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December 7, 2020

Submitted electronically to: <https://www.regulations.gov>

Francis S. Collins, MD, PhD
Director, National Institutes of Health
Office of the Director
One Center Drive
Room 126, Building 1
Bethesda, MD 20892-0160

Re: NOT-OD-21-018: Request for Information (RFI): Inviting Comments and Suggestions on the NIH-Wide Strategic Plan for COVID-19 Research

Dear Dr. Collins,

The Society for Women's Health Research (SWHR) is pleased to offer comments in response to the recently released NIH-Wide Strategic Plan for COVID-19 Research. We write specifically in response to Docket No. NOT-OD-21-018, "Request for Information (RFI): Inviting Comments and Suggestions on the NIH-Wide Strategic Plan for COVID-19 Research."

SWHR is a 30-year-old national education and advocacy nonprofit dedicated to promoting research on biological sex differences in disease and improving women's health through science, policy, and education. 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.

SWHR strongly supports the NIH's goal to rapidly mobilize diverse stakeholders, including the biomedical research community, industry, and philanthropic organizations, through new programs and existing resources, to lead a swift, coordinated research response to the ongoing global COVID-19 pandemic. With this in mind, the five key priorities identified in the plan: improving fundamental knowledge of the disease, advancing detection and diagnosis, advancing treatment, improving prevention, and preventing and redressing poor outcomes in disparity populations, are critical to achieving NIH's goal.

Across priority areas, SWHR hopes to draw attention to differences in disease course and outcomes as related to sex



and gender, as well as the multitude of ways the COVID-19 pandemic disproportionately impacts women. With these topics in mind, we offer specific recommendations, detailed below.

1. Better emphasize the influence of sex and gender across all five key priority areas.

The COVID-19 pandemic provides a stark example of why sex and gender must be critical considerations in pandemic response and preparedness. COVID-19 appears to be infecting similar numbers of women and men, but the majority of people dying are men.¹

These disparities are not surprising, given what we know about infectious disease. Cultural and behavioral differences between genders play a prominent role in disease exposure. Women and men also differ in immune responses to infection.² Infectious disease research has historically overlooked sex as a biological variable,³ meaning there is much we still do not understand about how sex affects immune response and disease outcomes.

For example, in considering priority area four, “Improve Prevention of SARS-CoV-2 Infection,” sex as a biological variable should be highlighted as a specific area of need within vaccine trials, and sex and gender should be considered within effective implementation models. Clinical data indicate women and men show differences in immune responses, adverse events, and disease protection following vaccination.⁴ Therefore, there should exist a priori hypothesis within all vaccine trials that sexes will differ in regard to vaccine response. Sex differences should be addressed in considering safety and efficacy, dosing, and scheduling of vaccines. Research into diagnostic and treatment measures must also consider how immune response and disease outcome may differ based on sex.

Per the World Health Organization’s 2007 publication, “Addressing sex and gender in epidemic-prone infectious diseases,” taking sex and gender into account can help us to better understand disease epidemiology, course, and outcomes.⁵ While the current iteration of the plan touches upon the need to conduct research to understand how risk differs based on these factors, SWHR encourages the NIH to more thoroughly highlight sex and gender across all five key priority areas.

2. In addressing long-term outcomes of COVID-19, encourage comprehensive research into sex and gender differences as potential factors placing patients at risk of diagnosis as post-COVID-19 “long haulers.”

As the COVID-19 pandemic progresses, we are seeing patients dealing with serious long-term side effects, despite otherwise testing negative for the disease. These patients, deemed “long haulers,” may have ongoing symptoms similar to those they experienced during acute stages of the disease, or they may face new symptoms. Common long hauler symptoms include brain fog, headaches, insomnia, joint pain, loss of taste or smell,

¹ Global Health 5050 (2020). COVID-19 sex-disaggregated data tracker. Accessed at: <https://globalhealth5050.org/covid19/>

² Van Lunzen, J, Altfeld, M (2014). Sex differences in infectious diseases – Common but neglected. *Jour Infect Diseases*, 209(suppl_3), S79-S80. doi: 10.10893/infdis/jiu159.

³ Ingersoll, MA (2017). Sex differences shape the response to infectious diseases. *PLoS Pathog.*, 13(12), e1006688. doi: 10.1371/journal.ppat.1006688.

⁴ Flanagan, KL, Fink, AL, Plebanski, M, Klein, SL (2017). Sex and gender differences in the outcomes of vaccination over the life course. *Annu Rev Cell Dev Biol.*, 33, 577-99.

⁵ World Health Organization (2007). Addressing sex and gender in epidemic-prone infectious diseases. Accessed at: <https://www.who.int/csr/resources/publications/SexGenderInfectDis.pdf>



shortness of breath, debilitating fatigue, coughing, and body aches.⁶ One paper estimates approximately 10% of patients experience this type of prolonged sickness.⁷

Interestingly, while men tend to face higher mortality rates as a result of COVID-19 diagnoses, women seem more likely to be diagnosed as long haulers. One study suggests women outnumber men 4:1 within the long hauler population. The authors note the typical long hauler is a young woman around 40 years of age without relevant medical history or biological abnormalities.⁸

Scientists have yet to gain insight as to what places individuals at risk for long-term side effects, but the fact that many long haulers are women suggests a potential sex-based component. SWHR is hopeful updates to priority area five, "Prevent and Redress Poor COVID-19 Outcomes in Health Disparity and Vulnerable Populations" will call for specific research into COVID-19 long haul patients, with an emphasis on understanding whether biological sex is a risk factor for long-term symptoms.

3. Address the impact COVID-19 has on routine health care, especially in regards to missed or delayed vaccination and screening or treatment delays for serious illness.

In the past months, many individuals have been hesitant or unable to attend health care visits because of the COVID-19 pandemic, leading to thousands of missed annual wellness visits, vaccinations, and cancer screenings. Further, those already diagnosed with cancer have had their treatments interrupted by lockdowns and hospital overload. The exact toll of the pandemic on cancer patients will not be clear for many years, but one model estimates an additional 10,000 cancer deaths in the next decade because of the pandemic.⁹

For women, missed health care visits have drastically decreased the number of cancer screenings in recent months. One analysis showed that breast and cervical cancer screenings fell by 94% in March compared to the 2017-2019 averages. While screening rates have recently begun to increase again, they have not yet returned to normal.¹⁰

SWHR recommends the NIH address these delays in screening, diagnosis, and treatment within priority area five, "Prevent and Redress Poor COVID-19 Outcomes in Health Disparity and Vulnerable Populations." Engaging in collaborative partnerships to find solutions to these delays should be prioritized in order to maintain population health post-pandemic. Investment in expanded telehealth infrastructure, cost-effective methods of self-screening, and methods of delivering health care outside the traditional clinic setting should be explored. Innovations that arise to meet the challenges of this public health crisis could benefit and transform women's health for years to come.

⁶ UC Davis Health. (2020). Long haulers: Why some people experience long-term coronavirus symptoms. Accessible from: <https://health.ucdavis.edu/coronavirus/covid-19-information/covid-19-long-haulers.html>

⁷ Greenhalgh T, Knight M, A'Court, C, Buxton M, Husain L (2020). Management of post-acute covid-19 in primary care. *British Medical Journal* (370), m3026.

⁸ Davido B, Seang S, Tubiana R, de Truchis P (2020). Post-COVID-10 chronic symptoms: A postinfectious entity?

⁹ Cooney, E (2020). Ignoring cancer care now may trade one public health crisis — Covid-19 — for another, NCI chief warns. STAT News. Accessible from: <https://www.statnews.com/2020/06/19/ignoring-cancer-care-covid-19-nci-sharpless/>

¹⁰ Mast C, Munoz del Rio A (2020). Delayed cancer screenings – A second look. Epic Health Research Network. Accessible from: <https://ehrn.org/articles/delayed-cancer-screenings-a-second-look/>



4. Strengthen emphasis on the specific needs of pregnant and lactating individuals within vaccine and treatment research.

SWHR is supportive of the plan's focus in priority area five, "Prevent and Redress Poor COVID-19 Outcomes in Health Disparity and Vulnerable Populations." Objective 5.2 highlights the need to "[u]nderstand and address COVID-19 maternal health and pregnancy outcomes." Research across a variety of infectious diseases — including the Zika virus, the H1N1 flu virus, and the SARS, MERS, and COVID-19 coronaviruses — suggests pregnancy places women at particular risk for complications.

Accordingly, pregnant and lactating individuals must be included within clinical trials related to disease treatment and/or vaccines. Within current COVID-19 treatment research, people who are pregnant and/or breastfeeding are actively being excluded from federally-funded studies, including the Adaptive COVID-19 Treatment Trial. One recent paper suggests that across more than 300 trials investigating possible COVID-19 treatments, there is near universal exclusion of pregnant people.¹¹

SWHR encourages the NIH to address this topic more specifically within Objective 5.2 in order to emphasize to stakeholders the importance of inclusion. Given COVID-19's outsized impact on the pregnant population, we must stress the need to protect pregnant and lactating individuals through research, instead of preventing them from participating in these studies.

SWHR also encourages the use of stronger language in priority area 4, "Improve Prevention of SARS-CoV-2 Infection," Objective 4.1, "Develop novel vaccines for the prevention of COVID-19." We appreciate the current language that states, "Once safety tests are completed, vaccines will be evaluated in pregnant women and children." However, given ongoing exclusion of the pregnant population within clinical trials, we suggest making it clear that study design should take into account the needs of the pregnant population and should clarify how methodology will allow for the assessment of pregnant individuals. We also strongly recommend including similar recommendations within discussions surrounding research on innovative treatments within priority area 3, "Advance the Treatment of COVID-19," Objective 3.1, "Identify and develop new or repurposed treatments for SARS-CoV-2."

5. In studying long-term socioeconomic and societal effects of COVID-19, consider the influence of gender on economic status as well as within the biomedical workforce.

SWHR applauds the NIH for recognizing how social or structural determinants of health, including mechanisms that generate inequalities within society, affect health care access and quality and how this in turn may impact COVID-19 risk and outcomes. We also commend the NIH for utilizing priority area five ("Prevent and Redress Poor COVID-19 Outcomes in Health Disparity and Vulnerable Populations") to call for improved understanding as to how social determinants of health, including gender, affect factors such as COVID-19 risk and resilience.

¹¹ Whitehead, CL, Walker, SP (2020). Consider pregnancy in COVID-19 therapeutic drug and vaccine trials. *The Lancet*, 395(10237), E92. doi: 10.1016/S0140-6736(20)31029-1



Gender plays an important role in considering long-term economic impact of the pandemic on individuals across the country. Among health care workers deemed essential during the pandemic, almost 7 million citizens are currently employed in low-wage medical support jobs, such as orderlies, phlebotomists, home health aides, and health care service workers. Over 80% of these individuals are women, and the large majority are people of color.¹²

Women also tend to do much of the unpaid caregiving and domestic work at home. Women — and especially women of color — are more likely than men to live in poverty, placing them at increased risk for food insecurity. Women of color are also overrepresented in some of the industries experiencing the biggest job losses due to COVID-19, including child care and hospitality. SWHR hopes the NIH will consider how gender, both directly and indirectly, affects not only COVID-19 risk and health outcomes, but socioeconomic wellbeing and financial stability.

Additionally, the biomedical workforce — more crucial than ever during a global pandemic — is dealing with difficulties of its own. COVID-19 is exacerbating pre-existing challenges facing women and people of color in STEM careers, leading to decreased productivity and loss of women in the workforce. In considering cross-cutting strategies within the NIH-wide Strategic Plan, SWHR strongly believes supporting the research workforce and infrastructure must include specific mention of populations disproportionately impacted, including women. Strategies to mitigate harm should prioritize addressing the needs of these populations most urgently.

SWHR applauds the NIH's efforts in developing this plan, which will act as a living document to reflect the ongoing battle against COVID-19. We are hopeful the agency will continue to take into account the specific research, prevention, treatment, and mitigation needs for women.

We are grateful for the opportunity to provide feedback on the NIH-Wide Strategic Plan for COVID-19 Research. 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

¹² Kinder, M (2020). Meet the COVID-19 frontline heroes. *Brookings Institute*. Accessed at: <https://www.brookings.edu/interactives/meet-the-covid-19-frontline-heroes/>