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Submitted electronically to CCRWHRFI@od.nih.gov.

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Re: Request for Information: Inviting Comments to Inform the National Institutes of Health on the Intersection of the SARS-CoV-2/COVID-19 Pandemic and the Health of Women

The Society for Women's Health Research (SWHR) is pleased offer comments to the National Institutes of Health (NIH) Office of Research on Women's Health (ORWH) and the NIH Coordinating Committee on Research on Women's Health (CCRWH) in response to the Request for Information (RFI): Inviting Comments to Inform the NIH on the Intersection of the SARS-CoV-2/COVID-19 Pandemic and the Health of Women.

SWHR—a more than 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, appreciates that ORWH and CCRWH are seeking information on research gaps and opportunities on the intersection of the health consequences of SARS-CoV-2 infection/COVID-19 and post-acute sequelae of SARS-CoV-2 infection (PASC), or long COVID, and the health of women. As noted in the RFI, there are several areas specific to COVID-19 and long COVID infections at the intersection of women's health—including sex and gender differences, reproductive health issues, and mental health conditions as well as gaps and opportunities related to the introduction of the COVID-19 vaccine—that provide opportunities for us to further our knowledge base in order to improve the health of women.

The COVID-19 pandemic represents a pivotal point in our nation's approach to science. At a systems level, it revealed our nation's capacity to prepare for and respond to a public health pandemic from both a research and public health perspective. At the population level, it reminded us of the importance of considering women's unique health lens through the context of a public health crisis and illuminated many societal inequities, including inequities that stem from our nation's health care system.

SWHR appreciates the opportunity to respond to this RFI. While there are many research opportunities and challenges for NIH to explore with respect to the intersection of COVID-19 and the health of women, SWHR will highlight a few areas for consideration as ORWH and CCRWH set their research priorities.

The Role of COVID-19 and Long COVID in Women’s Life Course

Unmistakably, much is still being learned about long COVID and its effects on the body, including why the disease appears in some but not others and why it seems to appear disproportionately in women. Beyond studying the biological drivers of long COVID, there are additional research opportunities that relate to women specifically.

Pregnancy and Postpartum. We saw firsthand during the COVID-19 crisis the ramifications that not including pregnant populations in clinical trials can have. As a result of this population not being included in trials related to the COVID-19 vaccine, women and their health care providers were left to make health care decisions based on incomplete data. Moving forward, we must ensure that pregnant populations are included in trials, as appropriate, to improve health outcomes and to capture this critical population. Potential research moving forward may explore whether long COVID can affect a woman’s reproductive health, the effect of long COVID on a pregnant person and whether any health conditions are prompted or exacerbated by it, and long COVID’s effect on a woman postpartum.

Women’s Mental Health. While there have already been reports of the COVID-19 pandemic’s general effect on mental health, including more adults reporting symptoms of anxiety or depressive disorders,¹ it will also be important to study how the mechanisms of post-COVID/long COVID could affect women’s mental health.

In a cohort study conducted by Jin Yin-tan Hospital and published in *The Lancet* on the health consequences of COVID-19, authors found that many COVID-19 patients experienced mental health symptoms, including anxiety and depression, six months after symptom onset.² Of note, the authors found that “being a woman and severity of illness were risk factors for persistent psychological symptoms. Female SARS survivors had higher stress levels and higher levels of depression and anxiety.” Determining whether these psychological symptoms and other common post-COVID symptoms, including concentration or memory problems and sleep disturbance, are the result of specific effects of COVID-19 on the brain, the immune system, or other organ systems; the traumatic aspects of having COVID-19; or the despair patients

¹ Panchal, N., Kamal, R., Cox, C., Garfield, R., (2021), The Implications of COVID-19 for Mental Health and Substance Use, Kaiser Family Foundation. <https://www.kff.org/coronavirus-covid-19/issue-brief/the-implications-of-covid-19-for-mental-health-and-substance-use/>. Accessed 2 May 2022.

² Huang, C., Huang, L., Wang, Y., Li, X., Ren, L., Gu, X., Kang, L., Guo, L., Liu, M., Zhou, X., Luo, J., Huang, Z., Tu, S., Zhao, Y., Chen, L., et al. (2021), 6-Month Consequences of COVID-19 in Patients Discharged from Hospital: A Cohort Study, *The Lancet*, 297: 220-232. [https://doi.org/10.1016/S0140-6736\(20\)32656-8](https://doi.org/10.1016/S0140-6736(20)32656-8)

experience from long-term breathing problems or fatigue,³ as described by Lauri Pasch, PhD, a psychologist at the University of California, San Francisco, will be vital for better understanding COVID-19 and improving health outcomes for women.

Strategic Approaches to Enhance the Inclusion of Women of Diverse Backgrounds in Research Studies and Clinical Trials

Equally important to identifying research opportunities at the intersection of the COVID-19 pandemic and the health of women is ensuring that women, including women of color and pregnant and lactating populations, are included in research studies and clinical trials and that the resulting data are stratified with respect to sex. Representation of these populations is critical not only for providing needed insight into the potential biological factors associated with long COVID, but also for ensuring that any diagnostics or treatments are safe and effective for each segment of the population.

While strides have been made related to the inclusion of women in clinical trials, in order to improve the *diversity* of women within studies and clinical trials, researchers must take steps to address the key barriers that inhibit their participation. Restrictive trial criteria (e.g., exclusionary criteria concerning comorbidities that predominately affect women or omitting pregnant and lactating populations) and accessibility or lack thereof (e.g., caregiving responsibilities, transportation to the trial site) are barriers that affect that participation of women and other vulnerable populations.

While SWHR recognizes that ORWH and CCRWH are aware of the myriad barriers to trial participation (lack of awareness of clinical trial opportunities, caregiving responsibilities, transportation logistics, ability to take time off of work, mistrust of clinical trials, language barriers, specific trial eligibility criteria, etc.), SWHR recommends the following as potential methods for enhancing the inclusion of women in research studies and clinical trials:

- **Engaging Communities as Partners.** To improve health equity, there is a need to engage communities as partners—and not just participants—in health research programming. Prioritizing community-based participatory research that incorporates multiple perspectives could yield more positive and inclusive results for research. There is also an overarching need to train all researchers, no matter their background, to work with communities and individuals that are different from them.
- **Diversifying the Health Research Workforce.** Diversifying the health research workforce is a crucial strategy to expand the target populations for research investments and affect how these populations are engaged with or represented in studies. Research has

³ What is Long COVID? The Physical and Psychological Symptoms and Management, Mental Health Resources for Crises, University of California, San Francisco Department of Psychiatry and Behavioral Sciences. <https://psych.ucsf.edu/copingresources/longcovid#:~:text=COVID%2D19%20patients%20had%20more,health%20symptoms%20are%20very%20significant>. Accessed 2 May 2022.

shown that researchers from underrepresented groups are more likely to research the particular health needs of underserved and underrepresented communities, especially their own.⁴

More diverse research teams also lead to improved outcomes. By including multiple perspectives, teams can more creatively solve problems and consider questions or aspects of the research work that might not otherwise be apparent.⁵ Moreover, researchers who look like or are familiar with the communities they study run into fewer communication barriers and perceptions of being an outsider, both of which can hinder community participation. Study participants may prove more forthcoming with information when they feel investigators are more understanding of their lived experiences, producing better research outcomes. This also highlights the need for trainees from diverse backgrounds to be equipped with the tools they need to pursue health research career paths. As for researchers who are from different backgrounds than study participants, investments should be made to build trust, addressing both communication and participation gaps.

- **Considering How to Reduce Trial Participation Burden.** As mentioned above, women disproportionately serve as family and community caregivers, often having to balance work and caregiving responsibilities.⁶ As studies and trials are being developed, every effort should be made to reduce the burden, to the extent possible, that participation in a clinical trial may involve. Special attention should be paid to the challenges that the targeted communities specifically face. According to a commentary in *Cell Reports Medicine*, attention should be given to “geographic location of trial sites; an understanding of how the community receives trusted information (thus informing educational information and invitations to participate); engagement with local institutions of faith, gathering places, and networks; and importantly, translation of all participant-facing materials....”⁷

Addressing Career Development and Other Needs to Promote Research Investigating Sex and/or Gender Differences in Health

There are still significant gender disparities in health care. A 2014 survey from The National Pain Report and the non-profit For Grace found that 90% of women felt they were discriminated against by the health care system and 84% felt they were treated differently because they were

⁴ Gibbs, K.D., Griffin, K.A. (2017), What Do I Want to be with My PhD? The Roles of Personal Values and Structural Dynamics in Shaping the Career Interests of Recent Biomedical Science PhD Graduates. *Life Sciences Education*. <https://doi.org/10.1187/cbe.13-02-0021>

⁵ Ibid.

⁶ Women and Caregiving: Facts and Figures, National Center on Caregiving at Family Caregiver Alliance. <https://www.caregiver.org/resource/women-and-caregiving-facts-and-figures/>. Accessed 2 May 2022.

⁷ Bierer, B.E., Meloney, L.G., Ahmed, H.R., White, S.A., (2022) Advancing the Inclusion of Underrepresented Women in Clinical Research, *Cell Reports Medicine*, Vol. 3, Issue 4, 2666-3791, <https://doi.org/10.1016/j.xcrm.2022.100553>

women.⁸ A 2018 piece in *Circulation* medical journal found that while women with acute myocardial infarction (AMI) were more likely to present with more than three non-chest pain symptoms (62% compared to 54.8% of men), their health care providers were less likely to attribute their symptoms to heart disease in comparison with men.⁹ For patients who have to meet a certain threshold of a given disease or condition, if women's symptoms are not taken as seriously by their providers, they could be at a disadvantage for being enrolled in a given clinical trial. There are important career development considerations and unconscious biases that must be addressed on the provider side in order for research into sex and/or gender differences in health to be successful.

For researchers, SWHR encourages the NIH to consider how to provide additional training for researchers on integrating sex as a biological variable (SABV) into the conduct and reporting of basic and clinical research. Ideally, this training would accompany information on how women have historically been excluded from clinical trials and how the gender bias in research has slowed our advancement in producing science and medical advances that benefit everyone. The NIH may wish to build off of the ORWH's SABV Primer Supplement, a course that includes modules designed to help the biomedical research community account for and appropriately integrate SABV across the full spectrum of biomedical sciences.

Additionally, while the NIH Policy on SABV represented an important step in addressing inattention to sex influences in biomedical research and enhancing reproducibility of biomedical research studies, the policy lacks accountability mechanisms, requesting that researchers "consider" design studies that take sex into account or explain why it isn't incorporated. SWHR encourages NIH to consider how it might incorporate additional accountability mechanisms into all aspects of its research process, including publications or, at a minimum, present incentives that would promote better adherence to the policy. Achieving policy adherence is critical for driving discoveries related to sex differences and for ensuring that future research is generalizable.

Finally, SWHR would urge that any research studies related to long COVID and the health of women need to be intersectional, allowing for data disaggregation by race or ethnicity plus gender. It is not enough to understand the impact of COVID-19 on women; we must also understand how it differs across groups of women.

SWHR thanks ORWH and CCRWH for the opportunity to provide feedback on this important effort. We are pleased to see the attention being paid to long COVID's effect on women

⁸ National Pain Report Readers' Survey of Women in Pain Attracts Robust Response (2014). <https://www.prnewswire.com/news-releases/national-pain-report-readers-survey-of-women-in-pain-attracts-robust-response-274878541.html>. Accessed 6 May 2022.

⁹ Lichtman, J.H., Leifheit, E.C., Safdar, B., Bao, H., Krumholz, H.M., Lorenze, N.P., Daneshvar, M., Spertus, J.A., and D'Onofrio, G. (2018), Sex Differences in the Presentation and Perception of Symptoms Among Young Patients with Myocardial Infarction. *Circulation*, 137:781-790. <https://doi.org/10.1161/CIRCULATIONAHA.117.031650>

through this RFI and look forward to continued opportunities to engage on this issue. If you have questions, please contact me at kathryn@swhr.org or SWHR's Chief Advocacy Officer Lindsey Horan at lindsey@swhr.org.

Sincerely,

A handwritten signature in black ink that reads "Kathryn G. Schubert". The signature is written in a cursive, flowing style.

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