

Invited Commentary

Suggested Principles for Sex and Gender Data in Ophthalmology Clinical Trials

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Xie et al¹ assessed how sex or gender terminology were applied in ophthalmology clinical trials associated with US Food and Drug Administration (FDA) drug approvals. Sex is a biological construct that is based on physiology, anatomy, hormones, and genetics.^{2,3}



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Gender is a multidimensional construct encompassing both gender expression and identity.^{2,3} Xie and colleagues reported that sex and gender terms were applied incorrectly (using sex and gender interchangeably, sex-related terms in reference to gender, and gender-related terms in reference to sex) 80.5% of the time in 85 clinical trials. They also found that while 96.5% of clinical trials reported sex and gender disaggregated demographic data, only 23.5% of clinical trials conducted sex- or gender-specific analysis for the main outcome, 2.4% of clinical trials conducted sex- or gender-specific analysis for the secondary outcome, and 3.5% conducted sex- or gender-specific analysis for adverse events. Based on these findings, the authors¹ call for more rigorous integration of sex and gender in clinical trials to improve their validity and equity. The authors note that even if a clinical trial is not powered to assess differences by sex or gender, which may not always be possible, characterizing outcomes by sex and/or gender in a consistent manner will enable future meta-analyses that may be sufficiently powered to assess gender- or sex-based outcomes. Current best practices for sex and gender data reporting are outlined in the Sex and Gender Equity in Research (SAGER) guidelines.¹ While the SAGER guidelines address issues of both sex and gender in research studies, current and future ophthalmology clinical trials also should implement the FAIR (Findability, Accessibility, Interoperability, and Reusability) principles to help the scientific community access and aggregate sex- and gender-based data across clinical trials.⁴

The first FAIR principle of findability highlights that datasets should be registered/indexed, identified, and described in both an unambiguous and clear method.⁴ Thus, trials need to ensure that sex and gender information is clearly documented. Clear documentation is augmented when researchers use standardized inclusive sex and gender language to enhance the searchability and to minimize barriers to locate pertinent sex and gender data within the dataset. The FAIR accessibility principle highlights that data should be accessible in many formats and be stored in a secured and trusted repository.⁴ The FAIR interoperability principle highlights the

need for data to be functional with other tools and datasets.⁴ Interoperability is also enhanced if representation of sex and gender is standardized through accepted coding systems. When clinical trial data are inconsistent or incorrectly coded, it is more difficult to merge datasets for broader insights. The FAIR reusability principle highlights the need for effective documentation for other research teams, including rich metadata.⁴ At the completion of a trial, it is good stewardship to prepare the data for others to use so the research community can effectively build new knowledge.

The FAIR principles do not cover all the issues of sex and gender reporting. For example, the FAIR principles provide limited guidance on ethical issues as they focus mainly on the technical aspects of data management, so proper consent and responsible use of data are not covered.⁵ Data privacy concerns are also not covered, which is especially pertinent given recent cybersecurity breaches. The FAIR reusability principle should be used wisely so as not to create privacy concerns for those participating in studies, particularly for participants in trials focused on rare eye conditions.

While the National Institutes of Health requires a rationale for sex and gender inclusion, exclusion, and representation, trials are funded by many different sponsors who may not have such requirements.⁶ To set a standard for clinical trials, it would also help if the National Institutes of Health required the 2-step method approach to sex reporting and gender reporting, where people are asked both their sex assigned at birth and their gender identity, and then researchers are required reporting enrollment and outcomes by these categories in their reports and in the reporting required by ClinicalTrials.gov.² If the FDA followed suit and required postmarketing surveillance strategies to collect sex- and gender-based efficacy and safety data, there may be sufficient power between the postmarketing surveillance and the aggregation of data across studies to assess for any important sex- or gender-based outcomes. Additionally, engaging communities of sex and gender minoritized individuals,⁷ communities of cisgender individuals, and communities across ages, educational levels, and ages in design and implementation of sex and gender data collection, would help make research forms more inclusive for a diverse participant population. Standardizing forms across governmental agencies would promote FAIR data reusability practices so that sex- and gender-based data could be aggregated and analyzed to inform best practices for individualized treatment guidelines.

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