CellPress

Med

Commentary

Progress and opportunities for women in clinical trials: A look at recent data and initiatives from the U.S. FDA

Kaveeta P. Vasisht,[1,*] Bridget M. Nugent,[1,*] and Janet Woodcock[2]

Recruiting and retaining diverse populations in clinical research is critically important. Over the years, we have seen improvements in the representation of women in clinical trials submitted in FDA marketing applications, and we are encouraged by the potential for new strategies to further their representation.

Why sex matters in clinical research

Sex (referring to biological traits) and gender (referring to self-identity and sociocultural norms) impact who we are and how we experience health, illness, and our response to therapies. Gender differences influence our interaction with the healthcare system, our preferences, attitudes, and communication styles. Sex differences have been discovered in nearly every cell type in the body and these differences impact myriad physiological functions, disease prevalence, and susceptibility.[1] Notably, sex differences have been shown to influence drug pharmacokinetics and pharmacodynamics.[2] Ideally, biological sex should be considered throughout the biomedical pipeline, starting with early discovery science, and resulting in medical products that are safe and effective in the population for which they are intended to be used. Studying sex- and gender-based differences and their clinical implications facilitates the delivery of personalized care for each individual.

We recognize that sex and gender are unique terms. Both are important influencers of health, treatment utilization, and outcomes. However, there are limitations in the collection of demographic data in clinical trials, as sex and gender terminology has been used interchangeably. In addition, clinical trial demographics generally reflect self- or investigator-reported gender of participants and thus representation is often evaluated by gender using the terms "woman" or "man."

For the purposes of this commentary, we are utilizing the gender terms "woman" or "man" throughout, except in cases where the data specifically describe demographic representation using the sex terms "female" and "male."

Although sex and gender are often concordant, they may not be aligned for all participants. This highlights the need for a more systematic approach to collecting demographic information in clinical research, as relevant in describing the sex- and gender-influenced outcomes of interest.

Recent snapshot of demographics captured in clinical trials

The U.S. Food and Drug Administration (FDA, the Agency) Center for Drug Evaluation and Research (CDER) developed Drug Trials Snapshots (DTS) with the goal of making demographic data broadly available and transparent.[3] Each snapshot presents information on participant demographics in the pivotal clinical trials used to approve novel drugs that are new molecular entities or original biologic products. Some of the trials included in the snapshots enrolled children. Demographic information is reported by sex, race, age, and ethnicity.

In the DTS summary for 2019, 72% of clinical trial participants were female.[3] This reflects the approval of drugs for sex-specific indications, including post-menopausal osteoporosis, postpartum depression, and hypoactive female sexual desire disorder and several novel drug approvals for conditions that have a higher female prevalence, such as rheumatoid arthritis, migraine, irritable bowel syndrome, multiple sclerosis, and iron deficiency anemia. In addition, female participation comprised an average of 63% of participants in trials supporting 40 novel drugs approved for non-sex-specific conditions.

Recently, DTS published a 5-year summary report of demographic data from pivotal trials for 231 novel drugs approved between 2015 and 2019 representing 292,766 clinical trial participants.[3] While the majority of the clinical trial participants were from outside the United States, the United States represented the highest proportion of participants from a single country. Overall, females represented 51% of global clinical trial participants and 56% of trial participants from the United States (Figure 1A). Globally, with respect to ethnicity, 14% of female participants and 11% of male participants identified as Hispanic or Latino. In addition, 76% of female participants identified as white, 10% Asian, 8% Black or African American, and 1% identified as American Indian or Alaska Native (6% were categorized as "other"). Of note,

[1]Office of Women's Health, U.S. Food and Drug Administration, Silver Spring, MD 20993, USA

[2]Office of the Commissioner, U.S. Food and Drug Administration, Silver Spring, MD 20993, USA

*Correspondence:
kaveeta.vasisht@fda.hhs.gov (K.P.V.),
bridget.nugent@fda.hhs.gov (B.M.N.)

https://doi.org/10.1016/j.medj.2021.04.010

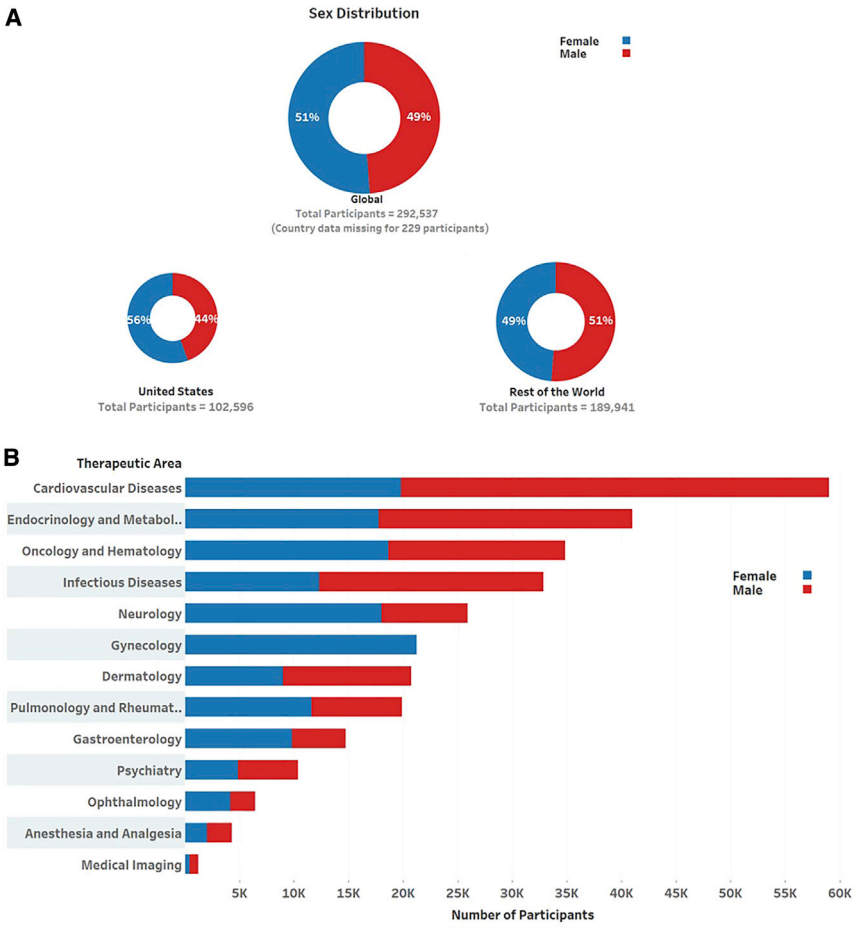

Figure 1. Drug Trial Snapshots (DTS)

5-year overview of global participation in clinical trials aggregated by sex based on a total of 292,537 particpants.[3]

(A) Sex distribution of clinical trial participation data from 2015 to 2019 displayed as percent male and female; 51% of participants were female and 49% were male.

(B) Number of global clinical trial participants by therapeutic area broken down by sex of trial participant. Clinical trial participation in the DTS data is stratified by sex using the biological terms of male and female. The aggregate data includes children and adults.

representation by race was comparable between females and males.

The 5-year summary report also provides a breakdown of female and male participants by general therapeutic area.[3] Notably, novel drug approvals in therapeutic areas of neurology, gastroenterology, and ophthalmology had an overall higher number of female participants compared to males and there was lower representation of females in drug approvals for infectious diseases and cardiovascular diseases (Figure 1B).

There has been an overall increase in representation of female participants in pivotal clinical trials for novel drug approvals since the first DTS summary report was published in 2015, which had 40% representation.[3] We also note opportunities for improvement to ensure diversity of not only sex, but also race, age, ethnic background, disease comorbidities, and socioeconomic influences on health disparities. Commonly cited barriers to participation in clinical trials include time commitment, risk of unknown treatment effects, distrust and wariness of research, and lack of understanding of clinical research.[4] Below we describe some of our efforts to help tackle these barriers.

Efforts to address challenges of inclusion

In 1994, the FDA Office of Women's Health (OWH) was established to promote inclusion of women in clinical trials and to provide leadership on topics related to the health of women. For decades, OWH has supported research to elucidate the pathophysiologic underpinnings of sex-based differences and influences on disease progression, to evaluate response to treatments, and to identify gender-based influences on patient preferences. In 2015, OWH published its Women's Health Research Roadmap, which established a strategic direction and research funding priority areas to maximize research impact. OWH-funded research has led to changes in regulatory policy and improvements in safety of FDA-regulated products for women.[5] In addition, OWH engages with scientists, educates the public on issues critical to the health of women, and conducts research to address data gaps in women's health, including analyses of women's participation in clinical trials.

Since heart disease is the leading cause of death for women in the United States, OWH conducted a decadal review that examined women's participation in pivotal cardiovascular trials submitted to the FDA supporting marketing applications between 2005 and 2015.[6] The study found that women were well represented in trials of drugs for systemic hypertension and atrial fibrillation, were overrepresented for pulmonary arterial hypertension, but were underrepresented in trials studying therapies for heart failure, coronary artery disease, and acute coronary syndromes. Exploratory analysis of the "inclusion/exclusion criteria" for five of the clinical trials found that eligibility criteria were not a contributing factor to under participation by women. Although

the sample size was small, the data suggest that lower enrollment of women in certain cardiovascular disease trials reflects the lower number of women referred for screening. Therefore, factors such as the identification of potential trial participants and ability of the candidate to participate may be critical contributors to lower enrollment of women.

In addition, to better understand representation in infectious disease trials, OWH is currently researching the participation of women in clinical trials supporting FDA approval of drugs for the treatment of human immunodeficiency virus (HIV) and assessing efficacy and selected safety events from 2011 to 2020.

The Office also conducts outreach to the public, researchers, and clinicians through our Diverse Women in Clinical Trials Initiative. This campaign was developed in collaboration with the NIH Office of Research on Women's Health (ORWH) and involves a consumer awareness campaign, as well as resources for health professionals and researchers.

In addition, the FDA has continued and advanced its efforts to support diverse participation in clinical trials through various initiatives. The Agency's policy initiatives have focused on promoting enrollment practices that lead to clinical trials that better reflect the population most likely to use the product if approved. In November 2020, the FDA issued a final guidance for industry titled, "Enhancing the Diversity of Clinical Trial Populations: Eligibility Criteria, Enrollment Practices, and Trial Designs."[7] This guidance recommends approaches that sponsors can utilize to broaden eligibility criteria, to expand inclusive trial practices, and to include unique trial designs and methodological approaches to increase enrollment of underrepresented populations in their clinical trials. Further, the guidance recommends that for most drugs, representatives of both sexes should be included in clinical trials in numbers adequate to allow detection of clinically significant sex-related differences in drug response.

Although the size and scope of this topic necessitates more attention, we would be remiss not to mention another critically important population of interest to OWH and the Agency: pregnant people. Still routinely excluded from research, there have been increased efforts toward promoting inclusion of pregnant people in clinical research. The FDA encourages participation of pregnant and lactating people when appropriate and have numerous guidance[8,9] and ongoing initiatives to help facilitate their representation in clinical trials. In addition, the FDA is actively engaged with the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC), which was established by the 21st Century Cures Act to advise the Secretary of Health and Human Services on gaps in knowledge and research on safe and effective therapies for use during pregnancy and lactation. OWH also funds research to expand knowledge of the safety and efficacy of medical products used during pregnancy. This includes research projects using real-world data to advance our understanding of the most commonly used medical products in diverse populations of pregnant and lactating people, utilizing artificial intelligence and other computational approaches to predict the efficacy and safety of drugs in pregnant people, and innovative methodologies to model drug passage into breast milk. In addition, OWH provides a public listing of active pregnancy exposure registries to bring awareness of opportunities to participate in research to pregnant people and health care providers.

Disruption, Innovation, and Opportunities

As the Agency continues to work and collaborate with stakeholders to improve women's participation in clinical trials, the COVID-19 pandemic has created unprecedented challenges and disruption across all sectors of society, including the conduct of clinical trials. These disruptions have, in turn, promulgated rapid and innovative solutions. The FDA recognized the potential impact that this public health emergency could have on the conduct of clinical trials of medical products and issued guidance for industry encouraging sponsors to consider alternate methods for clinical assessments such as telephone contact, virtual visits, and utilization of local laboratories when appropriate.[10] Years prior to the pandemic, the Agency issued guidance on electronic informed consent and is working on guidance pertaining to the design and conduct of decentralized trials and the use of digital health technologies in clinical investigations.[11] Trials that incorporate components of decentralization, digital health, electronic platforms, and other technologies may ease the burden of participating in a clinical trial and potentially improve recruitment and retention of diverse patients. For populations with limited or no internet access, holding consenting processes and interventions in locations that are more accessible to the participant may be beneficial.[7] Additionally, usual trial study sites are located at major medical centers or sites that frequently work with contract research organizations. To enroll chronically under-represented and diverse populations, a clinical research infrastructure must be supported at the community healthcare level, at sites near where people live and where they receive their healthcare.

Advances in our understanding of real-world data may also help to bridge current knowledge gaps. For example, the FDA and the National Center for Advancing Translational Sciences (NCATS) collaborated on the development of the CURE ID app,[12] which gathers information from the clinical community on novel uses of existing

drugs for difficult-to-treat infectious diseases via a website, smartphone, or other mobile device. Recently OWH funded the expansion of the CURE ID app to gather real-world information on the use of medications for oncology and infectious diseases in pregnancy.

While the pandemic has spurred innovation and collaboration, we have also witnessed a decrease in employment for women since the start of the pandemic and in 2020 women experienced higher unemployment compared to men.[13] This is likely due to greater disruption in employment sectors with higher rates of women and greater child and eldercare responsibilities among women.[14] Importantly, burdens related to caregiving responsibilities and financial constraints are commonly cited barriers for participation in clinical research. In addition, the careers of women in science and medicine could be disproportionately impacted by the pandemic, as women are publishing fewer research papers and are initiating fewer new research studies than men.[15] Shared identity between participants and clinical trial personnel enhances patient trust and can increase the likelihood of women participating.[4] Therefore, optimizing the potential of innovation and technology to promote inclusion of women in clinical trials will require prioritization of diverse women as investigators, study personnel, and participants.

We are encouraged by improvements in the participation of women in clinical trials in recent years. We also recognize that representation gaps remain. It is important for all sectors of medical product development to review the lessons learned from changes in clinical trial conduct resulting from the unparalleled challenges presented by the COVID-19 pandemic and identify those that enhance inclusiveness. Inclusion of women, representing diversity in age, race, ethnic background, socioeconomic status, and comorbid conditions should be at the forefront of collaborative efforts and innovative strategies to bridge gaps in representation. We are committed to working together with our federal partners and stakeholders to further advance the progress that has been made to protect and promote the health of all women.

ACKNOWLEDGMENTS

The authors thank the following FDA staff for their contributions: Dr. Milena Lolic for her expertise and assistance in interpreting Drug Trials Snapshots data, Dr. Leonard Sacks in CDER's Office of Medical Policy, and Dr. Susan Bersoff-Matcha in the Office of Women's Health.

AUTHOR CONTRIBUTIONS

K.P.V., B.M.N., and J.W. drafted the manuscript, reviewed it, and edited it. All authors agreed to submit the manuscript, read and approved the final draft, and take full responsibility of its content.

DECLARATION OF INTERESTS

The authors declare no conflicts of interest. The contents of this publication reflect the thoughts of the authors and do not represent the official views of, nor an endorsement by, the FDA, Department of Health and Human Services, or US government.

1. G. Neigh, and M. Mitzelfelt, eds. (2016). Sex differences in physiology (Academic Press).
2. Gandhi, M., Aweeka, F., Greenblatt, R.M., and Blaschke, T.F. (2004). Sex differences in pharmacokinetics and pharmacodynamics. Annu. Rev. Pharmacol. Toxicol. *44*, 499–523.
3. US Food and Drug Administration Drug Trials Snapshots. https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots
4. Myles, S., Tocci, C., Falk, M., Lynch, S., Torres, C., Brown, B., Leopanto Firman, B., Lake, M., Maser, C.A., Onativia, A., et al. (2018). A multicenter investigation of factors influencing Women's participation in clinical trials. J. Womens Health (Larchmt.) *27*, 258–270.
5. South, E.M., Zinn, R.L., Huang, C.J., and Vasisht, K.P. (2020). US food and drug administration office of women's health: promoting therapeutic optimization in women. J. Clin. Pharmacol. *60* (*Suppl 2*), S11–S17.
6. Scott, P.E., Unger, E.F., Jenkins, M.R., Southworth, M.R., McDowell, T.-Y., Geller, R.J., Elahi, M., Temple, R.J., and Woodcock, J. (2018). Participation of women in clinical trials supporting FDA approval of cardiovascular drugs. J. Am. Coll. Cardiol. *71*, 1960–1969.
7. US Food and Drug Administration (2020). Enhancing the diversity of clinical trial populations; eligibility criteria, enrollment practices, and trial designs guidance for industry. https://www.fda.gov/media/127712/download.
8. US Food and Drug Administration (2018). Pregnant women: scientific and ethical considerations for inclusion in clinical trials. Draft guidance document. https://www.fda.gov/media/112195/download.
9. US Food and Drug Administration (2019). Clinical Lactation Studies: Considerations for Study Design. Guidance for Industry. https://www.fda.gov/media/124749/download.
10. US Food and Drug Administration (2020). Conduct of clinical trials of medical products during the COVID-19 public health emergency. Guidance for indsutry, investigators, and institutional review boards. Draft. https://www.fda.gov/media/136238/download.
11. US Food and Drug Administration (2016). Use of electronic informed consent: questions and answers. Guidance for institutional review boards, investigators, and sponsors. https://www.fda.gov/media/116850/download.
12. US Food and Drug Administration (2020). CURE ID app lets clinicians report novel uses of existing drugs. https://www.fda.gov/drugs/science-and-research-drugs/cure-id-app-lets-clinicians-report-novel-uses-existing-drugs.
13. US Department of Labor (2021). Labor force statistics from the current population survey. Household data, seasonally adjusted. https://www.bls.gov/web/empsit/cpseea03.htm.
14. Alon, T.M., Doepke, M., Olmstead-Rumsey, J., and Tertilt, M. (2020). The impact of COVID-19 on gender equality. National Bureau of Economic Research, Report No. 26947: 0898-2937.
15. Viglione, G. (2020). Are women publishing less during the pandemic? Here's what the data say. Nature *581*, 365–366.