November 20, 2020

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Jeffrey Shuren, MD, JD
Director, Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire Avenue
Building 66, Room 5431
Silver Spring, MD 20993

Re: FDA-2020-N-0907: Medical Device User Fee Amendments for Fiscal Years 2023 Through 2027; Public Meeting; Request for Comments

Dear Dr. Shuren,

The Society for Women's Health Research (SWHR) is pleased to offer comments as a follow-up to the U.S. Food and Drug Administration (FDA) public meeting regarding the proposed recommendations for the reauthorization of the Medical Device User Feed Act (MDUFA) for fiscal years (FYs) 2023 through 2027. We write specifically in response to Docket No. FDA-2020-N-0907, "Medical Device User Fee Amendments for Fiscal Years 2023 Through 2027; Public Meeting; Request for Comments."

SWHR is a 30-year-old national organization dedicated to promoting research on biological sex differences in disease and improving women's health through science, policy, and education. SWHR's legacy includes working collaboratively with the FDA.

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.

In advance of MDUFA IV's expiration in September 2022, SWHR offers several recommendations, detailed below, that represent priorities for the millions of women nationally who rely on medical devices.

1. **Incorporate commitments to the Center for Devices and Radiological Health's (CDRH) Health of Women Program.**

   SWHR strongly supports the goals and mission of CDRH's Health of Women Program. We submitted comments last December[1] following the release of the program's strategic plan draft and are eager to monitor the program's development.

   The Health of Women Program's goals represent a significant step forward in addressing sex and gender differences. Better understanding of these disparities can benefit both women's health as well as population health. For example, acknowledging sex disparities in orthopedic function led to a prosthetic knee designed to cater to anatomical differences between women and men.[2]

   SWHR recommends including Health of Women Program commitments within upcoming MDUFA reauthorization. New investment in this program will allow CDRH to bring the important goals of the Health of Women Program to fruition.

2. **Continue work to prioritize diversity within clinical trials as related to sex, gender, race/ethnicity, age, and other important demographic variables.**

   SWHR commends the FDA's ongoing efforts to improve diversity within clinical trials. We hope CDRH will continue to prioritize diversity across all demographic variables. Clinical trials should mirror true patient population with respect to characteristics such as sex and gender; race and ethnicity; and age.

   Despite advances in technology, medical devices at times still fail to take into account the important outcome differences that may be dependent on sex and/or gender. Devices such as hip implants have lagged in accommodating the needs of women, despite evidence suggesting these implants are more likely to fail in women than in men.[3] On the other hand, there are some areas in which women may show greater benefit from devices than men. For example, while women experience more adverse effects following cardiac catheterization, research suggests they may benefit more from cardiac resynchronization therapy. Regarding orthopedic function, women tend to show worse knee function and higher rates of pain following total knee arthroplasty, but they also have lower rates of surgical revisions as compared to men.[4]

   Despite these facts, there exists relatively little oversight in ensuring all researchers perform sex- and gender-disaggregate analyses to better understand outcome differences. SWHR is particularly supportive of recent FDA guidance pertaining to diversity within clinical trial

[1] Society for Women's Health Research (2019). SWHR feedback to FDA on Health of Women Strategic Plan. Available from: https://swhr.org/swhr_resource/swhr-feedback-to-fda-on-health-of-women-strategic-plan/
[2] Das, Reenita (2018). Women's healthcare comes out of the shadows: Femtech shows the way to billion-dollar opportunities. https://www.forbes.com/sites/reenitadas/2018/04/12/womens-healthcare-comes-out-of-the-shadows-femtech-shows-the-way-tobillion-dollar-opportunities/#2ea04e766159 Accessed on November 4, 2020.
[3] Haughom, B.D., Erickson, B. J., Hellman, M.D., & Jacobs, J.J. (2015). Do complication rates differ by gender after metal-on-metal hip resurfacing arthroplasty? A systemic review. Clinical Orthopaedics and Related Research, 473(8), 2521-2529.
[4] Pinnow, E., Herz, M., Loyo-Berrios, M., & Tarver, M. (2014). Enrollment and monitoring of post-approval studies for medical devices mandated by the Food and Drug Administration. Journal of Women's Health, 23(3), 218-233. doi: 10.1089/jwh.2013.4343.

populations.[5] These efforts should be built upon within medical device trials. Ensuring researchers address sex and gender differences is not only integral to improving safety, but to advancing our understanding of how sex and gender affect all aspects of health.

3. Apply lessons learned from the COVID-19 pandemic to strengthen the agency's approach to decentralizing clinical trials and make research participation more available to an increasingly diverse range of patients.

Women are frequently the health care decision-makers for both themselves and for family members, and they are at times unduly burdened by in-person health care visits. Often, caregiving obligations make it difficult for women to participate in clinical research. Traditional clinical trials typically involve repeated site visits to receive a therapeutic or to engage in routine patient monitoring. Low participation in clinical trials may be in large part due to difficulties accessing in-person clinical sites.[6]

COVID-19 has had significant effects on health care in the U.S. In the midst of a global pandemic, decentralized and siteless trials are more appealing than ever. Decentralized trials can improve patient comfort and increase convenience for research participants.[7] SWHR encourages the FDA to view the current environment as an opportunity to reconsider the conventional trial model. Virtual, siteless, and direct-to-patient trials, as well as hybrid approaches, should all be considered. The FDA can play a major role in shepherding this transition and providing guidance to relevant stakeholders on best practices for moving toward more innovative clinical trials models.

SWHR urges the FDA to incorporate lessons learned during the time of COVID-19 to further evolve device trials, and we encourage the consideration of a shift to innovative trials models within upcoming MDUFA legislation.

4. Coordinate the FDA approach to digital health technologies in order to expand patient access to care while maintaining safety and privacy.

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 across the lifespan. Data gathered through the use of digital technologies may also help researchers learn about the real-world effects of interventions. 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.[8]

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[5] US FDA (2020). Enhancing the diversity of clinical trial populations – Eligibility criteria, enrollment practices, and trial designs. Accessed at: https://www.fda.gov/media/127712/download

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

[7] 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/

[8] Klonoff, DC, King, F, Kerr, D. (2019). New opportunities for digital health to thrive. *Journal of Diabetes Science and Technology,* 13(2), 159-163.

SWHR encourages the FDA to build upon its ongoing work in the digital health technology field in order to coordinate the use of digital technology within clinical trials. Given potential concerns with digital technology safety and privacy, we also encourage FDA to commit to continued investment in infrastructure that supports ongoing review and surveillance of digital health technology. The FDA should continue to support efforts to provide clarity and transparency surrounding these technologies to improve patient experience while still allowing for innovation within the digital health sphere.

5. Address concerns regarding the possibility of bias within artificial intelligence (AI) and machine learning technology.

AI and deep learning technologies represent major areas of innovation within today's health care environment. For example, AI technology has allowed for more rapid assessment of precancerous changes in the cervix and improved reading of mammograms.[9] However, AI algorithms can also perpetrate biases present in the data from which they learn.

SWHR is supportive of recent FDA efforts to draw attention to the potential of bias within the medical device sphere.[10] We encourage the FDA to continue to work to improve diversity within device trials, especially those that are reliant on AI technology. We look forward to the FDA's leadership in addressing bias in AI and machine learning.

6. Better integrate real-world evidence (RWE) within device approval and decision-making initiatives.

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 capture the impact of an intervention on patient quality of life or reflect differences in health outcomes based on heterogeneity. This type of data can enable more efficient research and development programs and provide information that clinical trials alone may not be able to capture. When generated and used appropriately, this data is an incredibly valuable resource to patients, researchers, and regulators.

SWHR recommends that the FDA continue incorporating these types of data within device approval and decision-making initiatives. SWHR's priority is always to ensure the patient's voice is heard and is integrated throughout the research and design, approval, and post-market monitoring processing. The use of RWE may be an important method of addressing these needs, especially as related to ongoing post-market review for safety and efficacy concerns. We encourage CDRH to continue to build RWE commitments into MDUFA V.

[9] Erickson, Lucy (2020). The promise and peril of AI in women's health. Accessed at: https://swhr.org/the-promise-and-peril-of-ai-in-womens-health/
[10] Jerich, Kat. (2020). At a meeting of the agency's Patient Engagement Advisory Committee, officials stressed the necessity of ensuring there's diversity in the data used to train algorithms. Health Care IT News. Accessed at: https://www.healthcareitnews.com/news/fda-highlights-need-address-bias-ai

7. Consider the needs of pregnant individuals within clinical device trials.

Each year in the United States, 6 million women are pregnant[11] and nearly 4 million women give birth.[12] Pregnant individuals have historically been excluded from most clinical trials. In 2018, the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC), established by the 21st Century Cures Act, released a report recommending the inclusion of pregnant women and lactating women in clinical research, although this effort focused primarily on medication-related trials as opposed to device trials. SWHR encourages the FDA to consider how best to address the needs of the pregnant individuals within device research and development, as this focus has largely been left out of recent efforts to include pregnant people within the clinical trials conversation.

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SWHR is grateful for the opportunity to provide feedback to the FDA on MDUFA V. We look forward to continued opportunities to collaborate with the FDA and other stakeholders over the coming months. If you have any questions, please do not hesitate to contact SWHR's Director of Public Policy and Government Affairs, Melissa Laitner, PhD, MPH, at melissa@swhr.org.

Sincerely,

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

[11] 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
[12] 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