' race and ethnicity.[3,14]

Raising awareness about the importance of diversity in medical research and clinical trials is crucial in addressing health disparities and closing the gaps for minority groups. To provide a comprehensive overview of the status of ophthalmology studies and the trends over time, we analyzed the gender and racial/ethnic composition of US ophthalmology clinical trials. We also analyzed factors associated with a higher reporting rate of race/ethnicity data and the enrollment of minorities.

Methods

This study followed the tenets of the Declaration of Helsinki[15] and received institutional review board/ethics committee approval from the University of California Davis. Given that no human subjects were involved, the requirement for informed consent was waived. We performed a retrospective cross-sectional analysis of completed ophthalmology clinical trials exclusively conducted in the US between 1997 and 2022. We included phase II/III, III, and IV trials with demographic data reported on ClinicalTrials.gov [16] and excluded studies that used nonparticipant units, such as the number of eyes instead of the number of individuals, or focused on specific gender, sex, race, or ethnic groups.

We categorized participants' race and ethnicity as White, Black, Asian, "other," and Hispanic based on the most commonly reported groups in the trial data. American Indian, Alaska Native, Native Hawaiian, and Other Pacific Islanders were combined within the "other" race category due to lower numbers and inconsistent reporting. Participants who identified as "other races," had "unknown races," or identified as "more than one race" were also recategorized into the "other" group. Most studies adhered to the US Census reporting guidelines; however, some integrated both race and ethnic information. For these studies, we used the 2010 Census data to estimate the distribution of races within the Hispanic ethnicity group.[17] We then added these numbers to the total count of participants of each respective race. This approach was taken to address and mitigate potential biases that could arise from the existing discrepancies. Missing data were treated as null. We collected and analyzed enrollment numbers, study phase, funding source, number of study centers (studies with >2 sites were classified as multicenter), trial starting year, and primary condition from ClinicalTrials.gov data. The primary condition was determined independently by 2 experts (F.M. and M.W.) who classified the trials into 8 groups, with any disagreements adjudicated by a third specialist (P.E-N.). These groups included cornea, glaucoma, neuro-ophthalmology, oculoplastic, oncology, pediatrics, retina, and uveitis. Categorization was based on study title, primary condition/disease, inclusion criteria, and age group of participants. Trials studying ocular surface conditions, cataracts, and/or refractive surgery were categorized as cornea. Funding source was classified into the following 3 groups based on the previous studies: industry-funded, NIH/National Eye Institute-funded, and other.[18]

Statistical Analysis

We calculated proportional enrollment of each racial/ethnic and gender group in the included clinical trials and compared them to the 2010 US Census data as the reference population.[6] Descriptive statistics and a one-sample Wilcoxon rank test were used to compare the trials and reference population differences. We constructed a multiple logistic regression model to analyze the role of various clinical trial features in reporting participant race/ethnicity. Additionally, a multivariable linear regression analysis was performed to investigate the association of each clinical trial feature with proportional enrollment of each gender, race, and ethnicity in the trials. Neuro-ophthalmology, oncology, and uveitis studies were excluded from regression analyses due to the small number of trials with demographic reports. Data were analyzed, and graphs were prepared using SPSS (IBM, SPSS 26) and Python (Python Software Foundation). All analyses were 2-sided, with a P value of < 0.05 considered statistically significant.

Results

Characteristics of Studies

Out of 653 completed phase II/III, III, and IV clinical trials registered between 1997 and 2022, 532 trials were exclusively conducted in the US. Of these, 235 trials involving 44 139 participants did not report demographics on ClinicalTrials.gov and were excluded from further analysis. Among these, 127 studies (54%) began before 2008, and 203 studies (86.4%) commenced before 2018. A total of 293 clinical trials, with a collective 69 082 participants, met the inclusion criteria and were included in the study. Less than half of the included trials (128, 43.6%) reported data on the race/ethnicity of the participants in addition to the gender composition of the enrollees (Fig 1). The reporting rate of race/ethnicity data increased by 12.2% per year between 1997 and 2020, excluding years with only 1 trial. After 2007, the average reporting rate was significantly higher (57.9%) compared with years prior (24.3%, $P = 0.02$).

Gender and Race/Ethnicity of Study Participants Compared with the Reference Population

Characteristics of the included clinical trials are summarized in Table 1. The studies reporting race/ethnicity indicated that the majority of the participants were White (74.2%), followed by Black (13.7%), Hispanic (8.3%), Asian (5.4%), and "other" (2.8%). Females accounted for 59.1% (40 851) of all participants. White race was reported in the highest number of trials (125, 42.6%), followed by Black (123, 41.9%), Asian (122, 41.6%), and "other" race groups (121, 41.3%). Hispanic ethnicity had the lowest reporting rate (83, 28.3%).

Our analysis of the trials revealed that White participants made up the majority, with a median enrollment of 76.67% (interquartile range [IQR] 69.0%−84.0%), which was

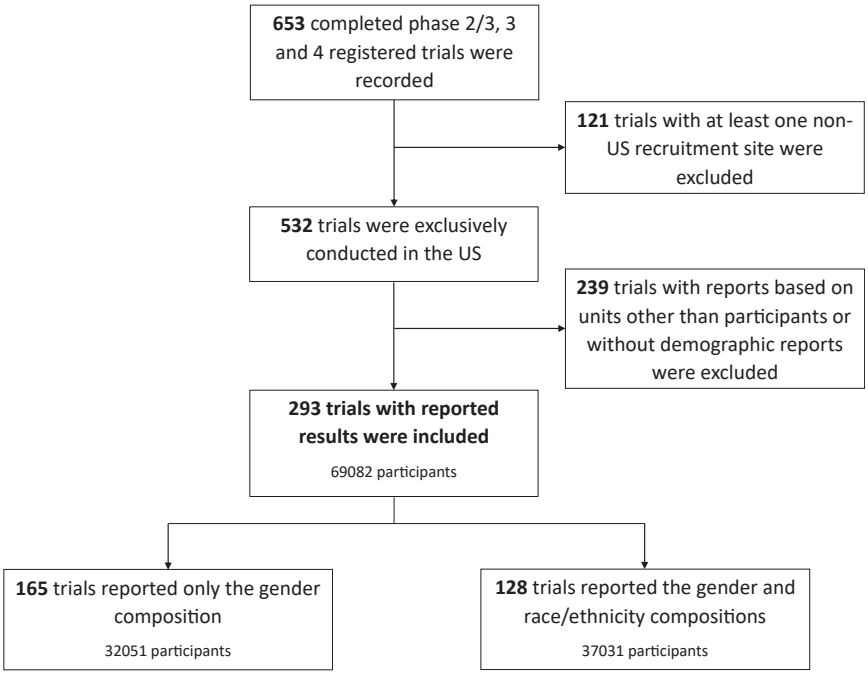

Figure 1. Flow diagram of the ophthalmology clinical trials registered on ClinicalTrials.gov between 1978 and 2022. US = United States.

significantly higher than the Census estimate of 72.4% ($P = 0.001$). Conversely, Asian, Hispanic, and "other" groups were significantly underrepresented in the trials. The "other" group had the largest discrepancy, with a median proportion of 1.7% (IQR: 0.2%−4.3%) compared with the 10.2% reported in the US Census ($P < 0.001$). This was followed by Asians (median: 1.8%, IQR: 0.4%−3.8%, US Census: 4.8%, $P < 0.001$) and Hispanics (median: 12.5%, IQR 6.3%−17.5%, US Census 16.3%, $P = 0.001$). The enrollment rate of Black individuals was not statistically significantly lower than the Census data (median: 12.4%, IQR: 6.2%−20.8%, US Census 12.6%, $P = 0.44$). Additionally, females were disproportionately represented in the trials with a median proportion of 57.5 % (IQR: 47.2%−65.8%), which is higher than the 50.8% recorded in the Census data ($P < 0.001$) (Fig 2).

In most clinical trials, ethnicity and race were reported separately, consistent with the Census data. However, 16 studies with 783 Hispanic participants reported race and ethnicity in a combined category. To evaluate the impact of this reporting discrepancy, we utilized the 2010 US Census data on how the Hispanic population reported their race to estimate the actual number of participants from each race in these studies. Our analysis revealed that this factor did not significantly alter the study results (Table S2-available at https://www.aaojournal.org).

Enrollment Based on the Primary Condition

Among the various categories of trials analyzed, female participants were generally enrolled at a higher rate compared with the US Census (Table S3-available at https://www.aaojournal.org). In retina trials, however, a significantly lower number of female participants were enrolled ($P = 0.04$), while pediatric trials had comparable female inclusion rates to the Census. The majority of cornea and retina trials predominantly enrolled White individuals at proportions exceeding the Census estimates (cornea, median: 81.1%, IQR: 74.4%−87.4%, $P < 0.001$; retina, median: 76.80%, IQR: 70.37%−94.1%, $P = 0.04$). Black and Hispanic enrollments were generally comparable to their representation in the Census across most subcategories of trials, with the exceptions of glaucoma clinical trials, which had a statistically significantly higher proportion of Black enrollments (median: 22.8%, IQR: 18.5%−29.4%, $P < 0.001$), and cornea trials with lower Hispanic enrollments (median: 10.6%, IQR: 6.0%−17.0%, $P = 0.04$). Most subcategories showed underrepresentation of Asians, except for glaucoma and oculoplastic trials, in which their representation did not differ significantly from Census data ($P = 0.2$ and 0.06, respectively). Furthermore, individuals from the "other" group were also underrepresented in most categories, with the exception of the pediatrics and oculoplastic clinical trials ($P = 0.1$ and $P = 0.7$, respectively) (Fig 3).

Factors Associated with Race/Ethnicity Reporting

In the multiple logistic regression models, we found that the phase of trials had a significant impact on the reporting of race/ethnicity, with the highest odds of reporting seen in phase II/III studies (adjusted odd ratio [aOR]: 6.6, 95% confidence interval [CI]: 2.0−21.6, $P = 0.002$), followed by phase III (aOR: 3.8, 95% CI: 1.5−10.0, $P = 0.005$), as compared with phase IV studies. Additionally, glaucoma, pediatrics, and retina trials had significantly higher odds of reporting the racial/ethnic composition of participants than

cornea trials (aOR [95% CI]: glaucoma 5.6 [2.0−15.4], $P = 0.001$; pediatrics 34.7 [6.6−182.4], $P < 0.001$; retina 4.7 [1.8−12.2], $P = 0.001$). Trials with 10 to 49 participants were less likely to report the race/ethnic composition (aOR: 0.2, 95% CI: 0.08−0.8, $P = 0.02$). Moreover, there was a significant increase in the reporting rates over time ($P < 0.001$), with each additional year associated with an average increase of 12.2%. However, other trial characteristics, such as funding source and the number of centers (single vs. multicenter), were not associated with any statistically significant difference in the reporting rates (Table S4-available at https://www.aaojournal.org).

Factors Associated with Diversity among Study Participants

Between 2000 and 2019, there was a significant increase in the proportional enrollment of females in trials, with an average annual increase of 3.2% ($P = 0.02$). Cornea studies were more likely to enroll females than glaucoma, pediatrics, and retina studies ($P < 0.001$). Glaucoma studies had higher enrollment of Black participants (adjusted mean difference [aMD]: 12.4, 95% CI: 6.2−18.5, $P < 0.001$) and lower enrollment of White participants (aMD: −12.6, 95% CI: −20.3 to −4.9, $P = 0.002$) compared with cornea trials. Additionally, studies with 50 to 99 enrollees recruited a higher proportion of Black participants ($P = 0.006$) and a lower proportion of White individuals ($P = 0.04$) compared with trials with 100 to 499 participants. Trials with lower numbers of participants, specifically those with 10 to 49 and 50 to 99 participants, had a higher proportion of Hispanic enrollees compared with trials with higher number of participants ($P = 0.03$, $P = 0.02$, respectively). Furthermore, representation of Hispanics was more prominent among trials in earlier phases (phase II/III aMD: 13.8, 95% CI: 0.7−26.9, $P = 0.04$; phase III aMD: 14.3, 95% CI: 1.5−27.1, $P = 0.03$). However, the enrollment rate of racial/ethnic minority groups was not associated with the number of study centers, funding source, or the year the study began. In other words, more recent studies did not recruit a more diverse group of participants (Table S5-available at https://www.aaojournal.org).

Table 1. Characteristics of 293 Included Clinical Trials and Demographics of Participants

Characteristics		
Participants	*Number of Participants (%*)*	*Number of Trials with Reporting (%)*
Gender		
Female	40 851 (59.1)	293 (100)
Race/ethnicity		
White	27 490 (74.2)	125 (42.6)
Black	5099 (13.7)	123 (41.9)
Asian	2015 (5.4)	122 (41.6)
Hispanic	3093 (8.3)	83 (28.3)
Other	1069 (2.8)	121 (41.3)
Trials	n	%
Actual enrollment number		
0−9	4	1.3
10−49	73	24.9
50−99	53	18.1
100−499	116	39.5
500−999	41	14.0
> 1000	6	2.0
Primary condition		
Cornea	150	51.2
Retina	61	20.8
Glaucoma	46	15.7
Pediatrics	15	5.1
Oculoplastic	9	3.1
Uveitis	6	2.0
Ocular oncology	3	1.0
Neuro-ophthalmology	3	1.0
Phase of the study		
II/III	27	9.2
III	139	47.4
IV	127	43.3
Funding source		
Industry	248	84.6
NIH/NEI	11	3.7
Other	34	11.6
Number of study centers		
Multicenter	102	34.8

NEI = National Eye Institute; NIH = National Institutes of Health.
*"Race/ethnicity" section numbers and percentages of participants are drawn from all trials reporting race/ethnicity.
NEI = National Eye Institute; NIH = National Institutes of Health.

Discussion

Disparities in health care access, utilization, and disease outcomes are exacerbated by the underrepresentation of minority groups in research. Disproportionate enrollment of racial and ethnic groups not only limits the generalizability of the trial findings but also creates mistrust among minorities toward the medical community and the treatments offered.[19] Over the past few years, significant efforts have been made to address this issue and prioritize diverse enrollment in federally-funded clinical trials.[7,8] However, the effectiveness of these initiatives remains unclear. Since 2007, the FDA Amendments Act has required certain clinical trials be registered on ClinicalTrials.gov with a summary of results to be reported within a year of the primary completion date.[20] However, conflicting interpretations of this act made it difficult to determine which trials must be reported and undermined the validity of independent compliance evaluations.[21] After considering feedback from the public and stakeholders,[22] the Department of Health and Human Services released a Final Rule in 2017 that clarified which studies are subject to the FDA Amendments Act, when and how they must be registered, and how results must be reported.[9] Despite this, compliance with reporting has remained poor, which might reflect regulators' lack of enforcement.[23]

In the current study, we analyzed gender, racial, and ethnic diversity of completed phase II/III, III, and IV ophthalmology clinical trials conducted between 1997 and 2022. We found that 44% of the trials did not report their results or lacked gender and race/ethnicity reports and were excluded from the analysis. These studies enrolled roughly 44 000 participants and primarily began before the

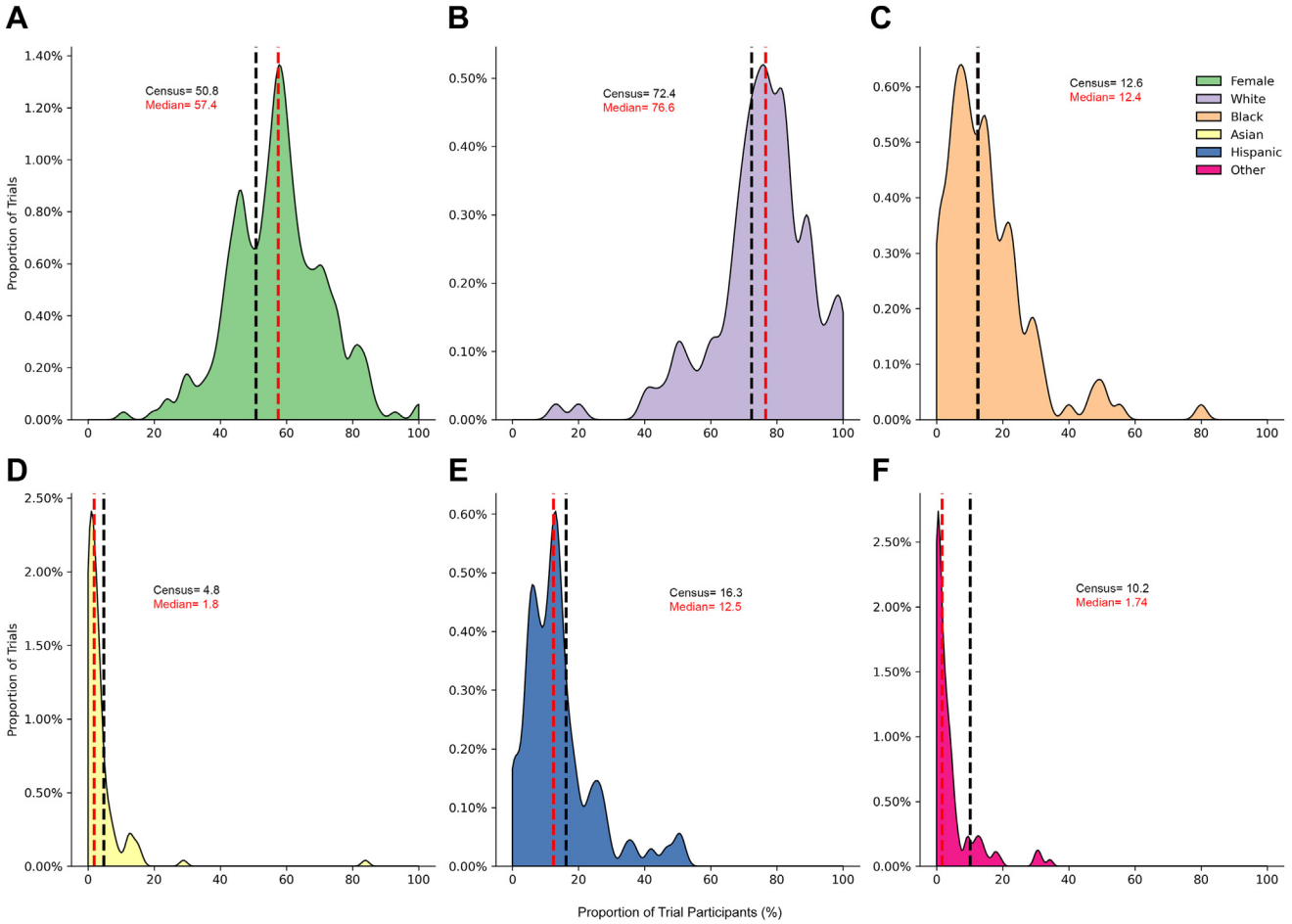

Figure 2. Demographic composition of the ophthalmology clinical trials between 1997 and 2022. Each graph compares the median proportional enrollment of each gender and race/ethnicity group (red dashed line) with the 2010 United States Census data (black dashed line). Graphs show that enrollment of female and White individuals in the trials was higher than Census estimates (**A, B**). Enrollment of Black individuals was comparable to Census estimates (**C**), while Asian, Hispanic, and "other" individuals were underrepresented in ophthalmology trials (**D**–**F**).

aforementioned regulations (54% before 2008 and 86.4% before 2018).[24] Previous researchers have indicated that the underreporting of research is not arbitrary, and it can be linked to the direction and nature of the outcomes.[25] This substantial underreporting in clinical trials may introduce bias and restrict access to crucial data, potentially resulting in poorly-informed medical decisions and the waste of resources. In the studies included, only 43.6% reported information about the racial/ethnic background of their enrollees. Although reporting rates increased over time, more effort is required to achieve meaningful outcomes. Our findings suggest that the phase of study, the primary condition, and the number of participants are associated with the rate of reporting, with higher reporting observed in earlier phases of studies and trials with larger participants. Lower reporting rates were observed in cornea trials and in studies with a smaller number of participants. This is consistent with earlier research on US clinical trials, which have confirmed higher reporting rates in phases I to III clinical trials compared with phase IV trials.[26] The higher reporting rates in the initial phases, compared with phase IV trials, can be attributed to the heightened surveillance and oversight of these foundational stages, essential for the subsequent approval of the treatments and progression to post-marketing and phase IV trials.[27]

Our findings showed that the trials had a higher enrollment of females compared to the Census data, and the numbers have increased over time. This trend can be attributed to the impact of biological sex on the prevalence of certain ophthalmic conditions, such as autoimmune disease, uveitis, and dry eye, or the higher utilization of preventive services and public health care by women.[18,28,29] While previous literature highlighted the critical underrepresentation of women in cancer and cardiovascular disease clinical trials,[30] other studies demonstrate that men are underrepresented in clinical trials on mental health, trauma, and preventative care.[18] Disproportionate enrollment of participants in clinical trials can lead to sex and gender bias, resulting in suboptimal care and adverse outcomes for patients.[29] Identifying and mitigating areas of research and drug development in which sex and/or gender bias exists are crucial in decreasing disparities and improving public health.

Our analysis revealed that the compositions of ophthalmology clinical trials do not adequately reflect the racial and

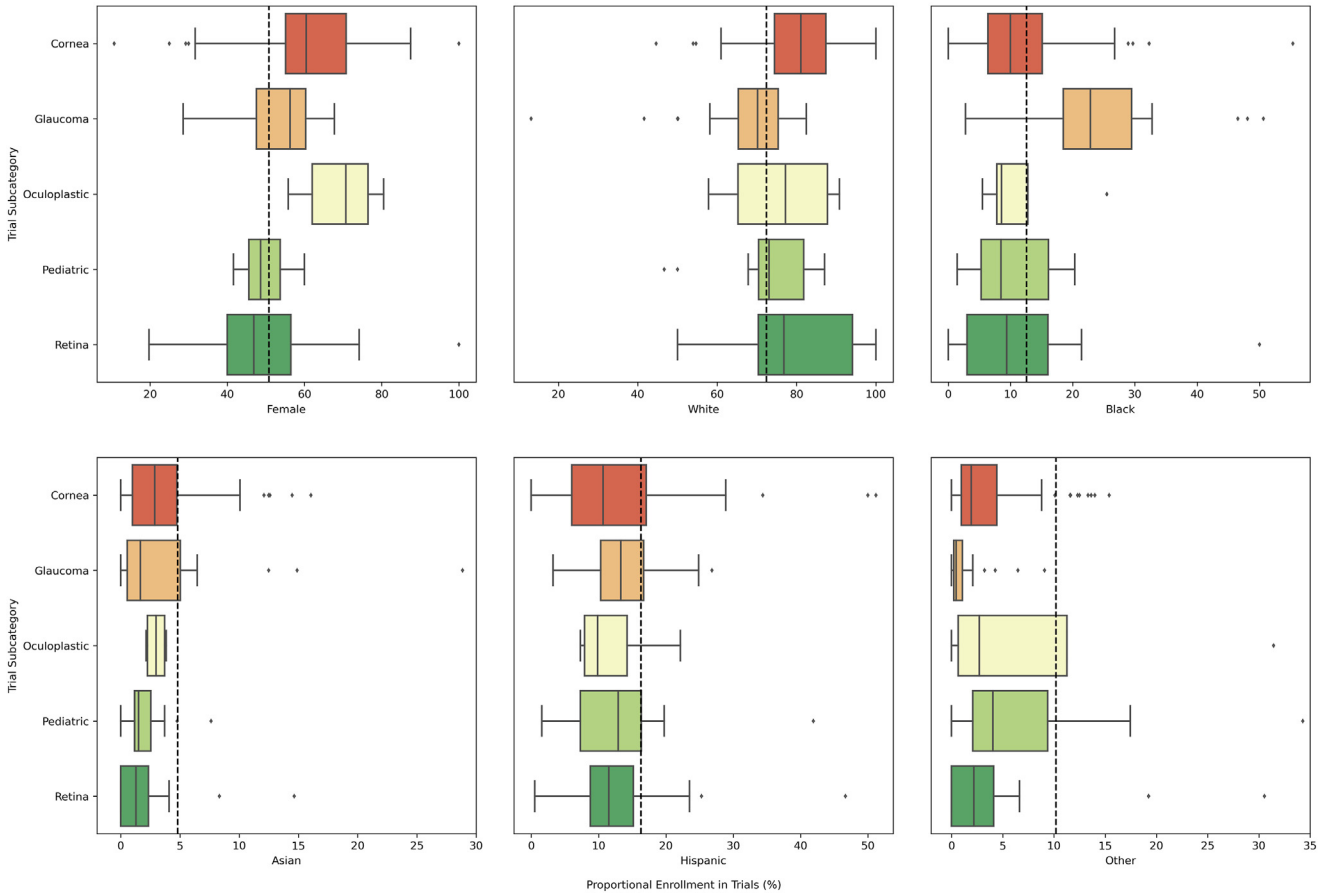

Figure 3. Gender and race/ethnicity representation of trials' subcategories. Each box plot shows the median and interquartile range of enrollment by trial subcategories for each gender and race/ethnicity group's proportion in clinical trials compared with the 2010 United States Census (black dashed line).

ethnic diversity of the US population. Among the clinical trials that provided data on race and ethnicity, Asians, Hispanics, and those categorized as "other" were underrepresented. Furthermore, we found that the trial phase, the number of participants, and the primary condition impacted the enrollment of racial/ethnic minorities. These findings mirror earlier research that specifically looked at retina clinical trials and revealed an overrepresentation of White participants compared with minority groups.[11,31,32] Interestingly, the enrollment of Black individuals was comparable to the US population estimates. This could be due to increased awareness among study teams and the implementation of targeted strategies to improve access to advanced health care services for the Black population.[21] However, further research is necessary to determine and compare the prevalence rates of various eye disorders among Black individuals to their enrollment rates in trials. For example, conditions like glaucoma and diabetic retinopathy are known to be more prevalent among this population.[33–35] This aligns with our data which showed a higher recruitment of Black individuals in glaucoma studies. On the other hand, studies have shown a higher prevalence and severity of dry eye disease among Asian populations,[36] yet they were notably underrepresented in cornea trials. Lower participation of minorities may also reflect structural distrust of these groups toward the health care system, cultural and linguistic barriers, and difficulties accessing health care services.[37] The requirement for study participants to travel to a central location for evaluations, administration of study drugs, and follow-ups can create significant physical and financial challenges. This is particularly true for individuals residing in remote areas or those with limited financial resources, further limiting their participation in trials. Establishing local centers staffed with health care professionals who are actively involved in research and hail from the same communities can bridge the accessibility gap. Additionally, diversifying leadership roles in research both at the grassroots and at higher levels, such as the National Eye Institute and NIH, can strengthen trust with underrepresented communities and foster a more inclusive environment at all tiers.[38]

Racial and ethnic diversity in the US population is on the rise. The diversity index, which measures the likelihood that 2 randomly selected individuals will belong to different racial and ethnic groups, climbed from 54.9% in 2010 to 61.1% in 2020[26]; Asian and Hispanic groups are the 2 fastest-growing populations.[26] In this study, we compared clinical trials data with the 2010 US Census due to the closer temporal proximity of most of the studies to that year. We demonstrated that Asian and Hispanic

populations had significantly lower trial enrollment rates, and their representation did not improve substantially over time. As the population becomes more diverse, underrepresentation of minorities in research will become an increasingly pressing issue, raising concerns about safety, efficacy, and generalizability of medical interventions. A holistic approach is needed to diversify clinical trial participants to reflect the changing racial/ethnic composition of target populations.[39]

This study has several limitations. Due to incomplete registration of studies conducted before 2007, we could not capture all clinical trials prior to this date. Moreover, among the registered trials, we excluded those that did not report demographic information. These limitations may affect the representation of clinical trials and the generalizability of the results to the rest of the database. Additionally, the reporting of race and ethnicity, particularly for Hispanic participants, was not consistent and well-defined across trials, which could lead to inaccurate estimates. Nonetheless, our study findings remained largely unchanged even after accounting for race groups within the Hispanic population. Furthermore, we benchmarked the demographic makeup of trials against the 2010 US Census rather than comparing with data from individuals with related disorders. We opted for this comparison as the prevalence of specific ophthalmic conditions among various subgroups was either not available or not well-defined. Yet, this approach may introduce bias, especially for conditions disproportionately affecting a particular sex or racial/ethnic group.

In conclusion, our study provides a comprehensive overview of demographic disparities in ophthalmology clinical trials spanning the past 2 decades. While some trials were more inclusive, the majority failed to capture the vast diversity of the US population adequately. It is imperative to consider the intrinsic heterogeneity within individual trials, acknowledging that certain conditions might exhibit lower prevalence in minority groups. Nevertheless, there remains a need to prioritize and enhance the equitable inclusion of diverse demographics in clinical trials to reduce disparities and ensure that scientific discoveries and drug development truly represent the broader community.

Footnotes and Disclosures

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[1] Department of Ophthalmology & Vision Science, Tschannen Eye Institute, University of California, Davis, Sacramento, California.

[2] California Northstate University College of Medicine, Elk Grove, California.

[3] Eastern Virginia Medical School, Norfolk, Virginia.

[4] Departments of Neurology and Neurosurgery, University of California, Davis, Sacramento, California.

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No animal subjects were included in this study.

Author Contributions:

Conception and design: Montazeri, Emami-Naeini

Data Collection: Montazeri, Wang, Atkuru, Emami-Naeini

Analysis and interpretation: Montazeri, Wang, Estrada, Liu, Emami-Naeini; Obtained funding: N/A

Overall responsibility: Montazeri, Wang, Atkuru, Estrada, Liu, Emami-Naeini

Abbreviations and Acronyms:
aMD = adjusted mean difference; **aOR** = adjusted odd ratio; **CI** = confidence interval; **FDA** = Food and Drug Administration; **IQR** = interquartile range; **NIH** = National Institutes of Health; **US** = United States.

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Correspondence:
Parisa Emami-Naeini, MD, MPH, Department of Ophthalmology & Vision Science, Tschannen Eye Institute, University of California, Davis Center, 4860 Y St., Sacramento, CA 95817. E-mail: parisaemami@gmail.com.

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