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Re: FDA-2020-N-1391: Office of Women's Health Strategic Priorities; Establishment of a Public Docket; Request for Comments

Dear Mr. Schiller and Dr. Vasisht:

The Society for Women's Health Research (SWHR) is pleased to offer comments on the U.S. Food and Drug Administration (FDA) Office of Women's Health's strategic priorities. We write specifically in response to Docket No. FDA-2020-N-1391.

SWHR is a 30-year-old national nonprofit dedicated to promoting research on biological sex differences in disease and improving women's health through science, policy, and education. Working collaboratively with the FDA is part of SWHR's legacy. SWHR championed the framework for the scientific discipline of sex-based biology, which encourages the inclusion of female subjects in clinical trials and analyzes the differences between women and men in relation to disease. Through the systematic collection and reporting of more accurate, sex-specific drug and device information and labeling, the FDA has been able to better serve both women and men.

SWHR celebrates the achievements of the OWH over the past 26 years in advising the FDA Commissioner and other agency officials regarding scientific, ethical, and policy issues relating to women's health. SWHR's long-term mission of expanding the exploration of sex as a biological variable

(SABV) in preclinical and clinical research activities is directly in line with the OWH's key goals. We applaud the OWH's long history of promoting research, education, and outreach about the importance of eliminating sex and gender disparities in health care.

In considering strategic priorities for the FDA OWH, we offer recommendations, detailed below, in line with the stated issues for consideration in the public docket.

Issue for Consideration: *Efforts to encourage analysis and detection of potential sex and gender differences in the safety, efficacy, and use of FDA-regulated products.*

SWHR Recommendation: Lead inter- and intra-agency conversations on how best to advance SABV and the inclusion of women within clinical trials.

Until about 25 years ago, essentially all health research was conducted on men, due to the persistent idea that female hormonal cycles were too difficult to manage in experiments — including the fear of harming potential pregnancies — and that using only one sex would reduce variation in results. This exclusion of females in health research extended to research on female animals, cells, and tissue. Researchers assumed that they could simply extrapolate their male-only study results to females, a dangerous precedent that overlooked fundamental differences between women and men.

Current research shows that within preclinical research, the dominance of male subjects and ignorance of SABV persists. As compared to a 2009 study,[1] recent research indicates that significantly more preclinical articles published in 2019 included both sexes in the sample population. However, little progress has been made in analyzing study results by sex. Among studies that included both sexes as subjects, only 42% included sex-disaggregated analyses, down from 50% of articles in 2009.[2]

Within clinical research, women made up 72% of all clinical trial participants for FDA-approved new drugs in 2019. However, the percentage of black participants decreased from 11% in 2018 to 9% in 2019, while Hispanic participants increased from 14% in 2018 to 18% in 2019. According to a recent estimate, African Americans make up about 13% of the U.S. population, while Hispanics account for about 18%.[3]

SWHR encourages the FDA OWH to act as a leader in advancing conversations around SABV and the inclusion of diverse populations of women across the lifespan within therapeutic and device research and the approval process. It is important to not only include both women and men in research, but to analyze outcomes for potential sex and gender differences. The OWH should promote policies encouraging those seeking approvals to ensure appropriate inclusion as well as robust analyses to understand sex and gender differences.

[1] Beery, A, Zucker, I. Sex bias in neuroscience and biomedical research. Neurosci Biobehav Rev. 2010;35(3):565-572.
[2] Woitowich, NC, Beery, A, Woodruff, T. Meta-research: A 10-year follow-up study of sex inclusion in the biological sciences. *eLife.* 2020;9:e56344. doi: 10.7554/eLife.56344
[3] Ortman, E. (2020). Women make up 72% of study participants for FDA-approved new drugs in 2019. Accessed from: https://swhr.org/women-make-up-72-of-study-participants-for-fda-approved-new-drugs-in-2019/

SWHR Recommendation: Lead agency efforts to improve the inclusion of pregnant and lactating women within clinical trials for vaccines, therapeutics, and devices and to encourage further research on already-approved products that have yet to be studied within the pregnant and lactating population.

Each year in the United States, 6 million women are pregnant,[4] nearly 4 million women give birth,[5] and more than 3 million women breastfeed.[6] Despite these profound statistics, there is a paucity of human data on safety and efficacy of vaccines, therapeutics, and devices in pregnant and lactating women. Exclusion of pregnant and lactating women in research has led to significant, unacceptable gaps in women's health and therefore must be an OWH priority when considering sex and gender differences in safety and efficacy of FDA-regulated products.

The Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC), established in the 21st Century Cures Act, released a report in 2018 recommending the inclusion of pregnant and lactating women in clinical research. We encourage the OWH to consider how best to improve the inclusion of pregnant and lactating women in the development and approval process. We recommend coordination with PRGLAC and implementation of its recommendations to remove regulatory barriers to research in pregnant and lactating women.

In line with PRGLAC's 2018 recommendations,[7] SWHR encourages the OWH to lead both inter- and intra-agency conversations that highlight the importance of research in pregnant women and lactating women, including the impact of not taking medication during pregnancy and lactation as well as the impact of not breastfeeding on both mother and child. We look forward to PRGLAC's upcoming report that will detail implementation recommendations and are hopeful the FDA will take the full body of PRGLAC's important work into consideration.

SWHR Recommendation: Utilize real-world evidence and real-world data to supplement traditional data collection methods in order to gain a full picture of the experiences of women and minority populations both during clinical trials and post-trials follow-up.

SWHR has been pleased to follow the FDA's work to include real-world evidence (RWE) and real-world data (RWD) within its regulatory framework. RWE, derived from data collected during routine health care practice (such as electronic health records, claims and billing activities, and product and disease registries) can help to capture the impact of a potential product on patient quality of life or reflect differences in outcomes based on heterogeneity.

This type of data can enable more efficient development programs and provide information that clinical trials alone may not be able to capture. When generated and used appropriately, RWE is an incredibly valuable resource to patients, researchers, and regulators. It may also be beneficial in capturing the different experiences of women that might not otherwise be reflected in traditional data collection methods. We encourage the OWH to determine what types of RWE

[4] Curtin, SC, Abma, JC, Ventura, SJ, Henshaw, SK (2013). Pregnancy rates for US women continue to drop. *National Center for Health Statistics Data Brief, 138.* Accessed at: https://www.cdc.gov/nchs/data/databriefs/db136.pdf
[5] Martin, JA, HaMilton, BE, Osterman, MJK, Driscoll, AK (2019). Births: Final data for 2018. *National Vital Statistics Reports, 68*(13). Accessed at: https://www.cdc.gov/nchs/data/nvsr/nvsr68/nvsr68_13-508.pdf
[6] Centers for Disease Control (2018). Breastfeeding report card, United States, 2018. Accessed at: https://www.cdc.gov/breastfeeding/pdf/2018breastfeedingreportcard.pdf
[7] PRGLAC report to the HHS Secretary and Congress (2018). Accessed from: https://www.nichd.nih.gov/about/advisory/PRGLAC/recommendations

may be most beneficial in capturing sex and gender differences and when the use of RWE may be most appropriate.

Issue for Consideration: *Efforts to anticipate, meet, and respond to existing and emerging issues related to women's health and FDA-regulated products.*

SWHR Recommendation: Apply lessons learned from the COVID-19 pandemic to make research participation more available to an increasingly diverse range of patients, which may include specific efforts to decentralize clinical trials.

Women are frequently health care decision-makers for both themselves and for family members, and they are often unduly burdened by in-person health care visits. Frequently, caregiving obligations make it difficult for women to participate in clinical research. Conventional clinical trials models typically involve frequent and at-times lengthy site visits to receive a care or to engage in routine monitoring. Low participation in clinical trials may be in large part due to difficulties accessing in-person clinical sites.[8]

COVID-19 has had significant effects on health care in the U.S. In the midst of a global pandemic, decentralized and siteless trials seem more appealing than ever and may have the added benefit of increasing participation and improving diversity within research. Decentralized trials can improve patient comfort and increase convenience for research participants.[9]

In considering the specific needs of women, SWHR believes the OWH can play a major role in modernizing the clinical trials model and providing guidance to the agency on best practices to promote diverse participation. We encourage the OWH to identify barriers to clinical trials participation among women and among historically underrepresented groups, and also to identify innovative models that may increase participation rates within these groups. The OWH can and should act as a leader within the FDA to champion initiatives that will increase the participation of diverse subgroups.

Virtual, siteless, and direct-to-patient trials, as well as hybrid approaches, should all be considered, and the rapid evolution of trials during the COVID-19 pandemic should be taken into account to best understand how these alternative models may provide additional benefit to women.

Issue for Consideration: *Direct outreach to diverse groups of women to promote access to relevant information about FDA-regulated products, encourage participation in clinical trials, and maintain dialogue about critical women's health topics.*

SWHR Recommendation: Continue efforts to gather patient input within the research, development, and approval processes and to prioritize diverse patient voices to the greatest extent possible.

[8] Spears, PA. (2020). Patient barriers to participation in breast cancer clinical trials. *Breast Cancer Management, 9*(1). doi: 10.2217/bmt-2020-0004

[9] National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Sciences Policy; Forum on Drug Discovery, Development, and Translation; Shore C, Khandekar E, Alper J, editors (2019). Virtual Clinical Trials: Challenges and Opportunities: Proceedings of a Workshop. Washington (DC): National Academies Press (US). 2, Opportunities to Improve Clinical Trials. Available from: https://www.ncbi.nlm.nih.gov/sites/books/NBK548971/

SWHR has been outspoken in the need to include the unique perspectives of women as patients, caregivers, and family decision-makers within the research and development process, as exemplified in SWHR's "Policy Principles: Patient-Focused Drug Development."[10] Obtaining meaningful input from historically marginalized populations of women is particularly crucial. Greater diversity in the patient population increases the potential of learning more about how different subgroups might respond to a new vaccine, drug, or device.

As detailed within our policy principles on patient-focused drug development, we encourage the OWH to explore all potential methods for patient experience collection, reporting, and analysis, including both qualitative and quantitative research, as well as mixed methods approaches. SWHR emphasizes that the choice and use of methods can and should differ based on the intended objective.

Additionally, the OWH should continue to establish clear and predictable processes for all stakeholders to engage with the OWH and the FDA more broadly. Within these processes, we encourage prioritization of the needs of women (e.g., child care and transportation needs, reimbursement, etc.) to ensure all women feel welcome and able to share their experiences.

Issue for Consideration: *Coordination and collaboration with other federal agencies and external stakeholders to support research and programming on women's health topics.*

SWHR Recommendation: Partner with relevant stakeholders to raise awareness and support women's health programming.

SWHR appreciates our long-term working relationship with the FDA OWH, and we are hopeful that continued collaboration will be prioritized in the long term. The white paper, "Dialogues of Diversifying Clinical Trials," co-written in 2011 by SWHR and the OWH, is a prime example of how stakeholder partnerships can drive conservations on sex and gender differences forward and disseminate these messages to larger audiences.[11]

We also encourage the OWH to explore similar partnerships with stakeholders that represent women's health needs and the needs of diverse populations such as the Black Women's Health Imperative, who has previously engaged on the topic of clinical trials research,[12] and the Black Mamas Matter Alliance, among other organizations that center the voices of women of color or historically underrepresented groups.

Issue for Consideration: *Identification of regulatory decisions that can benefit from participation of women across the lifespan (e.g., reproductive-age women, pregnant women, post-menopausal women, and elderly women) and women with certain health conditions.*

SWHR Recommendation: Explore how the regulation of digital health technologies can best prioritize the specific needs of women and minority populations, and how these technologies

[10] SWHR principles addressing disparities in drug development (2019). Accessed from: https://swhr.org/swhr_resource/swhr-principles-addressing-disparities-in-drug-development/
[11] SWHR and the FDA OWH. Dialogues on diversifying clinical trials. (2011). Accessed from: https://www.fda.gov/files/science%20&%20research/published/White-Paper-on-the-Dialogues-on-Diversifying-Clinical-Trials-Conference.pdf
[12] Black Women's Health Imperative, Friends of Cancer Research, and Stand Up to Cancer approved for a PCORI engagement award for Project TEACH (2020). Accessed from: https://bwhi.org/2020/01/28/black-womens-health-imperative-friends-of-cancer-research-and-stand-up-to-cancer-approved-for-a-pcori-engagement-award-for-project-teach/

may be appropriately applied to support the decentralization of clinical trials and to increase participation of diverse patient groups within research.

The use of digital health technologies (e.g., mHealth, health information technology, wearable devices, telehealth, etc.) can improve remote monitoring of patients and provide for real-time data capture within clinical trials. These technologies may be a means of increasing patient access to clinical trials and improving participation of women, people of color, and other underrepresented populations. Data gathered through the use of digital technologies may also help researchers learn about real-world effects. Additionally, mobile apps may be a potential avenue for allowing researchers not only to gather data, but also to consent and enroll participants in studies.[13]

Per Cox, Lane & Volchenboum's 2018 review article[14] on digital health technology within oncology trials, the "[n]ext steps for establishing mHealth methods and tools as legitimate and accepted measures in oncology clinical trials include continuation of regulatory definition by the FDA; establishment of security standards and protocols; refinement and implementation of methods to establish and document data accuracy; and finally, creation of feedback loops wherein regulators receive updates from researchers with better and more timely data, which should decrease trial times and lessen drug development costs."

SWHR encourages the OWH to explore how the use of digital technologies may hold particular benefits to women, people of color, and other underrepresented populations, and may increase the participation of these groups within clinical trials. The OWH should consider how researchers may use various alternative approaches of collecting certain information within clinical trials and include potential examples of less burdensome (potentially digital health-based) approaches in order to improve research participation.[15] Regulation around digital health technology and the use of digital technology within clinical trials must take into account the specific needs of women and minority populations.

In considering how the OWH may best address the rapidly changing landscape of women's digital health and innovation, we encourage the office to engage with the Women's Digital Health Alliance, housed at the American College of Obstetricians and Gynecologists (ACOG). The Women's Digital Health Alliance is a group of multidisciplinary experts and innovators across technology, health systems, and professional organizations that aims to assist physicians in navigating the vast landscape of patient-facing digital tools; promote quality, safety, and transparency in digital and mobile health; foster collaboration among women's health care physicians, stakeholders, patients, and innovators; and facilitate engagement between collaborators, digital innovations, and existing registries for women's health data exchange.

Issue for Consideration: *Generation of research and programming topics, interests, and areas of focus that predominantly affect women and/or would benefit from sex- and gender-related analyses.*

[13] Klonoff, DC, King, F, Kerr, D. (2019). New opportunities for digital health to thrive. *Journal of Diabetes Science and Technology,* 13(2), 159-163.
[14] Cox, SM, Lane, A., Volchenboum (2018). Use of wearable, mobile, and sensor technology in cancer clinical trials. *JCO Clinical Cancer Informatics.* Accessed from: https://ascopubs.org/doi/pdfdirect/10.1200/CCI.17.00147
[15] Laitner, M. Ovarian cancer: Challenges in diagnostic innovation. (2020). Accessed from: https://swhr.org/ovarian-cancer-challenges-in-diagnostic-innovation/

SWHR Recommendation: Identify areas where there is a clear need for innovation with regard to diagnosis and/or treatment of women's health-specific conditions as well as conditions that predominantly affect women.

Across areas of women's health, there exist an array of disorders that would benefit from improved screening and diagnostic technology, as well as improved treatment options. For example, for women confronting the possibility of an ovarian cancer diagnosis, certain diagnostic tests have not been modernized since the 1980s, leading to the possibility of surgery to definitively identify the presence of disease. Other patients — such as those with endometriosis — face long waits for diagnosis and treatment due to a lack of noninvasive diagnostics.[16] Additional conditions that would benefit from innovation include the human papillomavirus (HPV) and related cancers, premature birth, and preeclampsia.[17]

We encourage the FDA OWH to explore, identify, and prioritize health conditions that would most benefit from immediate innovation with regard to screening, diagnosis, and treatment. Encouraging research and development in these areas and bringing public attention both the health conditions as well as the potential innovations will benefit the health of women.

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SWHR is grateful for the opportunity to provide feedback to the FDA OWH on the strategic planning process. We look forward to continued opportunities to collaborate with the FDA OWH. If you have any questions, please do not hesitate to contact SWHR's Director of Science Policy, Melissa Laitner, PhD, MPH, at melissa@swhr.org.

Sincerely,

Kathryn G. Schubert, MPP
President and Chief Executive Officer
Society for Women's Health Research

[16] Ortman, E. (2019). Identifying barriers to care for women with endometriosis. Accessed from: https://swhr.org/identifying-barriers-to-care-for-women-with-endometriosis/
[17] Laitner, M. (2020). New screening and diagnostic technologies could pave the way for improvements in women's health. Accessed from: https://swhr.org/new-screening-and-diagnostic-technologies-could-pave-the-way-for-improvements-in-womens-health/