

Sex or Gender Reporting in Ophthalmology Clinical Trials Among US Food and Drug Administration Approvals, 1995 to 2022

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IMPORTANCE As critical determinants of scientific rigor, reproducibility, and equity, sex and gender should be considered in clinical trial design and reporting.

OBJECTIVE To evaluate the accuracy of sex and gender reporting and extent of sex- and gender-based analysis in clinical trials associated with US Food and Drug Administration (FDA) drug approvals between January 1, 1995, and December 31, 2022.

DESIGN, SETTING, AND PARTICIPANTS In this cross-sectional study of participants enrolled in FDA ophthalmology trials, the following trial documents were reviewed by pairs of independent reviewers in decreasing order of priority: peer-reviewed publication, ClinicalTrials.gov report, and FDA medical and statistical reviews. Trial protocols and supplementary materials were also reviewed.

MAIN OUTCOME AND MEASURES The proportion of trials that correctly applied sex and gender terminology, reported the method of assessing sex or gender, and conducted sex- or gender-based data analysis; incorrect application of sex and gender terminology was defined as interchangeable use of sex- and gender-related terms without a clear justification.

RESULTS Between 1995 and 2022, 34 ophthalmic drugs corresponding to 85 trials (34 740 participants) received FDA approval, of which 16 drugs (47.1%) corresponding to 32 trials (18 535 participants [37.6%]) were associated with peer-reviewed publications. Sixteen trials used sex and gender terminology correctly (19.5%). No trial reported how sex and gender were collected nor enrolled participants from sexual and gender identity minority populations. Most trials reported sex- and gender-disaggregated demographic data (96.5%), but few conducted sex- or gender-based analysis for data on dropout (1.2%), primary outcomes (28.2%), secondary outcomes (2.4%), and adverse events (9.4%). Erroneous sex and gender reporting was associated with later publication year (2008.5 vs 2001.0; median difference, 7.5; 95% CI, -6.0 to 11.0; $P < .001$) and higher journal influence metrics, including 2022 journal impact factor (13.7 vs 5.9; median difference, 7.8; 95% CI, -1.4 to 152.4, $P < .001$) and 2022 journal citation indicator (4.9 vs 2.1; median difference, 2.9; 95% CI, 0-20.0, $P < .001$).

CONCLUSIONS AND RELEVANCE In this observational study, over three-quarters of ophthalmology trials associated with FDA drug approvals conflated sex and gender and over two-thirds lacked sex- and gender-based analyses. More rigorous integration of sex and gender appears warranted for FDA, and presumably other trials, to improve their validity, reproducibility, and equity.

JAMA Ophthalmol. 2024;142(2):123-130. doi:10.1001/jamaophthalmol.2023.6088
Published online January 18, 2024.

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Sex and gender are gaining increasing recognition as important determinants of disease epidemiology, health outcomes, and health care disparities.¹ Sex is defined by the National Institutes of Health (NIH) as a biological characteristic, reflected genetically by chromosomes and physiologically by sex hormones, internal reproductive organs, and external genitalia.² In contrast, gender is an aspect of identity that is self-determined and influenced by sociocultural and environmental factors.² Whereas sex is described using terms such as *male*, *female*, and *intersex*, gender is described using socially constructed terms such as *women*, *men*, *transgender*, and *gender diverse*.

Recognizing that sex and gender are critical determinants of scientific rigor, reproducibility, and equity, the NIH Revitalization Act of 1993 was passed to promote the inclusion of women and other minority groups in health research.³ This act was subsequently amended to clearly define clinical research in 2001⁴ and provide tailored recommendations for clinical trials in 2017⁵ and 2020.⁶ Similar initiatives from health, funding, and regulatory agencies worldwide have been implemented to promote the integration of sex and gender in biomedical research.⁷⁻⁹ Current best practices are summarized in the 2016 Sex and Gender Equity in Research (SAGER) guidelines, which recommends accurate use of sex and gender terminology, routine collection of sex and gender disaggregated data, and discussion of implications when sex and gender data are not collected or analyzed.¹⁰ While such efforts have successfully increased female representation in clinical trials,^{11,12} the analysis and reporting of sex and gender remain poor. Reviews of literature across several medical disciplines have demonstrated that sex and gender are frequently conflated and that sex- and gender-based analyses are rarely performed.¹²⁻¹⁹ Poor reporting and analysis of sex and gender have also been demonstrated in randomized clinical trials (RCTs) associated with US Food and Drug Administration (FDA) drug approvals.²⁰

In the field of ophthalmology, sex and gender reporting has not been comprehensively investigated. Reviews of ophthalmology trials associated with FDA drug approvals over the past 2 decades have found that demographic data on sex and gender were reported for all trials and that neither sex or gender modified drug efficacy and safety.^{11,21} However, these studies did not appraise the accuracy of sex and gender reporting, nor evaluate the proportion of trials that performed sex- and gender-based analysis. The present study aims to determine the proportion of ophthalmology trials associated with FDA drug approvals that (1) accurately applied sex and gender terminology in published materials, (2) reported the methods used to assess participant sex and gender, and (3) disaggregated efficacy and safety data by sex and gender.

Methods

The design of this database study was based on international guidelines^{10,22,23} and epidemiologic investigations^{12,14,15,20} on sex and gender reporting in biomedical literature. Institutional review board approval was not required because this work does not qualify as human participant research. This

Key Points

Question How often was sex or gender terminology applied correctly in pivotal ophthalmology clinical trials associated with US Food and Drug Administration (FDA) approvals between 1995 and 2022?

Findings Among the included 85 trials corresponding to 34 ophthalmic drugs, over three-quarters applied sex and gender terminology incorrectly and over two-thirds lacked sex- and gender-based data analysis. No trial reported how sex or gender were collected nor reported if enrolled participants were from sexual orientation or gender identity minority populations.

Meaning More rigorous integration of sex and gender appears warranted for FDA and presumably other ophthalmology trials to improve their validity, reproducibility, and equity.

study was conducted in adherence to the Declaration of Helsinki and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Trial Identification

Ophthalmic drugs that received FDA approval between January 1, 1995, and December 31, 2022, were identified from the Drugs@FDA database.²⁴ The year 1995 was chosen as the cut-off because FDA drug labels were not publicly accessible for most ophthalmic drugs registered prior to 1995. Clinical trials were identified from FDA drug labels. For each trial, we reviewed the following documentation in decreasing order of priority: peer-reviewed publication, ClinicalTrials.gov report, and FDA medical and statistical reviews. If a peer-reviewed publication was available for a clinical trial, then no other data sources were reviewed. For trials that were associated with multiple peer-reviewed publications, the earliest publication that reported primary outcome data was reviewed. If a trial was not associated with a peer-reviewed publication, then both the ClinicalTrials.gov report and FDA medical and statistical reviews were assessed. Study protocols and supplementary materials associated with peer-reviewed publications and ClinicalTrials.gov reports were also examined.

Data Extraction

We extracted data on study characteristics (ie, publication year, country of corresponding author, RCT phase, drug indication, ophthalmic subspecialty, funding source, number of centers, sample size), sex and gender reporting (ie, definition of sex and gender, method of sex and gender data collection, correct or incorrect application of sex and gender terminology), and sex- and gender-based analysis (ie, disaggregation of data, treating sex and gender as covariates, other forms of analysis). For clinical trials that were associated with peer-reviewed publications, we extracted journal publication model and the following journal influence metrics from 2022 Journal Citation Reports (Clarivate), journal impact factor (JIF), 5-year JIF, journal citation indicator (JCI), and total citation count. Data extraction was performed independently by pairs of reviewers (H.K., J.L., D.S.) who underwent calibration training using a random sample of 10 studies. Disagreements were resolved through discussion.

Outcomes

The primary outcome was the proportion of clinical trials that correctly applied sex and gender terminology. Incorrect application was defined as any of the following practices in the absence of clear justification: (1) sex- and gender-related terms were used interchangeably; (2) sex-related terms were used incorrectly to refer to gender; or (3) gender-related terms were used incorrectly to refer to sex. Mention of only 1 sex- or gender-related term without corresponding mention of “sex” or “gender” was considered correct application of terminology. Secondary outcomes included the proportion of trials that described the method of collecting sex and gender data, enrolled participants from sexual and gender identity (SGM) minority groups, and performed sex- and gender-specific analysis.

Statistical Analysis

We summarized categorical variables using frequencies and percentages and continuous variables using medians and IQRs. χ^2 Test and Wilcoxon rank sum test were used to examine whether publication year, including time periods before and after revisions to the NIH Revitalization Act and introduction of the SAGER guidelines (ie, 2001, 2016, and 2017), ophthalmic subspecialty, number of study sites, trial phase, sample size, affiliation with a peer-reviewed publication, journal publication model, and journal influence metrics differed between studies that applied sex and gender terminology incorrectly vs correctly. All *P* values were 2-sided but not adjusted for multiple analyses. Paired median differences with 95% CIs were also calculated for continuous variables using a bootstrap method with 10 000 iterations and a set seed of 123. All analyses were performed using R version 4.2.1 (R Foundation for Statistical Computing).

Results

All Studies

Among 978 FDA new molecular entities approved between 1995 and 2022, 34 drugs corresponding to 85 trials were related to ophthalmic disease (3.5%) (eTable 1 in Supplement 1). All trials were RCTs and 32 trials (37.6%) corresponding to 16 ophthalmology drugs (47.1%) were associated with a peer-reviewed publication (Table 1). Among the remaining 53 trials, 7.1% had a report on ClinicalTrials.gov but no peer-reviewed publication and 55.3% had an FDA medical review and/or FDA statistical review only. Most studies were phase 3 (84.7%), multicenter (84.7%), and industry-funded (92.9%) RCTs that did not report a priori power calculations (49.4%).

Table 2 summarizes the sex and gender reporting of included trials. Only 19.5% of trials applied sex and gender terminology correctly. Fifty-four, 18, and 16 studies were published after 2001, 2016, and 2017, respectively; of these, 13.0%, 11.1%, and 12.5%, respectively, applied sex and gender terminology correctly. Among the 80.5% of trials that conflated sex and gender, 58.5% used sex- and gender-related terms interchangeably, 20.7% used sex-related terms in refer-

Table 1. Characteristics of 85 Studies Corresponding to 34 Food and Drug Administration (FDA) Drug Approvals

Characteristic	No. of studies (%)	
	All studies (n = 85)	Studies with peer-reviewed publications (n = 32)
Data source		
Peer-reviewed publication	32 (37.6)	NA
ClinicalTrials.gov	6 (7.1)	NA
FDA medical review and FDA statistical review	47 (55.3)	NA
No. of studies per drug, median (IQR)	3.0 (1.8-3.0)	2.0 (1.0-2.8)
Condition that the drug treats		
Allergic conjunctivitis	25 (29.4)	4 (12.5)
Bacterial conjunctivitis	1 (1.2)	1 (3.1)
CMV retinitis	7 (8.2)	0
Dry eye disease	4 (4.7)	4 (12.5)
Exudative AMD	12 (14.1)	9 (28.1)
Glaucoma	2 (2.4)	0
Neurotrophic keratitis	3 (3.5)	2 (6.3)
Ocular hypertension/glaucoma	20 (23.5)	3 (9.4)
Postoperative inflammation	4 (4.7)	2 (6.3)
Thyroid eye disease	2 (2.4)	2 (6.3)
Uveal melanoma	1 (1.2)	1 (3.1)
Vitreomacular adhesion and traction	4 (4.7)	4 (12.5)
Ophthalmic subspecialty		
Comprehensive/cataract	2 (2.4)	0
Cornea and external disease	33 (38.8)	11 (34.4)
Glaucoma	20 (23.5)	3 (9.4)
Ocular oncology	1 (1.2)	1 (3.1)
Ophthalmic plastic surgery	4 (4.7)	2 (6.3)
Retina	23 (27.1)	13 (40.6)
No specific subspecialty	2 (2.4)	2 (6.3)
Year of publication		
2017-2022	18 (21.2)	10 (31.3)
2011-2016	15 (17.6)	12 (37.5)
2005-2010	14 (16.5)	8 (25.0)
1999-2004	19 (22.4)	2 (6.3)
≤1998	19 (22.4)	0

(continued)

ence to gender, and 1.2% used gender-related terms in reference to sex. All except 3 studies, which did not use any sex or gender terminology (3.5%), reported sex- and gender-disaggregated demographic data either for the total sample (27.1%) or for each study arm (69.4%). Few studies disaggregated data on dropout rate (1.2%), primary outcome (5.9%), secondary outcomes (0%), and adverse events (5.9%) by sex or gender. Similarly, few studies performed sex- or gender-specific analyses for the primary outcome (23.5%), secondary outcomes (2.4%), and adverse events (3.5%). Notably, no studies defined sex or gender, explained why sex or gender or both were chosen, explained how adequate representation

Table 1. Characteristics of 85 Studies Corresponding to 34 Food and Drug Administration (FDA) Drug Approvals (continued)

Characteristic	No. of studies (%)	
	All studies (n = 85)	Studies with peer-reviewed publications (n = 32)
Country of origin		
US	69 (81.2)	27 (84.4)
Italy	3 (3.5)	2 (6.3)
Belgium	2 (2.4)	1 (3.1)
Canada	2 (2.4)	0
Austria	1 (1.2)	1 (3.1)
France	1 (1.2)	1 (3.1)
India	1 (1.2)	0
Netherlands	1 (1.2)	0
Spain	1 (1.2)	0
No corresponding author	4 (4.7)	0
RCT phase		
1	1 (1.2)	1 (3.1)
2	8 (9.4)	3 (9.4)
3	72 (84.7)	28 (87.5)
Not reported	4 (4.7)	0
No. of study sites		
Single-center	13 (15.3)	3 (9.4)
Multicenter	72 (84.7)	29 (90.6)
Sample size, median (IQR)	330.0 (120.0-596.0)	431.5 (177.3-712.3)
Power calculation		
Sufficient sample size	30 (35.3)	20 (62.5)
Insufficient sample size	13 (15.3)	6 (18.8)
Calculation not conducted	42 (49.4)	6 (18.8)
Journal publication model		
Subscription	NA	6 (18.8)
Open-access	NA	2 (6.3)
Hybrid	NA	24 (75.0)
Journal influence metrics, median (IQR)		
2022 JIF	NA	8.1 (4.2-13.7)
5-y JIF	NA	7.8 (4.6-12.8)
2022 JCI	NA	3.1 (1.6-4.9)
Total citations	NA	47 448.0 (9926.0-59 396.0)

Abbreviations: AMD, age-related macular degeneration; CMV, cytomegalovirus; JCI, journal citation indicator; JIF, journal impact factor; NA, not applicable; RCT, randomized clinical trial.

of different sex and gender groups would be ensured, reported how sex and gender data were collected, nor enrolled participants from SGM populations. A few studies discussed the implications of sex- or gender-based findings with respect to adverse events (2.4%) and external validity (3.5%), but no studies discussed implications for primary and secondary outcomes. Furthermore, no studies explored how sex and gender might interact with other social determinants of health to influence study outcomes.

Studies With Peer-Reviewed Publications

Sixteen drugs (47.1%) corresponding to 32 RCTs (37.6%) were associated with peer-reviewed publications (Table 1). Most studies were published after 2010 (68.8%) in journals with hybrid models (75.0%) and had sufficient sample sizes based on a priori power calculations (62.5%). The median 2022 JIF and JCI of journals were 8.1 (IQR, 4.2-13.7) and 3.1 (IQR, 1.6-4.9), respectively.

Only 30.0% of peer-reviewed publications applied sex and gender terminology correctly, with interchangeable use of sex- and gender-related terms being the most common error (50.0%). Except for 2 studies that did not use any sex- or gender-related terms (6.3%), all publications disaggregated data by total sample (31.3%) or individual study arm (62.5%). No peer-reviewed publications disaggregated data on dropout rate, primary outcome, secondary outcomes, and adverse events by sex or gender. Few publications performed sex- or gender-specific analysis for primary outcomes (6.3%) and secondary outcomes (3.1%). Only 1 article discussed sex- and gender-related implications of trial findings (3.1%) and this was in reference to external validity.

Comparative Analysis

Results of comparative analysis involving medians and proportions are presented in Table 3 and eTable 2 in Supplement 1. Studies with incorrect application of sex and gender terminology were more likely than those with correct application to have a later publication year (2008.5 vs 2001.0; median difference, 7.5; 95% CI, -6.0 to 11.0; $P < .001$), lower number of study sites (21.5 vs 22.0; median difference, -0.5; 95% CI, -16.0 to 22.0; $P < .001$), larger sample size (349.5 vs 298.0; median difference, 51.5; 95% CI, -260.0 to 328.0; $P < .001$), and higher journal influence metrics, including JIF (13.7 vs 5.9; median difference, 7.8; 95% CI, -1.4 to 152.4; $P < .001$), 5-year JIF (12.8 vs 5.4; median difference, 7.4; 95% CI, -0.5 to 109.4; $P < .001$), 2022 JCI (4.9 vs 2.1; median difference, 2.9; 95% CI, 0-20.0; $P < .001$), and total citations (47 448 vs 9926; median difference, 37 522; 95% CI, 16 568-355 117; $P < .001$). Association with a peer-reviewed publication, more than 1 study site, a trial phase of 3, sufficient sample size, and specific ophthalmic subspecialties were not correlated with incorrect sex and gender terminology use. Furthermore, studies published before and after 2001, 2016, and 2017 were similarly likely to use sex and gender terminology incorrectly.

Discussion

This analysis of ophthalmology clinical trials associated with FDA drug approvals between January 1, 1995, and December 31, 2022, showed several important findings. First, sex and gender were conflated in over three-quarters of trials, and erroneous reporting was associated with later publication year, fewer study sites, larger sample size, and greater journal influence metrics. Second, no trial explained why sex or gender were chosen and how sex- and gender-related data were collected. Third, sex- and gender-based analysis was performed in less than one-third of trials. Fourth, no trials enrolled indi-

Table 2. Sex and Gender Reporting in 85 Studies Corresponding to 34 Food and Drug Administration Drug Approvals

Characteristic	No. of studies (%)	
	All studies (n = 85)	Studies with peer-reviewed publications (n = 32)
Terms used		
Sex	53 (62.4)	19 (59.4)
Gender	54 (63.5)	14 (43.8)
Both sex and gender	28 (32.9)	5 (15.6)
Sex-related terms ^a	80 (94.1)	28 (87.5)
Gender-related terms ^b	35 (41.2)	17 (53.1)
Both sex- and gender-related terms	33 (38.8)	15 (46.9)
Sex-nonbinary or gender-expansive terms	0	0
Only sex, gender, 1 sex-related term, or 1 gender-related term was used	1 (1.2) ^c	0
No sex and gender terminology used	3 (3.5)	2 (6.3)
How terms were used		
Correct use of sex and gender terminology ^d	16 (19.5)	9 (30.0)
Incorrect use of sex and gender terminology ^d	66 (80.5)	21 (70.0)
Sex and gender terminology used interchangeably ^d	48 (58.5)	15 (50.0)
Sex-related terms used incorrectly to refer to gender ^d	17 (20.7)	5 (16.7)
Gender-related terms used incorrectly to refer to sex ^d	1 (1.2)	1 (3.3)
Disaggregation of data by sex or gender		
Demographics (total only)	23 (27.1)	10 (31.3)
Demographics (each group)	59 (69.4)	20 (62.5)
Dropout	1 (1.2)	0
Primary outcome	5 (5.9)	0
Secondary outcome	0	0
Adverse events	5 (5.9)	0
Both primary outcome and adverse events	2 (2.4)	0

(continued)

viduals from SGM populations. These gaps reduce confidence in the validity, reproducibility, and equity of seminal trials associated with FDA approval of commonly used ophthalmic drugs.

The findings of this study align with extensive evidence that sex and gender are poorly reported and analyzed in several medical disciplines, including oncology,²⁰ organ transplant,¹⁴ anesthesia,¹⁹ nephrology,¹⁸ infectious disease,¹⁵ neurology,¹⁶ and general medicine.^{12,13,17} These investigations found that 62.6% to 75.8%^{14,20} of studies used sex and gender terminology incorrectly and that 17.8% to 89.2%^{15,20} of studies conducted sex- or gender-specific analysis. These ranges are consistent with our study's findings of 80.5% and 31.8%, respectively. Furthermore, we noted in parallel with literature in other disciplines^{13,20} that not a single ophthalmology trial defined or distinguished between sex and gender, elaborated on why one was chosen over the other, or described how participant sex and gender were assessed. Even RCTs with high-impact journal publications were prone to conflating

Table 2. Sex and Gender Reporting in 85 Studies Corresponding to 34 Food and Drug Administration Drug Approvals (continued)

Characteristic	No. of studies (%)	
	All studies (n = 85)	Studies with peer-reviewed publications (n = 32)
Data not disaggregated but sex- or gender-specific analysis was performed		
Primary outcome	20 (23.5)	2 (6.3)
Secondary outcome	2 (2.4)	1 (3.1)
Adverse events	3 (3.5)	0
Both primary outcome and adverse events	3 (3.5)	0
Discussion of sex and gender		
Defined sex or gender	0	0
Explained why sex or gender was chosen	0	0
Reported how sex or gender data were collected	0	0
Discussed findings of sex- or gender-based disaggregation and/or analysis for primary outcome	0	0
Discussed findings of sex- or gender-based disaggregation and/or analysis for at least one secondary outcome	0	0
Discussed findings of sex- or gender-based disaggregation and/or analysis for adverse events	2 (2.4)	0
Discussed sex- or gender-related implications for external validity	3 (3.5)	1 (3.1)
Discussed how sex and gender may interact with other sociodemographic factors to impact outcomes	0	0

^a Sex-related terms include *male(s)*, *female(s)*, and *intersex*.

^b Gender-related terms include *man*, *woman*, *men*, *women*, *girl(s)*, *boy(s)*, *masculine*, and *feminine*.

^c Only male was used in this study.

^d Denominator used was 82 for all studies and 30 for studies with peer-reviewed publications due to exclusion of 3 studies that did not use any sex- or gender-related terms.

sex and gender. An incidental finding of this study was that no trials included participants from SGM populations. Similar paucities have been demonstrated in ophthalmology research pertaining to health care inequities²⁵ and in other medical disciplines, such as oncology²⁰ and anesthesia.¹⁹

Diverse, representative enrollment in clinical trials is critical for drawing conclusions on therapeutic efficacy and safety that are valid, precise, and generalizable. Comprehensive reporting and analysis of sex and gender are also important for ensuring reproducibility and equity. In ophthalmology, there is a growing body of literature that supports the modifying effects of sex and gender on disease characteristics, health outcomes, and eye care use. Sex variations have been demonstrated in the prevalence and natural history of common ophthalmic disorders, such as cataracts, exudative age-related macular degeneration, dry eye disease, macular holes, optic neuritis, and corneal arcus.²⁶⁻³¹ Male sex may increase the likelihood of requiring certain ophthalmic surgeries^{32,33} and developing postoperative complications.³⁴⁻³⁶ Women may be more likely than men to receive a dilated eye examination,³⁷

Table 3. Comparison of Studies That Correctly and Incorrectly Applied Sex and Gender Terminology

	No. of studies (%)		Difference, median (95% CI)	P value
	Studies that used sex- and gender-related terminology correctly	Studies that used sex- and gender-related terminology incorrectly		
All studies	n = 16	n = 66	NA	NA
Publication year, median (IQR) ^a	2001.0 (1998.3-2011.3)	2008.5 (1999.0-2015.8)	7.5 (-6.0 to 11.0)	<.001
No. full text	9 (56.3)	21 (31.8)	NA	.13
No. of multicenter studies	12 (75.0)	57 (86.4)	NA	.46
No. of centers, median (IQR) ^a	22.0 (1.8-31.8)	21.5 (5.0-44.3)	-0.5 (-16.0 to 22.0)	<.001
No. of phase 3 trials	12 (75.0)	57 (86.4)	NA	.42
No. of studies that met sample size calculation	8 (50.0)	22 (33.3)	NA	.34
Sample size, median (IQR) ^a	298.0 (91.8-567.5)	349.5 (127.0-606.0)	51.5 (-260.0 to 328.0)	<.001
Peer-reviewed publications n = 32	n = 9	n = 21	NA	NA
No. in journals with subscription-based publication models, median (IQR) ^a	0	6 (28.6)	NA	.20
2022 JIF	5.9 (3.2-8.1)	13.7 (4.2-158.5)	7.8 (-1.4 to 152.4)	<.001
5-y JIF	5.4 (3.2-7.8)	12.8 (4.9-115.7)	7.4 (-0.5 to 109.4)	<.001
2022 JCI	2.1 (1.1-3.1)	4.9 (2.1-24.7)	2.9 (0-20.0)	<.001
Total citations	9926 (9926-14 228)	47 448 (30 880-456 891)	37 522 (16 568-355 117)	<.001

Abbreviations: JCI, journal citation indicator; JIF, journal impact factor; NA, not applicable.

^a Studies that did not use any sex- or gender-related terminology were excluded from analyses.

comply or follow up with care,³⁸ and adhere to ophthalmic medication regimens.³⁹ Sex and gender differences compound the effects of race, ethnicity, and other sociodemographic factors on visual health and eye care access.⁴⁰ Failing to consider sex, gender, and their intersectionality with social determinants of health in trial design may mask important clinical differences and overlook opportunities for personalized care.^{12,14} To illustrate, given that women may be more compliant with ophthalmic care than men, gender may confound observed differences in therapeutic effects and complication rates if it is not appropriately considered in study design. Thus, it is imperative that clinical trials, especially those that inform regulatory decisions, include sex and gender as variables of interest and apply concepts related to sex and gender correctly. Improper use of terminology does not change the nature or magnitude of trial findings, but it detracts from one’s ability to interpret and apply this information.

It is unclear why sex and gender remain poorly incorporated in clinical research despite combative efforts at national and international levels. We found that erroneous sex and gender reporting was associated with later publication year, and that sex and gender reporting did not improve after publication of NIH Revitalization Act amendments (2001, 2017) or the SAGER guidelines (2016). One explanation is that efforts to date have been fragmented, unsophisticated, and poorly enforced by authoritative entities.⁴¹ For example, the editorial policies of biomedical journals on sex and gender are incongruous and uncoordinated. A 2022 review of 190 prominent journals across 10 medical specialties found that only 34.2% stated a sex and gender reporting policy, 24.2% distinguished between sex and gender, and 16.3% requested au-

thors to report methods of assessing sex and gender.⁴² Among the 10 specialties analyzed, ophthalmology journals were the least likely to provide a sex and gender reporting policy (25.0%). A separate review noted that only 1 of the top 10 highest impact factor ophthalmology journals provided detailed reporting guidelines for sex and gender in 2022.²² Even fewer journals recommend sex- and gender-based data analysis beyond simple demographic reporting.¹² Lack of editorial enforcement may disincentivize researchers from incorporating sex and gender in trial design and dissemination.⁴² It may also perpetuate cultural and systemic barriers that hinder the inclusion of SGM populations.²⁰

Several strategies may help to improve the reporting and analysis of sex and gender in ophthalmology. In parallel with health, funding, regulatory, and government agencies, scholarly journals should mandate comprehensive and standardized incorporation of sex and gender in all stages of research.^{12,14,15,18,20,41} Author guidelines on this topic have been increasingly adopted by high-impact journals since 2016,⁴³ indicating an ongoing evolution in the accurate integration of sex and gender that may extend to medical subspecialties and FDA-associated research in the future. Trial registries, such as ClinicalTrials.gov, may implement quality control checkpoints to ensure appropriate use of terminology and integration of sex and gender in participant randomization, covariate adjustment, subgroup analysis, and other aspects of trial design.¹⁸ Postgraduate institutions should be consulted to integrate education about best sex and gender research practices into medical and graduate training.¹⁴ Existing resources, such as the SAGER guidelines, may be leveraged to ensure that sex- and gender-related data are routinely collected, rigorously analyzed, correctly re-

ported, and comprehensively discussed. Other widely used guidelines, such as the International Committee of Medical Journal Editors recommendations and Consolidated Standards of Reporting Trials (CONSORT) statement, should be comprehensively updated with sex and gender research principles.^{12,41} In participant-facing stages of research, sex- and gender-sensitive practices should be implemented to create a safe and inclusive environment.⁴¹ For example, preferred names and pronouns should be solicited and data collection forms should include sex- and gender-nonbinary options for self-report.^{18,20} Additionally, sex- and gender-sensitive language (eg, participant instead of man or woman when gender has not been ascertained) should be used in all forms of communication.^{18,20} Research teams should include individuals from sex, gender, racial, and ethnic minority populations to promote the participation, trust, confidence, and care satisfaction of individuals from these populations.^{44,45} Funding bodies may consider creating incentives for enrolling minority populations and achieving well-powered, prespecified subgroup analyses.^{12,18} Educational and health care institutions may also consider increasing SGM representation in leadership positions, such as reviewer panels and steering committees.⁴¹ In cases where expedited access to a potentially vision-saving therapy is required and equitable representation of sex and gender cannot be achieved in a timely manner, the extent of underrepresentation and its implications should be reported.⁴⁶ Data should still be disaggregated by sex and gender so that future meta-analyses can draw tailored, well-powered conclusions about clinically important outcomes.^{12,15} In the meantime, postmarket surveillance strategies may be implemented to assess for sex- and gender-based differences in drug efficacy and safety. These efforts will promote equitable participation of underrepresented populations, ensure methodological rigor and reproducibility, strengthen health interventions and policies, and create a more inclusive ophthalmology community for all.^{12,14,15,18,20,41}

Strengths and Limitations

The strengths of this study include the broad time period assessed and the systematic, multisourced approach used for sex

and gender appraisal. However, several limitations should be considered. First, because we focused on trials identified in FDA drug labels, our findings may not be representative of all ophthalmology trials and do not apply to observational research. Second, since we could not access the source documents with which authors collected sex and gender data, we could not confirm whether authors accurately assigned sex and gender. Third, for studies that used sex and gender terminology correctly, we could not ascertain whether this practice was intended by the authors or corrected during the publication process. Fourth, a lack of sex- and gender-based analysis does not necessarily indicate that sex and gender were insufficiently considered. Trials may not have pursued sex- and gender-based analyses due to limitations in power; nevertheless, disaggregated data should have been reported to facilitate prospective meta-analyses. Fifth, the resampling technique inherent to our bootstrapping method resulted in wide 95% CIs for calculated median differences. These estimates should be interpreted alongside *P* values that were calculated without resampling methods.

Conclusions

This cross-sectional analysis of clinical trials associated with FDA approval of ophthalmic drugs demonstrated marked conflation of sex and gender terminology, underreporting of sex and gender assessment methods, and inattention to sex- and gender-based analysis. Increased consideration of sex and gender in trial design, enrollment, and dissemination is needed to draw stronger conclusions about therapeutic efficacy and safety. Particular attention should be given to increasing the inclusion of SGM groups, who remain poorly represented in ophthalmology research. Best practices for sex and gender analysis and reporting should be enforced by scholarly journals in collaboration with educational institutions, funding bodies, and regulatory agencies. International, coordinated efforts will help to promote equitable, rigorous research and a more inclusive ophthalmology community.

ARTICLE INFORMATION

Accepted for Publication: November 11, 2023.

Published Online: January 18, 2024.
doi:10.1001/jamaophthalmol.2023.6088

Author Contributions: Dr Margolin had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Mr Xie and Ms Kaur contributed equally to this work.
Concept and design: Xie, Kaur, Tao, Lee, Margolin.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Xie, Kaur, Tao, Solish, Margolin.
Critical review of the manuscript for important intellectual content: Xie, Kaur, Tao, Lee, Kohly, Margolin.
Statistical analysis: Xie, Solish.

Administrative, technical, or material support: Xie, Kaur, Tao, Solish.

Supervision: Xie, Kaur, Tao, Kohly, Margolin.

Conflict of Interest Disclosures: None reported.

Data Sharing Statement: See Supplement 2.

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