

58th Meeting of the National Institutes of Health (NIH)
Advisory Committee on Research on Women's Health (ACRWH)
Office of Research on Women's Health (ORWH)
Bethesda, MD
April 12, 2023

Members Present

Garnet L. Anderson, Ph.D.
Irene Aninye, Ph.D.
Amanda Bruegl, M.D.
Stephen Higgins, Ph.D.
Reshma Jagsi, M.D., D.Phil.
Hendrée Jones, Ph.D.
Alyson J. McGregor, M.D.
Thelma Mielenz, Ph.D.
Alexandra Noël, Ph.D.
Judy Regensteiner, Ph.D.
Michelle Robinson, D.M.D.
Yoel Sadovsky, M.D.

Phyllis Sharps, Ph.D.
Melissa Simon, M.D.
Kimberly J. Templeton, M.D.

ORWH Leadership Present

Janine Clayton, M.D., FARVO, Director
Samia Noursi, Ph.D., Associate Director for
Science Policy, Planning, and Analysis
Xenia T. Tigno, Ph.D. Associate Director for
Careers

Other NIH Leadership Present

Joni L. Rutter, Ph.D. Director, National Center
for Advancing Translational Sciences (NCATS)

Call to Order

Samia Noursi, Ph.D., ACRWH Executive Secretary and ORWH Associate Director, Science Policy, Planning, and Analysis, called the virtual meeting to order at 9:31 a.m. Committee members introduced themselves and approved the minutes of the 57th ACRWH meeting held on October 18, 2022.

ORWH Director's Report

Dr. Noursi introduced Janine A. Clayton, M.D., FARVO, Director, ORWH, who delivered the Director's Report:

Opening Remarks. Dr. Clayton honored the memory of Congresswoman Patricia Schroeder (1940-2023), a cosponsor of the Women's Health Equity Act of 1990 that created ORWH. She also shared new data on maternal mortality (MM) from a 2023 World Health Organization report that showed that the number of maternal deaths in the United States worsened from 2000-2020, while peer nations reduced MM. Dr. Clayton also reported on a 2022 Commonwealth Fund report on health care trends in high income countries that found that the U.S. has the highest death rates for avoidable or treatable conditions, the highest maternal and infant mortality, the highest rate of people with multiple chronic conditions, and an obesity rate that is nearly twice the average. To address such concerns, ORWH is partnering with six NIH Institutes, Centers, and Offices (ICOs) to issue new funding opportunities (RFA-OD-23-013 and RFA-OD-23-014) to advance rigorous research on understanding chronic conditions that are under-studied among women, using the framework endorsed by ACRWH at the 2021 Women's Health Conference.

NIH Updates. Joni L. Rutter, Ph.D., has been named Director of the National Center for Translational Science (NCATS), bringing the number of ICOs led by women to 11. Dr. Clayton noted release of the first "NIH-wide Strategic Plan for Diversity, Equity, Inclusion, and Accessibility, 2023-2027." She also acknowledged Renee Wegrzyn, Ph.D., Director of the Advanced Research Projects Agency for Health (ARPA-H) that celebrated its first anniversary on March 15, 2023.

Funding, Budget, and Legislative Updates. ORWH's total budget increased from \$51.5 million in FY2021 to \$60.6 million in FY2022. ORWH's FY2022 extramural grant investments totaled \$43,222,779. Its funding portfolio includes the Specialized Centers of Research Excellence (SCORE) (27.1 percent); Building Interdisciplinary Research Careers in Women's Health (BIRCWH), including supplements (25.0 percent); other IC Co-Funds (20.4 percent); Sex/Gender R01 (8.9 percent); Underrepresented, Understudied, and Underreported Populations (U3) Administrative Supplements (7.3 percent); Career Programs (7 percent); and Sex/Gender Administrative Supplements (4.3 percent). Each of these signature research programs is co-funded by several ICs. ORWH's FY2022 investment in Career Programs (including Loan Repayment Awards) totaled \$14,004,153. BIRCWH received 77.3 percent of these funds.

ORWH received \$76.48 million for FY2023, including \$5,000,000 to fund additional BIRCWH fellows at existing sites, \$10,000,000 to establish the Office of Autoimmune Disease Research within ORWH, and \$2,000,000 for ORWH to contract with the National Academy of Science, Engineering, and Medicine (NASEM) to conduct a study on the gaps in women's health research across all NIH ICs with a report of findings and recommendations due to Congress within 18 months.

Office of Autoimmune Disease Research (OADR). The recommendation to establish OADR originated in a 2022 NASEM report, "Enhancing NIH Research on Autoimmune Disease." Recognizing that autoimmune diseases predominantly affect women, Congress mandated that ORWH create OADR to coordinate development of a multi-IC strategic research plan; identify emerging areas of innovation and research opportunity; coordinate and foster collaborative research across ICs; annually evaluate the NIH Autoimmune Disease Research (ADR) portfolio; provide resources to support planning, collaboration, and innovation; and develop a publicly accessible central repository for ADR. NIH's investment in ADR has increased over the past five years, reaching \$946,356,182 in FY21. Providing pathways to interdisciplinary collaboration across ICOs is the key to meeting the challenges of ADR research.

Dr. Clayton reviewed current and future planned OADR activities in infrastructure, scientific direction, public engagement, and funding opportunities. With respect to Infrastructure, ORWH has created two full-time staff positions, including the OADR Director. ORWH is also tapping into NIH platforms such as the Office of Intramural Training and Education (OITE) and the Accelerating Medicines Partnership® Autoimmune and Immune-Mediated Diseases (AMP® AIM) to train the future workforce and host comprehensive scientific workshops focused on ADR; identifying existing datasets and frameworks both within and beyond NIH; and coordinating within NIH to develop a core set of ADR Common Data Elements to expand and codify the recognition of autoimmune diseases. With respect to scientific direction, ORWH has reviewed the comprehensive NASEM report regarding identified issues, areas for improvement, and recommendations to inform next steps. It is establishing a Coordinating Committee on Autoimmune Disease Research (CCADR) that will provide a structured forum to leverage the autoimmune disease research expertise housed across different ICOs to expand on existing opportunities and develop new initiatives. In addition, ORWH is developing an OADR Strategic Plan. With respect to public engagement, ORWH has recently met with patient advocate groups and is developing a Request for Information (RFI) to solicit input from the public and community constituents. Finally, with respect to funding opportunities, ORWH has issued an open call for ADR meritorious applications through existing co-funding platforms, identified FY23 funding pathways for both extramural and intramural projects, and plans to release ORWH-led funding announcements in FY24.

Policy and Scientific Updates. Dr. Clayton briefly reviewed the history of inclusion policies at NIH, noting the recent Workshop on Inclusive Participation in Clinical Research (March 30-31, 2023) sponsored by the National Institute on Minority Health and Health Disparities (NIMHD). She highlighted NIH inclusion

requirements for NIH-defined Phase III clinical trials that mandate that entities conducting such trials are designed for valid analyses by sex/gender, race, and ethnicity. Recently updated instructions for annual Research Performance Progress Reports (RPPRs) include a statement indicating the status of analyses of the primary outcome by sex or gender, race, and ethnicity, and reporting results of these analyses in the “Project Outcomes” section. Dr. Clayton also provided brief updates on other diversity- and equity-related policies and initiatives that are NIH-wide. These include a new report from the NIH UNITE program; a new Request for Applications (RFA) on “Understanding and Addressing the Impact of Structural Racism and Discrimination on Minority Health and Health Disparities” from NIMHD; Community Partnerships to Advance Science for Society (ComPASS); the Common Fund Transformative Research to Address Health Disparities and Advance Health Equity; updated eRA Commons guidelines that include racial discrimination as a specific concern grantee institutions can report; the NIH Data Dashboard that addresses structural racism; the Power of an Inclusive Workspace Recognition Project; the BRAIN Initiative’s Plan for Enhancing Diverse Perspectives; and the Diversity, Equity, Inclusion and Accessibility (DEIA) Prize competitions.

New sections of the NIH website include SABV Impact Pages and for the ORWH website an expanded Sex and Gender webpage that offers interactive explorations of how sex and gender impact health and disease.

ICO Collaborations. Dr. Clayton reviewed ORWH collaborations with ICOs.

HIV/AIDS. Despite immense scientific advances, women, and girls, including transgender and gender nonconforming people, remain disproportionately affected by HIV. About half of all new infections worldwide are among women. In 2021, 20 million women and girls were living with HIV, about 54 percent of all people with HIV. In 2022, Women’s HIV research funding at NIH was estimated at just under \$500 million. Despite this investment, research on women and HIV is underrepresented within the NIH HIV research portfolio. The Office of AIDS Research (OAR)’s signature program on HIV and women is a new partnership with ORWH that aims to promote the NIH vision for women’s health, where all women, including transgender women and individuals assigned female at birth, receive evidence-based, gender-affirming, tailored HIV prevention, care, and treatment. This program also supports women in science careers to reach their full potential. Together, OAR and ORWH recently launched an NIH-wide HIV and Women Working Group to identify gaps and priorities at the intersection of women’s health and HIV and hosted a joint symposium, “OAR-ORWH Symposium: Considerations from Across the Lifespan,” at the 13th International Workshop on HIV and Women on February 18, 2023.

Maternal Mortality. Dr. Clayton shared data from the National Center for Health Statistics (NCHS) for 2018-2021 that showed statistically significant increases in maternal mortality for White, Black, and Hispanic women across all age groups in 2021. According to a 2023 article by Thoma and DeClercq (*Obstetrics & Gynecology*), pregnancy-related mortality was significantly higher in 2021 across all races and ethnicity and rural–urban residence categories, compared with during- and pre-pandemic levels. To tackle the crisis of preventable maternal mortality, ICs within NIH have joined forces to implement the Improving Maternal Health and Pregnancy Outcomes Vision for Everyone (IMPROVE) initiative. In FY22, NIH received \$30 million in appropriations to launch a national network of Maternal Health Research Centers of Excellence (COEs) through the IMPROVE Initiative. On March 9, ORWH hosted an IMPROVE Awardee Workshop to share lessons learned from IMPROVE projects and identify research gaps in the field. A hybrid workshop on “Innovative Ways to Improve Maternal Health,” is scheduled for May 8-9, 2023.

Dr. Clayton congratulated the winners of the Maternal Health Diagnostic Challenge. First Place went to Dr. Bethany Hedt-Gauthier, Harvard University, Boston, who led the development of mHealth tools for community health worker-led home-based diagnosis of surgical site infections and anemia post-cesarian delivery. She also reported that ORWH and the Office of Disease Prevention led a 2-day Pathways to Prevention (P2P) Workshop in December focusing on “Identifying Risks and Interventions to Optimize Postpartum Health.” A report from the Workshop’s independent panel identifying research gaps and recommendations for advancing the field is available and open for comment through April 21, 2023.

Intimate Partner Violence (IPV). Dr. Clayton shared findings from a recent article by Scoglio et al. (*JAMA Open Network*, 2023) that measured mental health outcomes among women during the pandemic using data drawn from three prospective, population-based, longitudinal U.S. cohort studies. The analysis revealed that IPV experiences at the start of the pandemic were associated with higher reports of depression, anxiety, and posttraumatic stress symptoms, as well as poorer sleep quality, shorter sleep duration, increased use of alcohol, and use of alcohol or other substances to cope with stress. ORWH partnered with the National Institute of Nursing Research (NINR) and other ICOs on a recent RFI on “Future Directions in Violence Against Women Research” (NOT-NR-23-008).

Careers. A new NASEM report, “Advancing Antiracism, Diversity, Equity, and Inclusion in STEMM Organizations: Beyond Broadening Participation” (2023) contained eight recommendations. Dr. Clayton highlighted three of them: Develop and implement inclusive plans, promote an accessible culture, and address bias; collect data on demographics and educational outcomes, and fund research on best practices; and redress bias and discrimination in organizational processes. She also announced a new RFI on “Re-envisioning U.S. Postdoctoral Research Training and Career Progression within the Biomedical Research Enterprise” designed to understand the perspectives and experiences of recent, current, and potential postdoc trainees to explore ways to address fundamental challenges faced by the postdoc trainee community. Responses to the RFI are due by April 14, 2023.

With co-funding from nine ICOs, ORWH’s Galvanizing Health Equity Through Novel and Diverse Educational Resources (GENDER) R25 (RFA-OD-22-015) has been issued. Its objective is to help meet the need for gender-specific training in science, medicine, and allied health professions by supporting development of gender-focused courses, curricula, and methods for the extramural community. The initial application due date is June 27, 2023. The National Library of Medicine is the administrative lead.

Dr. Clayton described the “braided river” as a new metaphor for thinking about career paths (Batchelor et al, *EOS*, 2021). People take many paths through school and weave careers around an assortment of circumstances such as rearing families, serving in the military or volunteer corps, fulfilling caregiving responsibilities, and reengaging with formal education. These experiences bring new ideas that offer interdisciplinary solutions to science.

An RFA was published in November 2022 for the “Team Science Leadership Scholar Program (LSP) in Women’s Health, Autoimmune and Immune-Mediated Diseases” with a February 2023 receipt deadline. A joint initiative of ORWH, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and AMP® AIM, LSP is a pilot program to support and train women’s health scholars by helping them acquire and hone team science leadership and mentoring skills that will enable them to become large consortium team leaders. Dr. Clayton also announced a new RFA co-funded by ORWH and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) titled “Advancing Gender Inclusive Excellence (AGIE)” to address and intervene with systemic gender-based inequities impacting the STEMM (Science, Technology, Engineering, Mathematics, and Medicine) academic and research workforce. The opening date is May 1, 2023.

Dr. Clayton shared a sketch from last year's NIH Partnership Summit that had the theme "Reimagining Women in the Bioengineering, Technology, and Data Science Ecosystem." The report from the Summit is available on the ORWH website. The sketch visually highlighted the finding that women are outperforming as entrepreneurs while navigating an M-shaped career path; however, there remain funding gaps and a need to address the "sticky floor" issue. Women in data science were also celebrated during Women's History Month on the Office of Data Science Strategy (ODSS) Director's blog posted on March 31, 2023, that highlighted Dr. Clayton, among other female NIH leaders.

Events

Dr. Clayton congratulated the National Institute of Dental and Craniofacial Research (NIDCR) on its 75th anniversary. During Black History Month 2023, NIDCR and ORWH co-sponsored a "fireside chat" with Jeanne Sinkford, D.D.S., Ph.D., a legend in oral health, human subject research, and career development. She also announced that "Menopause and Optimizing Midlife Health for Women" will be the focus of the virtual 7th Annual Vivian W. Penn Symposium on May 16, 2023. Upcoming lectures in ORWH's Diverse Voices quarterly lecture series will include "Intersectional Approaches to Substance Use and Misuse" on July 27 and "Social Determinants and Uptake of Infectious Disease Control Measures" on September 28.

Research at the Intersection of Translational Science and Women's Health

Dr. Clayton introduced Joni L. Rutter, Ph.D. Director, National Center for Advancing Translational Sciences (NCATS). NCATS studies the science of translational research across all diseases.

There are over 10,000 diseases. Disease burden is moving in the wrong direction, despite an increase in tools and technologies to address them. For example, only 5 percent of the 10,000 diseases have treatments or cures. It takes 10-15 years of development to move a drug from early development to the medicine cabinet at an average cost of \$4.6 billion. Currently, tools used for drug development involve 2D cell culture and animal models that do not always predict human response. There is a need to move beyond this "one size fits all" approach. To that end, NCATS is re-engineering the translational pipeline by addressing long-standing operational, administrative/workforce development, and scientific bottlenecks so that new treatments reach people faster. For example, solutions to operational bottlenecks may include the use of adaptive clinical trial designs, master protocols, and basket/umbrella trials involving several small, related trials. The administrative burden of a trial start-up may be reduced by implementation of streamlined business and regulatory processes. Scientific bottlenecks, such as Insufficient tools and technologies to predict toxicity and efficacy of new drugs, can be ameliorated via platform-based tissue/organ on chips, 3D bio-fabrication, gene-targeted therapies, and drug development via artificial intelligence and machine learning. Thus, NCATS' vision identifies three audacious goals: 1) more treatments 2) for all people 3) more quickly. Specifically, the Center seeks to increase the number of effective treatments for diseases from a long-standing 5 percent to 25 percent, while dramatically increasing inclusivity in all areas it supports, and enabling diagnostics and therapeutics to reach people twice as fast as they currently do. To accomplish these goals, NCATS implements four approaches: 1) Understanding what's similar across diseases to spur multiple treatments at a time; 2) Developing models that better predict a person's reaction to a treatment; 3) Enhancing clinical trials so the results more accurately reflect the patient population; and 4) Leveraging real-world data and data science approaches to address public health needs.

Over two-thirds (68 percent) of NCATS' budget is earmarked for the Clinical and Translational Science Awards (CTSA) program that funds a nationwide network of research institutions with consortium-wide

resource centers and collaborative initiatives. The remainder of the budget is devoted to activities such as supporting intramural and extramural programs, including drug repurposing, diagnostics, ethics, and training; stimulating transformative efforts and platform approaches through the Cures Acceleration Network; and enabling patient-centric innovations for studying, treating, and diagnosing rare diseases.

Specific Efforts in Translational Science in Women's Health. Women have double the risk of experiencing an adverse reaction to drugs than do men. Although women now comprise roughly half the participants in NIH-funded clinical trials, the same is not true for preclinical research; most studies involve only male-derived cells and male animals. For ethical reasons, pregnant women often are not allowed to participate in studies of new drugs. As a result, there is a lack of information about women's health and female physiology, impeding understanding of how new and existing drugs affect women.

The CTSA program was established in 2006. With over 60 institutions, it is the largest within NIH to support clinical research. The CTSA Clinical and Translational Science (CTS) Pilot Award Program provides modest support for new and innovative research projects that provide valuable preliminary data to investigators planning more comprehensive studies and research applications. Approximately 11 percent of pilots (82 of 751) were solely focused on women's health research with 32 (4.3 percent) partially studying women's health. These studies included exploring recovery-oriented support factors to sustain opioid addiction recovery in parenting women, expanding knowledge about and evaluating services for incarcerated pregnant and postpartum women, improving cardiovascular risk prediction in women, and an integrated smoking cessation and breastfeeding program to reduce cancer disparities. CTSA's Trial Innovation Network (TIN) is an initiative providing clinical trial infrastructure for the HEAL Pain Management Effectiveness Research Network (ERN) as part of the NIH Helping to End Addiction Long-term (HEAL) initiative. Women's health studies within ERN include a clinical trial seeking to address opioid overprescribing after cesarean delivery and another to determine the effectiveness of perioperative ketamine for prevention of post-mastectomy pain syndrome (PMPS).

CTSA also supports the National COVID Cohort Collaborative (N3C) data enclave, which is the largest collection of real world COVID-19 data in the United States with records on over 17 million people. Its Pregnancy Clinical Domain Team aims to leverage N3C data to gain insights into pressing COVID-19 questions around pregnancy, including understanding the incidence, timing, and severity of COVID-19 in pregnant women and associated maternal and infant outcomes. One group used N3C to develop the Temporal Events Detector for Pregnancy Care (TED-PC) algorithm that can determine the gestational week of clinical events in electronic health records during pregnancy to help evaluate the impact of COVID-19. N3C data was also used to examine if comorbidities and biomarkers impact COVID-19 differently in men and women. Researchers evaluated associations of comorbidities, inflammatory biomarkers, and severe outcomes in over 570,000 adult patients admitted for COVID-19 at hospitals or emergency rooms in 2020 and 2021. The top four fatal comorbidities in both sexes among patients hospitalized for COVID-19, were the same (moderate to severe liver disease, renal disease, metastatic solid tumor, and myocardial infarction) but women had a higher magnitude of risk than men. Similarly, abnormal levels of several proteins were significantly associated with death in both sexes; the association was stronger in women than in men.

Revolutionizing Drug Development Approaches. New technologies and better predictive tools are needed to identify and test biomarkers, reduce trial risk, hone patient selection, and explain variable treatment response. This means moving beyond 2D cell lines and mouse models to 3D cell cultures and tissue chip approaches. Technology is now available to take blood from any individual, reverse the patient cells back into stem cells, re-differentiate them into virtually any cell type, and layer them to create organs, e.g., 3D bio-printed skin, lung chips, or multi-organ chips. The next step is to create an

entire “you on a chip.” An example of this strategy is a model of the entire female reproductive system built through the joint efforts of four investigators who had previously been working independently on each component: Teresa Woodruff, Ph.D., Northwestern University on the ovaries; Joanna Burdette, Ph.D. (University of Illinois Chicago) on the fallopian tubes; Julie Kim, Ph.D. (Northwestern), on the uterus; and Spiro Getsios, Ph.D. (Northwestern), on the cervix and vagina. Beth Sefton, Ph.D., at Northwestern, coordinates the work. The Woodruff/Burdette team have also built 3D organoids to test therapeutic treatments of endometriosis and polycystic ovary diseases, as well as the Evatar™, the female reproductive system on a chip, to evaluate how hormones travel within the system and what happens when hormonal changes occur. This work has been completed in collaboration with ORWH and will contribute to a better understanding of how females metabolize drugs, compared to males.

Another example of these new approaches is the Maternal-Fetal Interface on a Chip that aims to reproduce the structure, function, and responses of the fetal-maternal tissue interface (FMI), mimicking health and inflammation. Reducing inflammation at the FMI could help maintain pregnancy and prevent spontaneous preterm birth. The goal is to offer a personalized FMI model to test potential treatments and streamline clinical trials. One study tested the effect of maternal exposure to cadmium (Cd), an environmental toxin, and found significant cell death in maternal cells, but minimal effect on fetal cells.

Tissue Chips. Past experience has shown that people in space tend to age faster than they do on earth. Sending tissue chips into space allows scientists to study physiological issues in aging in a controlled environment. Ultimately, one goal is to study sex differences in aging with this approach. The “you on a chip” concept also lends itself to the development of digital twins. These could be used to overcome the limitations of external control arms in randomized clinical trials, i.e., a subject is his or her own control. A digital twin of one of the female astronauts might be deployed when Americans go to the moon in 2025 in NASA’s Artemis 3 mission.

NCATS is committed to developing new methodologies, such as human cell-based physiological systems for women’s health, that will assess changes in metabolic activity of specific cell types; identify the effects of exposure to hormonal treatment or chemical substances on aspects of reproduction and fertility; include studies of diseases, causes, and adverse events occurring during pregnancy such as pre-eclampsia, infertility or preterm birth, endometriosis and infertility; and allow the co-culture of different cell types under normal and disease states of the female reproductive tract and changes occurring during conception and pregnancy.

Small Molecule Studies. Dr. Rutter highlighted one example of NCATS’ work in small molecule studies that addressed the challenges of breast cancers (particularly triple-negative and HER2+) that metastasize to the brain. Many therapeutic agents effective against breast cancer can’t be used to treat brain metastases, because they cannot cross the blood-brain barrier. NCATS investigators are collaborating with researchers at the University of Manitoba, Winnipeg, to develop high-throughput screening approaches to identify molecules for treating breast-to-brain metastasis. The project developed the only current hematogenic HER+/ERα+ breast-to-brain metastasis human cell model, screened over 6,500 compounds, including about 2,500 cancer drugs; and identified a mechanism by which metastatic breast cancer cells use resident brain cells to avoid being killed by drugs that target the HER2 receptor.

Rare Diseases. Rare diseases is another area in which NCATS works. There are a variety of rare diseases that primarily affect women, e.g., Rett Syndrome. NCATS uses a “more than one disease” approach in studying rare diseases, a public health challenge. Individual medical costs for people with rare diseases is

3-5 times higher than for people who do not have a rare disease, totaling \$400 billion/year in medical costs for the 25-30 million people in the United States who live with a rare disease. To address this challenge, NCATS is focused on developing and streamlining delivery approaches, including somatic cell gene editing, the Accelerated Medicines Program® – Bespoke Gene Therapy Consortium (BGTC), and Platform Vector Gene Therapy – (PaVe-GT).

Advancement of Women in Biomedical Careers. The Women Scientists Advisors (WSA) group within the Division of Preclinical Innovation (DPI) at NCATS developed a new initiative in 2022 in which women scientists from DPI engage with the external Bethesda/DC-area community, particularly students in grades K-12. For grades 6-12, there are panel discussions and 1-on-1 “speed chatting” activities with opportunities for students to ask scientists about their careers. For students in K-5 there are “Translational Science in Action” role playing games, developed by WSA, where students pretend to be scientists approaching various scripted problems and learn science is about teamwork, curiosity, and persistence. This initiative increases visibility of women scientists and encourages development of students’ scientific literacy.

Closing Remarks. Since November 2022, NCATS has been engaged in a strategic planning process and will soon be issuing an RFI. Dr. Rutter encouraged ACRWH members and others to respond by highlighting areas that NCATS should include in its new Strategic Plan.

Discussion. The following key points were made during the discussion following Dr. Rutter’s presentation:

- Currently, the negative and positive feedback system that is prevalent in humans has not been captured on a chip; solving that issue might help address the longevity of the chips. Nor have scientists yet understood how to remove toxicities in cells. These are areas that NCATS is addressing.
- Studies that show people aging faster in space contradict Einstein’s theory of relativity which would suggest people in space should be getting younger. However, in micro-gravity, it is the lack of gravitational pull that seems to have the aging effect. Some studies have demonstrated sex differences in bone loss in people in space.
- NCATS is working to incorporate sex differences in the non-reproductive “organs on a chip.” It has created stem cells to reflect not only sex differences but also differences in diverse populations. These are currently in development mode.
- Dr. Clayton praised NCATS for incorporating SABV into its work; Dr. Rutter thanked ORWH for its leadership in this area.
- ACRWH members praised NCATS’ inclusion of K-12 students and its career programs, noting it is very critical for developing interest in STEM early and debunking fear among budding scholars.

NIH Inclusion Update

Juliane Caviston, Ph.D., Health Science Policy Analyst, ORWH, introduced Dawn Corbett, M.P.H. NIH Inclusion Policy Officer in the Office of Extramural Research (OER). Ms. Corbett reviewed key dates in the history of NIH’s policies that addressed the inclusion of women in research (1986), of women and racial/ethnic minorities (1994), of children (1998), and of individuals of all ages (2019), as well as new Phase 3 clinical trial requirements (2022) that project outcomes be reported by sex and race/ethnicity. Despite these efforts, a 2022 NASEM consensus study report, “Improving Representation in Clinical Trials and Research: Building Research Equity for Women and Underrepresented Groups,” concluded that disparities in research access and inclusion will persist unless a major paradigm shift in tactics and processes occurs.

To improve policy oversight and enforcement, NIH has established the Human Subjects System (HHS) that captures all human subjects and clinical trial information at the individual level in one place. HHS allows NIH to look at requirements such as SABV for each study. NIH has also enhanced its reporting on individuals in clinical research. In 2022, it began deploying a new report that shows NIH inclusion data by age (for studies implemented after the age-related inclusion policy took effect), by IC, and by Research, Condition, and Disease Categorization (RCDC) category.

Ms. Corbett presented enrollment data in NIH clinical research from FY2021 and FY2022. There were approximately 13 million participants in FY2021. After adjusting for a large social media intervention study in FY2022, there were approximately 11 million participants in FY2022. Women accounted for 58.5 percent in FY2021 and 55.8 percent in FY2022 (adjusted). Similarly, women accounted for 61.2 percent of participants in NIH-defined Phase 3 clinical trials in FY2021 and 60.6 percent in FY2022 (adjusted). White participants accounted for more than six in ten clinical research participants conducted in the U.S. in both years. Black or African American participation remained steady across the two years at 13 percent, as did American Indian/Alaskan Native participation (0.9-1.0 percent). Both Asian (5.0 to 3.4 percent) and Hawaiian/Pacific Islander (0.8 to 0.3 percent) participation rates decreased between FY2021 and FY2022. “Unknown/not reported” participants decreased from 14.2 percent to 12.2 percent. For U.S.-based NIH-defined Phase 3 clinical trials, White participation was approximately 75 percent for both years. Black or African American participation declined from 14.2 percent in FY2021 to 11.4 percent in FY2022 (adjusted), while other racial groups remaining relatively stable. However, the number of “unknown/not reported” participants increased from 4.7 percent to 8.6 percent across the two years. Hispanic/Latino participants declined from 39.5 percent in FY2021 (due to a single study) to a more typical 12.1 percent in FY2022 (adjusted). There was a decrease in the percentage of children (from 19.6 percent to 13.6 percent) enrolled in NIH clinical research across the two years and a slight increase in the percentage of adults and older adults. The percentage of “unknown/not reported” increased to 4.6 percent in FY2022, a rate considered low.

Discussion. Key discussion topics following Ms. Corbett’s presentation included:

- In response to a question about how sex and gender are being operationalized, Ms. Corbett explained that NIH policy is that either sex or gender is applicable depending upon the question being asked. The definition of woman is not limited to biological sex; investigators can choose how they wish to define individuals. The way NIH collects data encourages flexibility.
- “Male” and “female” participants are identified in NIH reports of clinical trial enrollment. This is aggregated data based on how investigators used the terms as appropriate for their studies. Male or female categorization can be based on either sex or gender. The “unknown/not reported” category includes people who do not identify as either male or female.
- NIH inclusion policies originated when women were being excluded from research. There are now evolving concepts of sex and gender and their effects on health outcomes. ORWH hosted a Gender and Health workshop to explore these issues and expanded concepts that emerged from that workshop may be found on the ORWH website. Better tools to measure sex and gender are also needed and currently under development.
- NIH does not collect data on gender minorities because NIH does not have an inclusion policy that specifically addresses them. Such data would be helpful in understanding the magnitude of the issues that they face but may be difficult to measure. ORWH is working with the Sexual and Gender Minority Research Office (SGMRO) at NIH to explore these issues, including consideration of recommendations that emerged from a recent NASEM report. ORWH has proactively been making funds available to expand the rigor of tools to measure gender, as there is currently no single accepted measure. Even when sex and gender data is collected, it is often not included in analyses in

scientific journals. This is an ecosystem issue, not just an NIH issue. However, NIH does play a role in peer review and supports integration of sexgender consideration into the grant review process.

- NIH/OER is working consistently to assure that inclusion is meaningfully incorporated into NIH research; feedback on how to do this is appreciated.

Open Discussion

Dr. Clayton facilitated an open discussion among ACRWH members. Key points included:

- There is a need to research IPV among women physicians; this is an area not usually discussed.
- There is limited data available on the impact of COVID 19 on maternal mortality. There is concerning new data indicating that rates of COVID are particularly high in some Hispanic populations and among Hispanic women. It's also important to look not just at pregnancy-related causes of MM, but also at pregnancy-associated causes such as suicide and homicide. The issues need to be examined from a more holistic perspective. Improving MM rates is a priority of the Biden administration.
- Research on many conditions that impact women more than men, such as autoimmune diseases, is siloed without integration. Another example is emergency medicine. For example, in the emergency room (ER); a recent study showed that women wait longer in the ER to be seen, as well as to be tested and diagnosed. There is a need to look at integrated approaches. Dr. Clayton concurred, noting that fragmentation of care is an important issue for women, and it is important for ORWH to support efforts to ameliorate the problem in collaboration with the ICs.
- Opioids and racial discrimination are critical issues in MM that were prioritized in the second year of the IMPROVE initiative, along with COVID.
- There is a need to undertake research on the impact of violence against women in STEMM fields to reduce the stigma and fear of negative career impacts that many women in the field experience. Current research revealed that women experience higher rates of violence in science degree institutions and in STEMM graduate programs than in non-STEMM fields. The NIH Director charged a Working Group to consider this issue; in response to one of its recommendations, NIH is funding research on interventions on sexual and gender harassment in STEMM (NOT-OD-21-150). ORWH has a supplement program that addresses sexual harassment. Two applications were funded last year and the investigators featured in ORWH's *Women's Health In Focus at NIH* quarterly.
- The impact of autoimmune diseases on oral health is often overlooked. ORWH has supported research on oral health over the years. The fall 2022 issue of *Women's Health in Focus at NIH* is themed around oral health.

Autoimmune Research Spotlight

Dr. Noursi introduced Lisa Begg, Dr.P.H., RN, Senior Research Program Officer, ORWH, who introduced the two speakers for this session on autoimmune disease research: Mariana J. Kaplan, M.D. Chief, Systemic Autoimmunity Branch, NIAMS, and Andrew Mammen, M.D., Ph.D. Chief, Muscle Disease Section, NIAMS.

Innate Immune Dysregulation and Autoimmunity: Sex Differences and Impact on Organ Damage in Women with Lupus

Dr. Kaplan focused on how sex differences affect the immune system and how these effects may impact the development and perpetuation of some autoimmune diseases. She reviewed several of the systemic autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis, that are challenging to diagnose and treat. Some of them are observed early in life and others emerge later in response to environmental stress and stochastic events among those who are genetically predisposed. Patients can go through long periods of flare and remission cycles. Because of this long exposure to

oxidative stress and patients living longer due to improved treatments, clinicians are seeing more chronic complications such as cardiovascular disease (CVD), bone problems, fibrosis, and cancer, that may confer significant morbidity and mortality.

The prevalence of autoimmunity, both systemic and organ-specific, is significantly higher in women than in men. This is particularly true for some autoimmune diseases, e.g., for every man with lupus, there are about ten women with the disease. The reasons for the prevalence of autoimmune diseases among women is complex, an interplay of genetic factors, the presence of two X chromosomes, hormones, and changes that occur during pregnancy. Overall, women are better than men at fighting disease but are also more susceptible to autoimmunity. Both innate and adaptive components of the immune system have been observed in women vs. men, but the roles that each play are not completely clear.

Systemic lupus erythematosus (SLE) is an autoimmune syndrome that affects primarily women of childbearing age. It is characterized by profound clinical heterogeneity with periods of flare and remission. The defining characteristic of SLE is the presence of autoantibodies that target nucleic acids and/or proteins binding to nucleic acids. There is also dysregulation in the type I interferon (IFN) pathway that is crucial to fighting infection. With this disease, premature CVD is an important cause of morbidity and mortality. In young women, the risk of CVD is 50 times higher than in women who do not have the disease. The dysregulation in the immune system is thought to play a far greater role in the development of CVD in these women, rather than traditional risk factors such as smoking.

For many years, it was believed that there were abnormalities in the ways cells die that may be driving the generation of autoantigens inside the cells of patients with autoimmune disease that ultimately killed the cells. It is now known that there are many ways by which cells die. Learning how, where, and what type of cells die may be crucial to understanding how a specific type of cell death may promote autoimmunity in a cell host. Dr. Kaplan's research group is specifically interested in how neutrophils die. Neutrophils are the most abundant white blood cells in humans. They are constantly being produced by bone marrow, but they are also constantly dying. If there are abnormalities in the mechanisms of cell deaths of neutrophils, this could have important implications for how autoantigens get generated, autoantibodies get formed, and how various forms of cell death cause organ damage. Neutrophils are difficult to study: They die often, and they are very sensitive to manipulations in vitro. But through technological advances, scientists now know that neutrophils' job is not only to go to the site of the infection, kill microbes, and die, but that they play a much more central role in shaping the neurological landscape of health and disease. This led Dr. Kaplan's laboratory to investigate how mechanisms of neutrophil death and heterogeneity of neutrophils may be playing a role in autoimmunity.

Dr. Kaplan and her colleagues have focused on a particular kind of neutrophil cell death called the formation of extracellular traps (NETs). This is a very dramatic process whereby the neutrophil extrudes its nuclear material bound to a variety of proteins present inside it. When the extracellular nets form, not only are they good at their intended purpose of trapping microbes, but they also expose a variety of autoantigens that are known to be the key targets in the immune system and play a role in the pathogenesis of a variety of autoimmune diseases. It is not only microbes that trigger the formation of these NETs but also a variety of other inflammatory stimuli. Patients with autoimmune diseases such as lupus make more NETs than others. They have a subset of neutrophils that are continuously making NETs and the ability to get rid of these NETs is impaired in many patients. NETs circulate in the body and are deposited in organs, exposing autoantigens that may pose a threat to the immune system.

Dr. Kaplan became interested in sex differences in neutrophils several years ago when her laboratory partnered with David Furman, Ph.D., and Mark Davis, Ph.D., at Stanford University. They compared the transcriptome of blood from healthy young adult men and women and found striking differences between the sexes in gene expression related to neutrophil biology. The neutrophils in healthy men are more immature than the ones in women, a finding that was replicated in multiple cohorts. This discovery translated into the finding that neutrophils in females are considerably more activated than neutrophils in males, i.e., they express markers on the cell surface at higher levels which may endow them with more inflammatory features. Another striking observation was that under normal conditions or when exposed to bacteria, the neutrophils in women are more likely to make NETs than are the neutrophils in men. If women are better at making NETs, this may be a factor that induces more autoantigens and make women more predisposed to generating autoantibodies if they have the right genetic make-up. What was also interesting was that these changes in neutrophil maturation and biology change throughout a person's pregnancy. When women become pregnant, they acquire more of the neutrophil phenotype characteristic of men, i.e., the neutrophils became less mature. Once the woman delivered the baby, the phenotype reverted to that of the pre-pregnancy state and became more mature. These changes in maturation level may be due to a hormonal factor.

The metabolism of male and female neutrophils is also different, which may reflect what they use as a source of energy and how inflammatory they may become. Male neutrophils have more mitochondria, most likely because they are more immature, and they rely more on mitochondria as a source of energy. In contrast, female neutrophils rely more on glucose and glycolysis. Interestingly, if the investigators added the female hormone estradiol to the male neutrophil, it acquires the bioenergetics of the female neutrophil, suggesting that some differences between females and males may be due to sex hormones. Next, the researchers looked at differences in gene expression between male and female neutrophils. They found that the main genes expressed differentially between males and females were type 1-IFN regulated genes. Female neutrophils always upregulate type 1-IFN genes, suggesting they are hyper-responding to type 1-IFNs. If female neutrophils respond better to type 1-IFNs, they may be more likely to be dysregulated in the context of autoimmunity but also better able to fight certain infections. How exactly is this happening? The results from the pregnancy studies suggested that the effect may come from sex hormones rather than the extra X chromosome. There have been previous studies that hormones can regulate neutrophil function, e.g., change their numbers or lead to other abnormalities. However, scientists knew very little about sex differences in neutrophil function.

To determine if sex differences in neutrophils are due to sex hormones or to the X chromosome, the researchers (noting it is hard to study neutrophils in vitro and manipulate them with hormones) considered hints from studies that came from different patient populations. They found that comparison of the type 1-IFN responses of young adult males and females to males with Klinefelter's syndrome (individuals who look like males but carry an XXY chromosome), the latter's neutrophils should look more like the female neutrophils if the response was due to the presence of a second chromosomal X. But instead, they looked very similar to the male neutrophils, ruling out the second X as a causative factor. In studies with prepubescent children where the sex hormone effect should be much more blunted, no differences between boys and girls were observed in the type 1-IFN response. This suggests that sex hormones are playing a significant role in regulating the behavior of neutrophils. It opens the door to the possibility of hormonal strategies as a way to regulate neutrophil function in certain disease states as a mechanism to make the cells less inflammatory and less likely to induce autoimmunity. This remains ongoing work in Dr. Kaplan's laboratory.

Women with lupus are at high risk for CVD and have a lot of inflammation and coronary plaque formation, all of which occurs at an accelerated pace. The same neutrophils that are important in generating autoantigens appear to be playing some role in driving the CVD in lupus patients. Having the subset of neutrophils that make more NETs is associated with more vascular inflammation and more noncalcified plaque. These findings have implications for complications in autoimmune diseases, as well as for understanding differences between men and women in cardiovascular disease risk. Targeting specific neutrophil subsets may contribute to the mitigation of vascular disease and end-organ damage in SLE and other autoimmune diseases.

Sex Differences Among Patients with Different Forms of Autoimmune Muscle Disease

Dr. Mammen's presentation focused on four types of autoimmune muscle disease that together comprise a heterogeneous family of diseases: **Dermatomyositis** is most common among younger patients. It is characterized by symmetric proximal muscle weakness progressing over weeks or months; a typical skin rash progressing over weeks or months; elevated muscle enzyme levels; autoantibodies; myopathic electromyography; and abnormal muscle biopsies. **Antisynthetase syndrome** is characterized by the presence of autoantibodies recognizing one of the aminoacyl-tRNA synthetases; of these synthetases, Histidyl-tRNA synthetase (Jo1) is the most common. People with antisynthetase syndrome may experience arthritis, myositis, mechanic's hand, Reynaud's phenomenon, veil rash, and interstitial lung disease. **Immune-mediated Necrotizing Myopathy (IMNM)** is characterized by necrosis of the myofibers as seen in a muscle biopsy and the presence of autoantibodies targeting the signal recognition particle and HMG-CoA reductase. Patients experience severe weakness, often progressing from walking to a wheelchair within a few months. This disease is often difficult to treat, especially in young women. **Inclusion body myositis (IBM)** is the most common myopathy in patients over 50 years old. In contrast to other types of myositis, IBM has an insidious onset: Patients may not recognize how weak they are until they start falling, although they have developed difficulty walking upstairs years earlier. People with IBM experience a unique pattern of asymmetric weakness in their quadriceps, distal finger flexors, wrist flexors, ankle dorsiflexors, and obicularis oculi. As seen in a muscle biopsy, IBM is characterized by rimmed vacuoles and invasion of myofibers by CD8+ T cells. Currently, IBM is quite refractory to typical immune suppression approaches, but new approaches are being developed.

Sex Difference Among Myositis Types. Each of these autoimmune muscle diseases, except IBM, is more common among women than men: The percentage of females with dermatomyositis is 70 percent; with antisynthetase syndrome, 69 percent; with IMNM, 64 percent, and IBM, 39 percent.

A Deeper Dive into IBM. Dr. Mammen reviewed studies based on clinical, histologic, radiologic, and electrophysiologic data from all patients with IBM and other forms of myositis enrolled at The Johns Hopkins University Myositis Center from 2003-2018. Among the 335 patients with IBM, 64 percent were male with an average age of 58.7 years. Over half (52 percent) had initially been misdiagnosed; the average delay to diagnosis was 5.2 years. Black patients had significantly weaker arm abductors, hip flexors, and knee flexors compared with non-Black patients. Compared to males, female patients with IBM had stronger knee extensors, stronger finger flexors, increased prevalence of dysphagia, slower rate of strength decline, and less spontaneous activity on electromyography (EMG). Female patients also experienced an increased rate of misdiagnosis and mistreatment, and a longer time to correct diagnosis (6.2 vs. 4.7 years). Thus, female IBM patients have a distinct clinical phenotype and trajectory compared to men. These unrecognized differences may have contributed to delay of correct diagnosis in women. Further, women with IBM may have different responses to therapies, which may influence the design of future clinical trials in IBM.

Discussion: The following topics were addressed in the discussion:

- In response to a question about the intersectionality of sex and race/ethnicity in lupus, Dr. Kaplan reported that she and her colleagues have compared patterns across racial/ethnic and age groups and hope to have more information on this topic in the future. They have observed lower neutrophil numbers among African Americans/Blacks, but it is still unclear what the impact is.
- Internists rarely have the skills needed to diagnose IBM in women; there is a misunderstanding that it is normal for older adults to become weaker and a referral to a specialist may not occur until the patient starts falling. Therefore, Dr. Mammen and his colleagues are targeting rheumatologists and neurologists as recipients of increased information about IBM. A counterargument, however, is that all clinicians need to be aware of these diseases so they can make appropriate referrals.
- Lupus is less common in men, yet the disease can be much severe and result in organ damage. A full explanation for why this occurs is not yet available, but research on the issue is ongoing.

2024–2028 NIH-Wide Strategic Plan for Research on the Health of Women: Update

Dr. Noursi, ACRWH member Alyson McGregor, M.D., and Kelly Chandler, Ph.D. Health Science Policy Analyst, ORWH, provided updates on the development of ORWH's 2024-2028 Strategic Plan. Dr. Noursi explained that the goal for the Strategic Plan is to provide a roadmap on women's health research to be published in January 2024. She reviewed the process model that ORWH is using to develop the plan, beginning with the collection and analysis of data from multiple sources that was provided to the Strategic Plan Working Group. Dr. McGregor, Working Group co-chair with Dr. Noursi, stated that the charge to the Strategic Plan Working Group was to address the current state of science on the health of women, identify research gaps, and establish goals and objectives that ORWH needs to prioritize for 2024 – 2028. The Working Group—consisting of ACRWH members, representatives of NIH ICOs, and federal partners--solicited input from collaborators to identify the five content areas that were approved by the ACRWH on October 18, 2022. Dr. Chandler provided an overview of the five content areas and their respective objectives are outlined below:

1) Consider how the intersection of social and biological factors affect the health of women:

Objective 1: Develop and support innovative research on the health of women in social, cultural, and historical context, with particular attention to the interplay of biological, behavioral, social, structural, and environmental factors.

Objective 2: Expand research to address health disparities experienced by diverse populations of historically marginalized women, with attention to intersectionality and health equity.

Objective 3: Support research on upstream causes of health disparities and modifiable factors or points of intervention to mitigate disparities rooted in structural sexism, structural racism, and other social determinants of health.

Objective 4: Support innovative behavioral and social sciences research (BSSR) to enhance knowledge of biological, behavioral, social, environmental, and structural processes and promote equity-focused health research for women.

Objective 5: Develop and support research to investigate the multiple domains of gender (identity, roles and norms, relations, power) and their influence on health.

Objective 6: Expand research to advance the health of women across the life course, including during key social and biological transitions.

2) Support the development of data science, innovative research methods and measurements, and promote cutting-edge technologies for the health of women:

Objective 1: Increase data-sharing and improve data management practices to align with FAIR principles and enhance the utility of new and existing data on the health of women.

Objective 2: Promote the use of advanced statistical modeling, data visualization, artificial intelligence (AI), and machine learning (ML) methods for research on the health of women.

Objective 3: Utilizing longitudinal and repeated measurement designs and analytic approaches to characterize the health of women over time and across the life course.

Objective 4: Support the development of cutting-edge computational tools and technologies to facilitate disease screening, prevention, diagnosis, and treatment of diseases that affect women.

3) Support biomedical workforce training and promote women scientists' career development to advance the health of women:

Objective 1: Integrate knowledge of sex and gender influences on health and disease at all levels of training to accelerate the translation of that knowledge into practice.

Objective 2: Develop the next generation of researchers to advance science on the health of women, including through non-traditional, interdisciplinary avenues toward biomedical and health science research careers.

Objective 3: Support and develop programs to recruit, support, retain, facilitate re-entry, and advance women at all stages of their research careers, from early career to leadership positions, especially mid-career scientists.

Objective 4: Promote and support policies, mentoring, networks, collaborations, and opportunities to advance the cross-sectoral careers of women scientists, with special attention to populations underrepresented in the U.S. biomedical, clinical, behavioral, and social sciences research enterprise, and persons with disabilities.

Objective 5: Promote and disseminate interventions to reduce barriers and facilitate recruitment, retention, re-entry, and reintegration to advance the behavioral and biomedical careers of women.

4) Advance basic science and translational research to improve the health of women:

Objective 1: Advance mechanistic, basic, and translational research into the effect of sex and gender on biology, disease pathogenesis, therapeutics, and health outcomes that uniquely or differently affect women.

Objective 2: Enhance the use of cell and animal models, organoids, engineered tissue matrices, in silico, and related systems, to define the role of sex and gender in biomedicine.

Objective 3: Enhance research on the role of sex and gender on intrinsic processes (e.g., sleep, stress, pain) and in response to extrinsic factors (e.g., microbiome, nutrition, toxins) across the lifecourse.

Objective 4: Stimulate interdisciplinary, systems-based approaches spanning biomedical domains such as molecular and cellular biology, genomics, immunology, and physiology.

5) Encourage community engagement and promote implementation science for the health of women:

Objective 1: Train and educate researchers, clinicians, and public health practitioners on community-engaged research on implementation science methods and practice.

Objective 2: Develop, promote, and leverage methods and practices that include bidirectional listening and culturally responsive communication and support for community participation and engagement in research.

Objective 3: Promote engagement science (e.g., methods and processes) related to implementation, behavior, and health outcomes relevant to improving the health of women.

Objective 4: Expand implementation science focused on improving public health practices and healthcare delivery tailored to the needs of women.

Objective 5: Expand implementation science aimed at investigating and intervening on the social, policy, environmental, structural, and systemic factors that influence sex and gender disparities in the health of women.

Dr. Chandler noted that ORWH's next Strategic Plan will be informed by the current plan. She presented a proposed theoretical model that maintains ORWH's life course perspective, but explicitly addresses

the social determinants of health (SDOH) on women, as well as biological factors. Dr. Noursi concluded the presentation by reviewing next steps: refining metrics to evaluate implementation of the strategic plan in collaboration with ICOS; drafting the narrative for review and clearance; and release of the plan in January 2024 and of an implementation and evaluation guide in Summer 2024.

Discussion: The following key points were made in the discussion:

- SABV for clinical research should be addressed in the strategic plan. One potential way to do so is to include it in a discussion of cross-cutting and overarching themes.
- In terms of the convergence of content areas 2 (data science research and management) and 3 (workforce education), make sure that women are not just subjects but also researchers. It is anticipated there will be discussion of this in the text of the strategic plan.
- Any potential redundancies/overlaps in the content areas and objectives will be eliminated as co-chairs review the goals and objectives of each area before the report is finalized.
- Concern was expressed that the inclusion of the fetus as part of the life course in the multidimensional model could lead to the politicization of women's health. However, it is important to acknowledge that many influences on a person's health occur during the in-utero period. One way to address this issue is to include an arrow before the timeline with "in utero and intergenerational influences on development and health." Another is to change "in utero" to "childbearing," a broader category that can include the many ways conception occurs and how the products of conception grow in the uterus.
- Expand the "adulthood" category on the life course portion of the model to early- mid-, and late-adulthood to convey a greater sense of the continuum of a person's life.
- In content area 5, objective 4, include caregivers (primarily women) who experience substantial levels of chronic disease in research on aging and caring for those with dementia.

Concept Clearance: Research Supplements to Promote Re-Entry, Re-integration, Re-training and Re-tooling into Health-Related Research Careers

Dr. Noursi introduced Xenia T. Tigno, Ph.D. Associate Director for Careers, ORWH, who reviewed ORWH's Research Supplements to Promote Re-Entry into Biomedical and Behavioral Research Careers awards that were first issued in 1992 and subsequently re-issued six times. The purpose of these supplements is to support individuals with high potential to re-enter an active research career after an interruption for family responsibilities or other qualifying circumstances; encourage individuals to re-enter research careers within the missions of all the program areas of NIH; and provide supplements to existing NIH research grants for the purpose of supporting full-time or part-time research by these individuals to update their existing research skills and knowledge. Twenty-three ICOs participated in the re-entry program in addition to ORWH. Most supplements (74 percent) were attached to R01 awards. The latest re-issuance was NOT-OD-21-134 which will expire on October 7, 2023.

Eligible applicants for these awards included both men and women, although women were more likely to apply because of family and other disruptions to their research careers. Between 2012-2021, 144 applications for these supplements were received, resulting in 88 awards (a 61 percent success rate). Using documentary evidence in the absence of sex/gender data, ORWH estimates 80 percent of applicants were female. Over one-half (55 percent) cited childrearing as a reason for the applicant's hiatus from research.

In 2021, ORWH made some changes, approved by ACRWH, to enable it to address other contemporary challenges faced by women, such as sexual harassment, to provide an exit ramp to a new and safer

environment where the applicant could continue her career. The *Re-entry Supplements* program is intended to provide mentored research training opportunities for a minimum of one year to individuals with doctoral degrees who have interrupted their research careers for family responsibilities or other qualifying circumstances so they may re-enter biomedical research. The *Re-integration Program* addresses the critical need to provide individuals, including predoctoral students, who are adversely affected by unsafe or discriminatory environments resulting from unlawful harassment, to rapidly transition into new, safer, and more supportive research environments. Since these changes were made, 22 new applications have been received, 20 for re-entry and 2 for re-integration (both of the latter were funded). Nineteen of the 22 applications were from women. Thirteen of the 20 re-entry applications were funded (65 percent success rate).

ORWH is now seeking to re-issue NOT-OD-21-134 with an additional component: a *Re-training and Re-tooling Program* to provide support and protected time for an intensive, supervised, immersive experience in a laboratory, academic institution, government organization, non-profit or charitable organization, publishing, and other forms of science-related industry, to early-career and mid-career scientists. The intent of the program is to facilitate inter-disciplinary partnerships and cross-sector collaborations that would enable the Scholar to acquire specialized skills and novel perspectives that would augment the chances for the advancement of their careers. The proposed change is responsive to the 2023 NASEM report “Promising Practices for Addressing the Underrepresentation of Women in Science, Engineering, and Medicine: Opening Doors.”

The *Retaining and Retooling* program would consist of administrative supplements providing up to \$90,000/year in salary and \$50,000/year in program-related expenses. Eligible trainees must be a citizen or non-citizen national of the United States or have been lawfully admitted for permanent residence by the time of the award. Scientists who come from diverse and underrepresented groups in the U.S. biomedical, clinical, behavioral, and social sciences are encouraged to apply. Candidates in all career stages beyond the postdoctoral level (at least 2 years minimum) may apply. Especially encouraged are women in mid-career positions who have never or currently are not receiving any RPG awards. Apart from scientists employed in academic institutions, other scientists with experiences in government or industry equivalent to those of post-doctoral candidates are also eligible.

It is envisioned that the supplement Scholar will be engaged in career development at a laboratory, institution, or organization different from his or her current place of employment. The training period may range from three months to one year. The goal of the retraining/ retooling award is to support the Scholar’s transition to independence in a multitude of career options, including as research and teaching faculty, entrepreneurial, industry, science policy, science communication, intellectual property, regulatory affairs, consulting, drug discovery, approval, and production, science education, and health care, and research administration positions.

There are no changes in eligibility for the re-entry and re-integration components of the program. The number of awards available is contingent upon NIH appropriations and the submission of a sufficient number of meritorious applications. Council action to renew the Re-Entry Supplement Funding Opportunity Announcement (FOA) is requested.

Discussion: The following key points were made during the discussion of Dr. Tigno’s presentation:

- ORWH is currently evaluating the careers of the original recipients of the re-entry grant program. It is difficult to trace the trainees because only the names of principal investigators and/or mentors

were tracked in NIH's system until recently. It is also difficult to track people with similar names; this is where the Open Researcher and Contributor ID (ORCID) can play a valuable role.

- Clinician-scientists are eligible to apply for the supplements; more clinician scientists are needed and creative ways to encourage them to re-enter their research careers should be implemented.

Vote: A motion to renew the Re-Entry Supplement Funding Opportunity Announcement was accepted with 14 in favor.

Concept Clearance: FY 2023 Building Interdisciplinary Research Careers in Women's Health (BIRCWH) — Postdoctoral Opportunities

Dr. Begg presented a concept clearance to expand the number and scope of administrative supplements to BIRCWH. ORWH, the NIH lead on the program, and multiple ICs contribute over \$15 million per year to support BIRCWH. Today, there are over 19 active BIRCWH programs geographically distributed across the country; since funding began over 20 years ago, 42 institutions have received funds. More than 750 Scholars have completed the program, 88 percent have stayed in research, and 42 percent are Physician-Scientists. Eighty percent of the Scholars are women and 20 percent are men.

In recognition of the program's effectiveness, ORWH has been allocated funds from the 2022 Omnibus spending bill to support funding of an additional trainee at each of the current 19 BIRCWH programs. These funds for Administrative Supplements must be spent in FY2023. Direct costs of \$90,000/year for each BIRCWH grantee will be provided. Eligible trainees include citizens or non-citizen nationals of the United States or those who have been lawfully admitted for permanent residence by the time of the award. Scientists who come from diverse and underrepresented groups in the U.S. biomedical, clinical, behavioral, and social sciences are encouraged to apply. Applications are only open to the 19 active BIRCWH grantees. These non-competitive administrative supplements will be reviewed by ORWH and its IC partners for compliance with NIH policies and career development requirements.

Discussion: The following key points were raised during a discussion of this concept clearance:

- Eight BIRCWH programs have a formal collaboration with an Historically Black College or University (HBCU), minority-serving institution (MSI), or tribal authority.
- Eligibility for the new additional position is at the one-year post-doc or instructor level. This is most likely someone who comes on board this year but is eligible to become a full Scholar next year.
- While there is no specific funding in BIRCWH to support delays due to the pandemic, NIH staff has been told to be as flexible as possible on this issue and BIRCWH Principal Investigators were good at helping Scholars stay on track. At the University of Colorado BIRCWH program, the board recommended changing its Scholars' two-year terms to three years to give them an opportunity to complete research that had been interrupted by the pandemic.

Vote: The concept clearance was approved with 14 in favor.

Open Discussion

Dr. Clayton acknowledged the dedicated efforts of ORWH staff; ACRWH members concurred and applauded the accomplishments of ORWH. ACRWH members raised the following points:

Women's health research priorities

- Continue to emphasize maternal mortality as a priority; learn what other counties/regions are “doing right” learn from them. Public comments on research needs and gaps in maternal health in response to an RFI from Pathways to Prevention may be made until April 21.
- Menopause remains an area that is under-studied; findings on hormone replacement therapy from the Women's Health Initiative need updating. Support research to enhance biological understanding of menopause to increase information on symptoms to women in perimenopause.
- Emphasize the impact of caregiving on women's physical and mental health. The effect of caregiving on the careers of women in STEMM is the topic of an upcoming NASEM report.

Strategic plan model

- There are sex-specific differences present from birth, but the model does not distinguish between boys and girls until adolescence.
- Add perimenopause to the adulthood concepts.
- Acknowledge that having children impacts a woman's risk for various diseases; adulthood is not a linear process.

Reproductive rights

- Recent changes in reproductive rights and access to abortion present the opportunity to collect data on the impact of policy changes on women's health.

Using Evidence-based Interventions

- NIH should advocate for the implementation of evidence-based interventions, especially for people or conditions that are over-represented in minority groups. Many community clinics are not using evidence-based approaches. Dr. Clayton noted that NIH's role is to create new knowledge; it works with its federal partners to translate and disseminate new discoveries into delivered care.
- The field of implementation science needs to be strengthened to more easily adapt packaged evidence-based interventions into practice in different settings. There is also a need to expand implementation efforts in innovative settings, such as libraries.

Public Comment

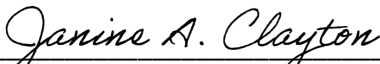
Public comment was received following the meeting from Kiwanis member Jester Jersey, who suggested that federal health agencies such as NIH partner with service-based community organizations, like Kiwanis, that can provide trusted messaging and additional credibility to government health campaigns.

Closing Remarks

Dr. Clayton thanked Team ORWH, presenters, and ORWH partners across ICOs for their support before adjourning the meeting at 3:44 p.m.

Certification

We certify that the contents above are accurate and complete.


Janine Austin Clayton, M.D., Director
Office of Research on Women's Health


Samia Noursi, Ph.D., Executive Secretary
Advisory Committee on Research on Women's Health

Date May 24, 2023

Date May 16, 2023