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Article

An Evaluation of Sex- and Gender-Based Analyses in Oncology Clinical Trials

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Abstract

Background: The objective of this study was to evaluate whether sex- and gender-based analyses and proper sex and gender terminology were used in oncology trials leading to regulatory drug approval. **Methods:** The Food and Drug Administration (FDA) Hematology/Oncology Approvals and Safety Notifications page was used to identify all anticancer therapies that received FDA approval between 2012 and 2019. The trials used to support FDA drug approval were collected along with all available supplemental tables and study protocols. Documents were reviewed to determine if there was a plan to analyze results according to sex and gender and to determine if consistent sex and gender terminology were used. **Results:** We identified 128 randomized, controlled trials corresponding to a cancer medicine, which received FDA approval. No study specified how sex and gender were collected or analyzed. No study reported any information on the gender of participants. Sex and gender terminology were used inconsistently at least once in 76% (97 of 128) of studies. Among the 102 trials for nonsex-specific cancer sites, 89% (91 of 102) presented disaggregated survival outcome data by sex. No study presented disaggregated toxicity data by sex or gender. **Conclusion:** The majority of pivotal clinical trials in oncology fail to account for the important distinction between sex and gender and conflate sex and gender terminology. More rigor in designing clinical trials to include sex- and gender-based analyses and more care in using sex and gender terms in the cancer literature are needed. These efforts are essential to improve the reproducibility, generalizability, and inclusiveness of cancer research.

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Sex and gender are important determinants of cancer care and outcomes. Sex and gender affect access to cancer screening; diagnostic workup; and how patients select, metabolize, adhere to, and report side effects of treatment (1-4). As a result, the conduct of sex- and gender-based analyses are essential to the methodological rigor, reproducibility, and inclusiveness of oncology research (5).

Sex and gender are interrelated but have distinct concepts. *Sex* refers to a set of biological attributes associated with chromosomes, gene expression, hormone levels, and reproductive anatomy (6). *Gender* refers to the socially constructed roles and behaviors that influence self-identity and self-expression and is affected by social, environmental, cultural, and behavioral factors (6). Gender exists along a continuum with diversity in how it is experienced and expressed over time (7). The terms *male*, *female*, and *intersex* are used to describe the sex of human patients. These are defined by sex-related biological factors; possessing a 46XY karyotype and male reproductive organs defines a biological male, and a 46XX karyotype with female reproductive organs defines a biological female. *Intersex* refers to those with patterns of chromosomes or reproductive organs that do not fit with binary notions of male or female bodies (6-9). The terms *masculine* or *feminine*, *man* or *woman*, and *boy* or *girl* are some, but not all, of the terms that should be used to describe the gender of patients. There are no standardized definitions for gender, and there are many ways to ask about and characterize it. Masculine and feminine traits are informed by cultural and societal norms. Gender identity is dictated by the internal sense of gender. Thus, *man* refers to individuals who self-identify as men, and *woman* refers to individuals who self-identify as women. *Genderqueer* or *nonbinary* are terms that can be used for those who do not fit into binary classifications of a man or woman (6-11).

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Proper collection, reporting, and disaggregation of sex and gender data are particularly important for oncology clinical trials. Clinical trials can only be used to meaningfully inform clinical practice if they enroll a representative population of patients. If sex and gender are not included as important variables of interest, our understanding of how to interpret the results of those trials will be commensurately limited. Moreover, when reporting the results of trials, conflating sex and gender terms lead to confusion and imprecision and detract from the inclusiveness of oncology research.

Prior studies have shown that sex and gender are inconsistently considered and reported in clinical practice guidelines (12). The purpose of this study was to evaluate the use of sex and gender analyses and terminology in the major oncology clinical trials, which led to drug registration with the Food and Drug Administration (FDA).

Methods

Objectives

The main objectives of this study were to 1) describe the proportion of oncology clinical trials leading to FDA drug registration, which reported disaggregated data by sex and gender; 2) describe the proportion of clinical trials that reported how sex and gender were collected and analyzed; and 3) describe the proportion of trials where gender and sex terminology were conflated in the study materials.

Selection of Randomized Controlled Trials

The US FDA Hematology/Oncology Approvals and Safety Notifications website (13) was used to identify all anticancer therapies receiving FDA approval between 2012 and 2019, as described previously (14). The corresponding clinical trial manuscript, supplemental data, and study protocols were retrieved from PubMed. The present study relied exclusively on published literature; therefore, consistent with the guidelines of Sunnybrook Research Institute, the study was exempt from the need for formal ethics review.

Data Extraction and Analysis

The manuscript, supplemental data, and study protocols for each study were reviewed independently by 2 authors. Data points were extracted in duplicate into a prepiloted electronic database. All available published materials were searched for descriptions of how sex and gender data were collected and assessed.

All available published materials were searched for use of the following words: *sex*, *gender*, *male*, *female*, *man*, *men*, *masculine*, *feminine*, *woman*, and *women*. The Sex and Gender Women's Health Collaborative proposed standardized definitions were used to determine if sex and gender terms were correctly used (8). These criteria were chosen for ease of application to biomedical research studies. Two reviewers (MH and VAK) independently reviewed published materials for inconsistencies and errors in terminology. A trial was scored as having an inconsistency or error if any of its associated published materials demonstrated 1 or more of the following: 1) in the demographic information (ie, see Table 1) referring to sex but using gender terms *men* and *women* or referring to gender but using sex terms *male* and *female*; 2) referring to sex terms (*male* or *female*) in tables and figures, but using gender terms (*men* or *women*) in the published text or referring to gender terms in tables and figures and sex terms in the published text; and 3) alternating between sex and gender terms in the tables and figures, published text, protocols, or supplemental materials, without a clear distinction of why one set of terms is used over the other. Differences of opinion between reviewers were resolved by consensus with a third author (MJR).

Table 1. Characteristics of the trials (n = 128) published from 2012 to 2019 leading to Food and Drug Administration regulatory drug approval[a]

Characteristic	No. of trials
Study design	
Randomized controlled trial	113
Nonrandomized study	15
Cancer therapy	
Small molecule	35
Therapeutic proteins[b]	42
Chemotherapy	8
Combination	33
Hormonal	3
Other[c]	7
Disease site	
Hematologic	37
Lung	18
Breast	14
Gastrointestinal	14
Skin	13
Genitourinary	9
Prostate	5
Ovarian	5
Other[d]	13

[a]Trials had sample sizes ranging from 53 to 2840 patients, and the year of patient enrollment ranged from 2001 to 2019.
[b]Includes monoclonal antibodies and checkpoint inhibitors.
[c]Includes lenalidomide (n = 4 trials), oncolytic virus talimogene laherparepvec (n = 1 trial), lanreotide (n = 1 trial), radium-223 (n = 1 trial).
[d]Includes cervical (n = 1 trial), endometrial (n = 1 trial), head and neck (n = 2 trials), neuroendocrine tumors (n = 2 trials), neuroblastoma (n = 1 trial), NTRK solid tumors (n = 1 trial), sarcoma (n = 3 trials), thyroid (n = 2 trials).

Results

The search strategy identified 128 studies corresponding to 127 drug indications approved by the FDA between 2012 and 2019 (Table 1). Of these studies, 88% (113 of 128) were randomized controlled trials. Full trial protocols were retrieved for 63% (81 of 128). Supplemental content was retrieved for 34% (43 of 128). Of the trials, 20% (26 of 128) evaluated sex-specific cancers—cancers that arise from tissues specific to males or females; these include prostate, breast, endometrial, ovarian, and cervical cancer. Of the identified studies, 97% (124 of 128) were industry sponsored, and 70% (89 of 128) used medical writers.

No study described how sex and gender information was collected or assessed. No study described any distinction between sex and gender terminology or provided any rationale for their use of terminology. No study reported any information on the gender of participants.

Among all 128 articles, at least 1 inconsistency in the use of sex and gender terms was identified in 76% (97 of 128) of studies (Table 2). Among the 81 trials for which full protocols were available, 90% (73 of 81) contained at least 1 inconsistency.

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Table 2. Quantification of inconsistencies in the use of sex and gender terms

Trial type	Total trials, No.	Inconsistent use of sex and/or gender terms, No. of trials (%)
All trials	128	97 (76)
Trials with full protocol available	81	73 (90)
Sex-specific cancers[a]	26	15 (58)
Nonsex-specific cancers[b]	102	82 (80)

[a]Sex-specific cancers include breast, prostate, endometrial, ovarian, and cervical.

[b]Nonsex-specific cancers include hematologic, lung, gastrointestinal, skin, genitourinary, head and neck, neuroendocrine tumors, neuroblastoma, NTRK solid tumors, sarcoma, and thyroid.

Among the 102 trials for nonsex-specific cancer sites, 80% (82 of 102) had at least 1 inconsistency. Among the 26 sex-specific cancer trials, 58% (15 of 26) demonstrated at least 1 inconsistency. Four trials were supported by the National Institutes of Health (NIH; published 2010, 2012, 2014, 2017). Of these 4 trials, 2 demonstrated an inconsistency in sex and gender terminology.

Among the 102 trials for nonsex-specific cancer sites, 89% (91 of 102) presented disaggregated data by sex or gender (Table 1), and 65% (66 of 102) presented disaggregated data by sex or gender in the subgroup analysis of primary and secondary outcomes. None of the trials presented disaggregated adverse events by sex or gender.

Discussion

In this study evaluating sex and gender analyses in the major oncology trials leading to regulatory drug approval in oncology, several important findings have emerged. First, no trials made it clear in the article text, supplemental information, or trial protocols how sex and gender data were collected and assigned. Second, no trials distinguished between sex and gender terms or explained why one set of terms would be chosen over the other. Third, sex and gender terms were frequently conflated and incorrectly used. Collectively, this study demonstrates that the oncology research community needs to take more care in the collection and reporting of sex and gender terminology to promote better and more inclusive science.

The results of this study extend previous work describing the important need to improve the inclusiveness of the oncology research community to patients from sexual orientation and gender identity minority (SGM) populations. Patients from SGM populations have unique risk factors for cancer (15) and experience disparities in access to cancer screening (16,17), treatment (18), and outcomes (19,20). A recent qualitative study of 273 SGM patients from across the United States identified that many patients were negatively affected by their providers' lesbian, gay, bisexual, transgender, and queer knowledge, skills, and assumptions (21). Patients endorsed fear of disclosing their gender identities to their oncologists because of a perceived lack of safety. Based on the findings of their study, the authors' recommendations for improvements included providing safe environments for disclosure of gender identity by using inclusive language; asking about lesbian, gay, bisexual, transgender, and queer identities; responding to disclosure respectively; and asking about and using patients' correct names and pronouns. Organizations including the NIH and the American Society of Clinical Oncology have called for research to better understand the health disparities affecting SGM populations (22,23). However, a lack of collection and reporting of sexual orientation and gender identity data has been identified as a major barrier to this goal (24,25). Our study provides further evidence to support the paucity of data collection and reporting particularly as it is applies to gender. In addition to supporting the generation of evidence to better care for SGM populations, incorporating routine collection and reporting of gender data is a small step forward to improve the inclusiveness of clinical trials to make all patients feel welcome.

Recently, the American Society of Preventative Oncology released a report on potential barriers to collection and reporting of sexual orientation and gender identity (SOGI) data in cancer care. They included perceptions that patients will be uncomfortable answering SOGI questions because of fears of stigmatization, clinician discomfort with SOGI, and a general lack of knowledge about which questions to ask (26). There is evidence that a disconnect exists between health-care workers and patients regarding willingness to share SOGI. A study in emergency departments in the United States found that 78% of clinicians thought patients would refuse to disclose SOGI information; however, only 10% of patients indicated they would refuse to disclose (27). As discussed above, a qualitative study on the experiences of SGM patients with cancer found they are often afraid to disclose SOGI information because of a perceived lack of safety. Patients also described uneasy interactions with oncologists when assumptions were made about support networks and partners. These negative experiences lead to worse perceptions of clinical care and motivate patients to find other providers. Patients explained how important inclusive language (ie, using *partner* instead of *husband* or *wife*) and avoiding assumptions (ie, by asking about preferred pronouns) is to improve therapeutic relationships (21). More studies are needed to assess patient preferences regarding the collection of SOGI in clinical trials. These initial studies indicate that patients are more willing to disclose SOGI if they are asked in culturally sensitive ways and that the asking and sharing of this information can strengthen therapeutic relationships.

Differentiating between sex and gender is also critical as sex differences have been shown to influence cancer biology and response to therapy. For instance, modern sequencing technology has helped identify sex differences in the pattern of cancer-driver gene activation (28). Furthermore, it has been reported that 53% of therapeutic targets and biomarkers in diverse cancers has a sex-related molecular pattern (2). Sex differences in body composition also influence the pharmacology of cancer drugs. For example, it is estimated that females have approximately 26% increased exposure to 5-fluorouracil (ie, less drug clearance compared with males) (3). Another recent analysis found that the magnitude of benefit of immune checkpoint inhibitors is potentially sex dependent (29). Additionally, sex differences in lab test reference ranges may influence clinical trial eligibility (30).

Although less studied, there is evidence that gender may impact clinical trial outcomes. Studies have shown that women tend to have greater health-care-seeking behavior than men measured by willingness to visit family physicians for physical and mental health concerns (31). This has implications for the differential identification of adverse events among men and women enrolled in a trial. Additionally, women and men in same-sex relationships are less likely to have health insurance coverage compared with their counterparts in different-sex

Table 3. Quantification of inconsistencies in the use of sex and gender terms with trials disaggregated by drug class

Drug class	Total trials, No.	Disaggregation by sex or gender in Table 1, No. (%)	Disaggregation by sex or gender in subgroup analysis, No. (%)	Inconsistent use of sex and/or gender terms, No. (%)
Small molecule	35	29 (83)	18 (51)	29 (83)
Monoclonal antibodies	20	14 (70)	8 (40)	12 (60)
Checkpoint inhibitors	22	21 (95)	13 (59)	20 (91)
Chemotherapy	8	6 (75)	6 (75)	7 (88)
Combination	33	23 (70)	19 (58)	24 (73)
Hormonal	3	0 (0)	0 (0)	1 (33)
Other[a]	7	6 (86)	4 (57)	4 (57)

[a]Includes lenalidomide, oncolytic virus (talimogene laherparepvec), lanreotide, radium-223.

Table 4. Quantification of inconsistencies in the use of sex and gender terms with trials disaggregated by disease site

Disease site	Total trials, No.	Disaggregation by sex or gender in Table 1, No. (%)	Disaggregation by sex or gender in subgroup analysis, No. (%)	Inconsistent use of sex and/or gender terms, No. (%)
Hematologic	37	29 (78)	21 (57)	27 (73)
Lung	18	18 (100)	12 (67)	15 (83)
Breast	14	8 (57)	2 (14)	8 (57)
Gastrointestinal	14	13 (93)	13 (93)	14 (100)
Skin	13	13 (100)	8 (62)	12 (92)
Genitourinary	9	8 (89)	6 (67)	7 (78)
Prostate	5	0 (0)	0 (0)	1 (20)
Ovarian	5	1 (20)	0 (0)	5 (100)
Other	13	9 (69)	6 (46)	8 (62)

Table 5. Quantification of inconsistencies in the use of sex and gender terms with trials disaggregated by year of publication

Year of publication	Total trials, No.	Disaggregation by sex or gender in Table 1, No. (%)	Disaggregation by sex or gender in subgroup analysis, No. (%)	Inconsistent use of sex and/or gender terms, No. (%)
2012	10	7 (70)	4 (40)	7 (70)
2013	8	7 (88)	6 (75)	6 (75)
2014	15	11 (73)	8 (53)	11 (73)
2015	22	18 (82)	12 (55)	18 (82)
2016	26	23 (88)	15 (58)	21 (81)
2017	11	8 (73)	4 (36)	9 (82)
2018	8	7 (88)	5 (63)	7 (88)
2019	24	15 (63)	12 (50)	16 (67)
2020	3	3 (100)	2 (67)	2 (67)

relationships (32). This has implications for the affordability of novel therapies and supportive care medications and the ability to travel to enroll in clinical trials. Recent studies have also shown that transgendered individuals have higher rates of venous thromboembolism and ischemic stroke potentially related to hormone therapies (33). Additionally, feminine gender traits were associated with poorer outcomes after acute coronary syndrome, independent of female sex (34).

Thus, gender and sex are important to capture when trying to determine the safety of a novel therapy. Precise use and reporting of sex and gender terminology is thus an issue of not only inclusivity but also scientific rigor. Clinical trials that do not analyze and report data by sex and gender risk drawing incorrect conclusions by failing to account for the differences outlined above and others that may not yet be known. For this reason, increased reporting and analyzing of data using sex and gender will benefit not just SGM populations but all individuals across the sex and gender continuum affected by cancer.

Ensuring inclusion of sex- and gender-based analyses is an important responsibility of funding agencies (5,35). The 1993 NIH revitalization act requires NIH-funded clinical trials to include women and other minorities (36). In 2016, the sex as a biological variable policy further emphasized an "expectation that scientists will account for the possible role of sex as a biological variable in vertebrate animal and human studies" (37). The 21st Century Cures Act explicitly supports increased participation of and reporting on SGM populations in research (38). In December 2010, the Canadian Institutes for Health Research signaled its recognition of the importance of sex and gender on health outcomes and started requiring all grant applicants to respond to 2

questions: Are sex (biological) considerations taken into account in this study? Are gender (sociocultural) considerations taken into account in this study? Responses to these questions are mandatory and meant to stimulate incorporation of these differences in experimental design.

Similarly, the proper usage and reporting of sex and gender terminology is an important responsibility of journal reviewers and editors (5,9,39). Multiple publications have authored editorial policies requiring the correct use of sex and gender terminology (7,9,40). We believe the ideal practice at this time is outlined in the Sex and Gender Equity in Research guidelines. Some key principles of these guidelines are using sex and gender terms carefully to avoid confusing them and differentiating study subjects by sex and gender where it is possible and relevant. If a sex and gender analysis is not performed, the guidelines call for an explanation of why (7). Clayton and Tannenbaum (9) outline useful recommendations for how to present sex and gender data in research. They model a sample demographic table that separates participants by sex using the terms *male* and *female* and by gender using the terms *men* and *women*. They also advocate that all tables and figures in results sections identify the magnitude of effect according to sex, gender, or both.

The findings of the present study must be interpreted within the context of the limitations. First, because we do not have access to the raw source documents and screening checklists, it is possible, although unlikely, that studies collected information on gender but did not report it. Second, for studies without unedited protocols, we are unable to tell if the incorrect and conflated usage of sex and gender terminology was present within the submitted manuscript and was corrected during the editorial process. Similarly, we cannot determine if editors changed correct sex and gender terminology during the production process. Additionally, even if studies did not use any incorrect applications of sex and gender terminology, it does not mean that sex and gender were in fact appropriately considered in the trial design and reporting. Finally, we used the Sex and Gender Women's Health Collaborative proposed standardized definitions for sex and gender terms because of ease of application to biomedical research studies. There are many different approaches to characterizing and classifying sex and gender that might be appropriate to use in this type of analysis (11). However, it is possible that applying a different set of definitions would yield slightly different results.

In summary, this review of all major oncology clinical trials leading to regulatory drug approval by the FDA identified a complete absence of collection and reporting of gender information and frequent conflation in sex and gender terminology. To promote better scientific research and to make all patients, clinicians, and researchers feel welcome within the oncology community, a rededicated effort to improve the incorporation of sex- and gender-based analyses and proper reporting of sex and gender terminology is needed.

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Data Availability

The datasets were derived from sources in the public domain, including the US Food & Drug Administration Drug Approvals website (https://www.accessdata.fda.gov/scripts/cder/daf/) and the associated published manuscripts for each cancer medicine.

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