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Challenges with sex-specific subgroup analyses in oncology clinical trials for drug approvals between 2015–2020

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ABSTRACT

Introduction: Women continue to be underrepresented in oncology clinical trials, leading to poor, underpowered subgroup analyses that cannot be generalized to cancer patients in practice. In 2014, the US Food and Drug Administration (FDA) released an Action Plan, which included actions to improve the quality and reporting of demographic subgroup data. We sought to evaluate the five-year progress since the release of this report by assessing the credibility of sex-specific subgroup analyses in oncology clinical trials.

Methods: We reviewed the FDA Hematology/Oncology Approvals website for New Molecular Entities (NMEs) that were approved for adults from 2015 to 2020. Publications and their supplementary indexes were reviewed by two authors (K.J. & A.R.) against ten criteria that gauge the credibility of subgroup analyses by assessing factors related to study design, analysis, and context. One point was awarded for each criteria met, for a maximum score of 10.

Results: We identified a total of 73 NMEs approved for cancer treatment between 2015–2020, of which 61 met our eligibility criteria. Of these, 32 studies (52 %) reported a subgroup analysis by sex and were included in our analysis. Phase 2 (41 %) and Phase 3 (53 %) studies represented most studies. No study met ≥ 3 credibility criteria.

Conclusion: Only half the studies included in our analysis reported outcomes by sex, which suggests the activities stipulated in the 2014 US FDA Action Plan might be ineffective. This is concerning as uncredible sex-specific subgroup analyses can lead to wrongful clinical decision-making and poor patient outcomes.

Policy summary: Our findings suggest sex-specific subgroup analyses in oncology are not credible and users of these data should interpret results with caution. Regulatory bodies, such as the US FDA, ought to mandate subgroup analyses by demographic groups in drug applications. Peer-reviewed journals could ensure investigators disclose study results by sex as a condition for publication.

1. Introduction

"The whole of medicine depends on the transparent reporting of clinical trials" [1]

Clinical trials are considered the gold evidentiary standard for assessing health-care interventions. When adequately conducted, designed, and reported, these studies can inform clinical practice and improve patient outcomes. To assess the validity of a study result, and if the intervention effect can be generalized to clinical practice, readers depend on assessing complete and transparent trial information. Unfortunately, numerous assessments of oncology clinical trials have found that critical information about the trial methodology and results are often not reported in publications [2–4].

The results from subgroup analyses are especially important to disclose as the heterogeneity of demographic factors can influence health outcomes. Indeed, one pertinent area that the scientific community has begun to appreciate is the effects of biological sex differences on the pharmacodynamics and pharmacokinetic properties of a therapeutic. Despite this knowledge, research suggests women continue to be enrolled at lower rates in oncology clinical trials [5–7]. Low participation rates in clinical studies lead to poor, underpowered subgroup analyses, meaning study results cannot be generalized to cancer patients

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outside of trials.

Over the years, numerous regulatory initiatives have attempted to increase female participation in clinical studies and improve the quality and reporting of study results by sex [8]. For example, in 2012, the United States (US) Congress enacted the Food and Drug Administration (FDA) Safety and Innovation Act [9] which, in part, required the US FDA to review the inclusion and analysis of demographic subgroups in drug approval applications. In 2014, the FDA released its Action Plan [10], which included actions to improve the quality and reporting of demographic subgroup data. Indeed, the 1993 Revitalization Act [11] (which mandated women be included in National Institutes for Health (NIH)-funded trials) also specified that women ought to be enrolled in trials in adequate numbers to ensure valid analyses of the intervention effect in subgroups.

Despite these regulatory measures, research suggests that subgroup analyses remain inadequately performed [12,13]. In oncology, most of the literature in oncology has evaluated the representation of minority participants in clinical trials based on "proportionality" - the distribution of female participants to the incidence or prevalence of a disease in the population. However, little attention has been given to the frequency and quality of the sex-specific subgroup analyses in oncology. To evaluate the five-year progress since the release of the FDA Action plan [10] and assess the credibility of sex-specific subgroup analyses, we reviewed FDA drug approvals for new molecular entities (NMEs) in cancer between 2015−2020.

2. Methods

We reviewed the FDA Hematology/Oncology Approvals website [14] for drugs that were approved for adults from 2015 to 2020 (excluding sex-specific indications such as breast, prostate, ovarian, and cervical). We extracted the list of approvals, along with the National Clinical Trial (NCT) number, and related publications. In the case the drug approval was based on multiple clinical trials, we extracted and evaluated each study separately. Other variables included year of approval, number of subgroups, and trial phase. Publications and their supplementary indexes were reviewed by two authors (K.J. & A.R.) against ten criteria outlined by Sun et al. (Table 1) [15]. These criteria gauge the credibility of subgroup analyses by assessing factors related to study design, analysis, and context (Table 1), and has been used in similar studies [12,13]. One point was awarded for each criteria met, for a maximum score of 10. Data analysis was performed using Excel Software Version 16.9.

Table 1
Credibility of subgroup analysis criterion by Sun et al. 2012 [15] (n = 32).

Criteria		Number of studies (%)
Design	1 **Is the subgroup variable a characteristic measured at baseline?**	32 (100)
	2 Was the subgroup variable a stratification factor at randomisation?	1 (3)
	3 **Was the hypothesis specified a priori?**	21 (66)
Analysis	4 Was the subgroup analysis one of a small number of subgroup analyses tested (≤5)?	0 (0)
	5 **Was the test of interaction significant (interaction p < 0.05)?**	9 (28)
	6 Was the significant interaction effect independent if there were multiple significant interactions?	1 (3)
Context	7 Was the direction of the subgroup effect correctly pre-specified?	0 (0)
	8 Was the subgroup effect consistent with previous studies?	0 (0)
	9 Was the subgroup effect consistent across related outcomes?	0 (0)
	10 Was there indirect evidence to support the apparent subgroups effect?	1 (3)

Bolded criteria deemed "critical" by Sun et al. 2012 [15].

3. Results

We identified a total of 73 NMEs approved for cancer treatment between 2015–2020, of which 61 met our eligibility criteria. Of these, 32 studies (52 %) reported a subgroup analysis by sex and were included in our analysis (Fig. 1). Phase 2 (41 %) and Phase 3 (53 %) studies represented most studies. No study met ≥ 3 credibility criteria (Fig. 1). The two criteria that were met by more than 50 % of the studies was whether the subgroup was a characteristic measured at baseline (100 %) and whether the SGA was prespecified (66 %) (Fig. 1). None of the included studies provided any contextual information for the analysis except one, which indicated the sex-specific subgroup analyses was performed to meet "regulatory requirements." All trials, except one, reported performing more than five subgroup analyses.

4. Discussion

Our findings, although limited to NMEs, suggest that sex-specific subgroup analyses supporting regulatory approvals are inadequately performed. This is concerning as uncredible sex-specific subgroup analyses can lead to wrongful clinical decision-making and poor patient outcomes. Our results are similar to previous studies [12,13], however, we extend these findings by purposively evaluating sex-specific subgroups to explore the generalizability of cancer research given numerous policy initiatives for the inclusion of women in clinical studies over the past three decades. We found only 52 % of studies reported outcomes by sex, which suggests the activities stipulated in the 2014 US FDA Action Plan [10] might be ineffective.

Our study is limited to publicly available data. The US FDA base approvals on confidential clinical study documents which might include additional data not privy to the public. Further, authors may not have sufficient space in manuscripts to report all methodological considerations pertaining to the conduct of subgroup analyses. However, since many aspects of cancer treatment are based on published materials (i.e., clinical decision-making, meta-analyses, and practice guidelines), reporting health outcomes by sex is critical to include in publications. Further, we could not find this information in supplemental appendices either, which do not have an imposed word limit, which raises questions about whether these analyses are being done.

Given that studies conduct multiple subgroup analyses, Sun et al. [15], acknowledged constraints of including all information relevant to each of the ten criteria. However, three criteria were deemed critical: the use of variables measured at baseline, prespecifying of subgroup hypotheses, and statistical significance of the interaction test. Our study found most sex-specific analyses did not meet these criteria: 66 % of studies included sex as one of the prespecified analyses, and only 28 % reported a significant interaction test. This information is fundamental to assessing whether the result is meaningful or whether it arose by chance.

Opportunities exist to improve the reporting and use of subgroup data. Our findings suggest clinicians, policy makers, and other users of data from clinical trials, should interpret subgroup claims with caution. Further, when evaluating a subgroup claim, users should assess results using the credibility criteria used in this study (Table 1). Further, investigators ought to fully report the conduct of subgroup analyses and peer-reviewed journals should ensure these analyses are included in the manuscript or supplemental analyses as a condition for publication.

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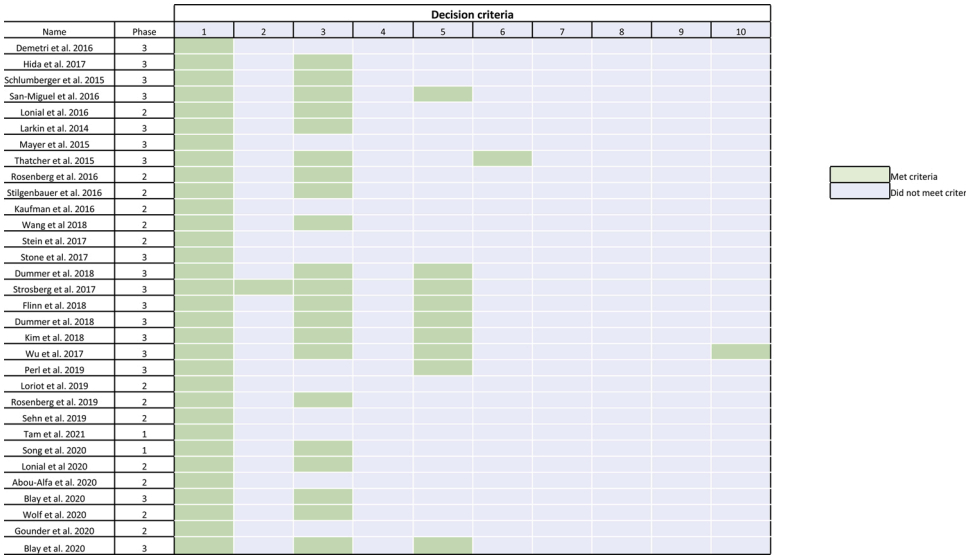

Fig. 1. Subgroup credibility scores by study (n = 32).

Declaration of Competing Interest

Dr Prasad reports receiving royalties from his book Ending Medical Reversal; that his work is funded by the Laura and John Arnold Foundation; that he has received honoraria for grand rounds/lectures from several universities, medical centers, and professional societies and payments for contributions to Medscape; Dr Prasad hosts the podcast Plenary Session, which has Patreon backers. Dr. Raymakers, Meyers, and Ms. Jenei have no disclosures to report.

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