

**NIH 48<sup>th</sup> 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 10, 2019**

**Members Present**

C. Noel Bairey Merz, M.D.  
Wendy R. Brewster, M.D., Ph.D. (by phone)  
Geert J. de Vries, Ph.D.  
Roger B. Fillingim, Ph.D.  
Kimberly D. Gregory, M.D., M.P.H.  
Rachel Jones, Ph.D., R.N.  
Carolyn M. Mazure, Ph.D.  
Margaret M. McCarthy, Ph.D. (by phone)  
Louise D. McCullough, M.D., Ph.D. (by phone)  
David C. Page, M.D.  
Marcia L. Stefanick, Ph.D.  
Susan F. Wood, Ph.D.

**Guests**

Sabra Klein, Ph.D.  
Alyson McGregor, M.D.  
Judy Regensteiner, Ph.D.  
Michelle Robinson, D.M.D.  
Neel Shah, M.D., M.P.P.

**ORWH Leadership**

Janine Clayton, M.D., Director  
Elizabeth Spencer, B.S.N., Deputy Director  
Margaret Bevans, Ph.D., RN  
Vicki Cargill, M.D.  
Chyren Hunter, Ph.D.  
Samia Noursi, Ph.D.

**HHS Leadership Present:**

Dorothy Fink, M.D., Deputy Assistant Secretary for Women's Health/Director, Office on Women's Health

**Call to Order and Introductions**

Elizabeth Spencer, B.S.N., ACRWH Executive Secretary and ORWH Deputy Director, called the meeting to order at 9:02 a.m., and announced that it was being recorded and videocast. Ms. Spencer introduced new ACRWH members: Roger B. Fillingim, Ph.D., Stacie Geller, Ph.D., Margaret M. McCarthy, Ph.D., and Elena Rios, M.D. Staff and Committee members introduced themselves.

The minutes of the October 23, 2018 meeting were unanimously approved.

**ORWH Director's Report**

Janine Clayton, M.D, ORWH Director and NIH Associate Director for Research on Women's Health, acknowledged new NIH leaders, including Noni H. Byrnes, Ph.D., Director of the Center for Scientific Review; Joni Rutter, Ph.D., Deputy Director, National Center for Advancing Translational Sciences; and Tara A. Schwetz, Ph.D., NIH Associate Deputy Director; along with the contributions of her staff, Team ORWH. She noted that April is National Minority Health Month and encompasses Black Maternal Health Week (April 11-17). Black women have much higher rates of maternal mortality and morbidity (MMM) than white and Hispanic women do. There is broad interest in MMM across NIH, represented by multiple Institute and Center (IC) presentations to the NIH Coordinating Committee on Research on Women's Health (CCRWH). The ORWH portal/resource page will soon have information on relevant Funding Opportunity Announcements (FOAs), events, and resources for mothers. "Improving Maternal Health" will be the theme for the 4<sup>th</sup> Annual Vivian W. Pinn Symposium on May 15, 2019, celebrating the 20<sup>th</sup> anniversary of National Women's Health Week.

**Scientific Collaboration:** Dr. Clayton discussed the opioid public health crisis including use among pregnant women. Among delivering women, opioid use grew dramatically over the decade between 2004-2005 and 2014-2015, especially in rural areas. The opioid-related maternal mortality rate for women has also rapidly

increased. The Helping to End Addiction Long-term (HEAL) Initiative is a trans-agency effort to advance scientific solutions to this crisis. Four of the components of HEAL include basic science research on pain and addiction; implementation science to develop and test treatment models; research to integrate both behavioral interventions and medication-assisted treatment for opioid use disorder; and development of non-addictive pain treatment. Dr. Clayton reported that ORWH is participating in 14 HEAL FOAs, including the HEALthy Brain and Child Development Initiative.

On March 13, 2019, the federal charter for the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) was renewed for two years. With the renewal, the Task Force will be able to provide advice and guidance to the Secretary of the Department of Health and Human Services (HHS) on implementation of the recommendations.

**Research Program:** ORWH's total budget was \$43.73 million in FY2018. In FY2018, the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) program was allocated the largest percentage (30 percent) of ORWH extramural funding, followed by other IC co-funds (23 percent), Specialized Centers of Research (Excellence) on Sex Differences (SCORE) (17 percent), Sex/Gender Administrative Supplements (14 percent), Understudied, Underrepresented, and Underreported (U3) Administrative Supplements (10 percent), and R56 (6 percent). ORWH partners with ICs in all of its work. ORWH strives to partner broadly with the ICs and almost all are represented in FY2018.

The R56 High-Priority, Short-term Project Award is an initiative of the NIH Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) involving ORWH, the Office of Dietary Supplements (ODS), and the Office of AIDS Research (OAR). It is designed to provide funding to investigators to increase their success in subsequent Research Program Grants (RPG). In the past two years, 57 percent of recipients went on to obtain an R01 or similar grant on the topic funded by the R56 award.

The SCOR program started in FY2002 and evolved into the SCORE program in FY 2018. Since FY 2002, NIH has invested more than \$180 million in the program, which is the only disease-agnostic, interdisciplinary, and translational research initiative at NIH. The new SCORE is supported by a cooperative agreement and includes a new career enhancement core.

ORWH has invested \$32.9 million in the Sex & Gender Administrative Supplements since FY2013 and supported 341 supplements. The program has been renewed for FY2019.

The newest ORWH supplement program is the U3 Administrative Supplement. ORWH has supported 23 awards since FY2017 and has renewed the program for FY2019.

Dr. Clayton addressed a question previously presented by the ACRWH related to sex and gender and peer review. She stated that SABV expertise in sex and gender analysis has been added to the Office of Disease Prevention (ODP) database. ODP created the Prevention Research Expertise Survey (PRES) to populate its database of peer reviewers. Dr. Clayton asked ACRWH members to encourage colleagues with such expertise to respond to the PRES survey to become peer reviewers.

**Women in Biomedical Careers:** Dr. Clayton stated that Women in biomedical careers remains one of the key mission areas at ORWH. She participated in the launch of an historic issue of *Lancet* championing the advancement of women in science, technology, engineering, mathematic, and medicine (STEMM). The journal included an article on the effectiveness of Athena Scientific Women's Academic Network (SWAN) and ADVANCE. ORWH hopes these programs will inform NIH's next steps

In October 2018, the annual BIRWH meeting brought scholars together for mentoring, networking, and advancing, under the theme, “Mentoring as Medicine.” Dr. Clayton highlighted NIH’s variety of ways for promotion of women scientists and career-enhancing networking. For example, there have been ten high-profile women speakers at the prestigious NIH Wednesday afternoon lecture series since the fall, highlighting women’s scientific accomplishments.

Following the release of the 2007 National Academies of Science, Engineering, and Medicine (NASEM) report, *Beyond Bias and Barriers: Fulfilling the Potential of Women in Academic Science and Engineering*, NIH established the Working Group on Women in Biomedical Careers. The working group, currently co-chaired by Dr. Clayton and NIH Director Francis Collins, M.D., Ph.D., introduced family-friendly policies and programs, and funded research on causal factors and interventions to support women in science. Fourteen grants totaling \$169 million over four years and involving 11 ICs and 4 offices in the Office of the Director (OD) addressed research on unconscious bias, mentoring, and institutional flexibility. A new NASEM study is underway, addressing the underrepresentation of women in STEMM, examining how women’s participation varies across disciplines; how the intersection of race and gender impacts on women of color in STEMM; what interventions produced sustained improvements in representation and leadership; and why effective interventions haven’t been scaled up or adopted more. The study will yield actionable recommendations to improve representation and leadership.

Dr. Clayton continued that with ORWH funding and broad IC participation, the NIH Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative’s Advanced Postdoctoral Career Transition Awards offer independent research support, facilitate the transition of outstanding postdoc researchers from mentored positions to tenure-track or equivalent faculty positions, and help awardees from diverse backgrounds launch independent research careers. These are K99/R00 awards that provide an extra year of funding to help women launch independent research careers.

**Building Connections:** Dr. Clayton congratulated ORWH staff for their achievements in scientific scholarship, noting seven new publications to which staff members contributed. She also highlighted ORWH’s accomplishments when it took over the main NIH Social Media account in January 7-11, 2019, resulting in 76 posts and 2.939 engagements.

To promote women’s health issues, Dr. Clayton participated in a *Lean In* podcast with Serena Williams and Esther Choo, M.D., about why women get overlooked in healthcare. Other examples of visibility in the media include an online report from the Commonwealth Fund titled “Closing the Medical Research Gap” about why it’s important to study how disease impacts men and women differently; an interview on the NBC Today show in conjunction with Black Maternal Health Week about NIH’s efforts to reduce MMM; and a discussion of gender bias in medicine on NBC Today.com.

Future women’s health events include the May 5, 2019 meeting of the Organization for the Study of Sex Differences (OSSSD), where the theme will be Advancing Science for the Health of Women: The NIH Office of Research on Women’s Health. ORWH will host a symposium with its leadership team at the meeting. The 4<sup>th</sup> Annual Vivian W. Pinn symposium focusing on “Maternal Health: Behind the Numbers” will be held on May 15, 2019. The Winter 2019 issue of *Women’s Health in Focus at NIH* is available.

#### **NIH Workplace Climate and Harassment Survey/Anti-Harassment Program**

Dr. Clayton introduced Hannah Valantine, M.D., MRCP, Chief Officer of the NIH Scientific Workforce Diversity Office, who described the development and implementation of the NIH Workplace Climate and Harassment

Survey. She explained that the National Academies Consensus Study Report (June 2018) identified three types of sexual harassment behaviors: gender harassment; unwanted sexual attention; and sexual coercion. The report also identified significant impacts of harassment on women, such as their leaving the institution or scientific field, stepping down from leadership positions, depression and suicidal attempts, poor self-esteem, loss of personal autonomy, shame, guilt, anger, and alienation. Among its 15 recommendations were for institutions to address sexual harassment, move beyond legal compliance to address culture and climate, and measure progress.

Dr. Valentine explained that Dr. Collins established a working group to address gender harassment and culture and climate, including measuring progress via the NIH Workplace Climate and Harassment Survey, a confidential and anonymous climate survey for all NIH staff, contractors, students, and fellows. Its goals are to: Assess the NIH workplace climate; identify potential elements of NIH organizational climate associated with sexual harassment for intervention; determine the impact of sexual harassment on career choices; and measure outcomes of sexual harassment (e.g., job, psychological, and health). The hope is that other institutions will use the instrument in order to develop nationwide data.

The Survey was launched at the end of January 2019; data collection just ended. The response rate as of March 26, 2019 was 44 percent, representing approximately 16,000 responses. The response rate among federal employees, the largest group of respondents, was 56.2 percent. By June there will be a preliminary report and, by September, recommendations for action.

The Survey is a small part of the overall NIH response to sexual harassment. To provide greater oversight, an anti-harassment steering committee led by NIH Principal Deputy Director Larry Tabak, D.D.S., Ph.D., was created to oversee process improvements and program design. The Civil Program expanded to address all allegations of harassment and related inappropriate conduct and to oversee the administrative inquiry process. New policies include the Preventing and Addressing Harassment and Inappropriate Conduct Manual Chapter (1311) and a Personal Relationships in the Workplace Policy Statement. New tools include a new web form and hotline that provide an enhanced allegation reporting systems for both anonymous and non-anonymous reports; a web presence spanning all partner sites; and training & education.

Jessica Hawkins, Supervisor of the NIH Civil Program, reported on the implementation of the NIH Anti-Harassment Program. The Civil Program, which houses the effort, has been in existence for many years, primarily focused on workplace violence. In December 2017, Dr. Collins announced that NIH would now be addressing harassment allegations in an objective manner through the Program. The Civil Program's mission is to foster civility throughout the NIH community. It launched its communication program in October 2018. The Program addresses uncivil behavior, such as harassment, sexual harassment, inappropriate conduct, intimidation, bullying, or other unproductive, disruptive, and/or violent behaviors. The Civil Programs is based on a three-step process of Recognize, Report, Resolve.

**Recognize:** Recognition refers to building an understanding of harassment via in-person trainings and micro-trainings on the website, including mandatory harassment training.

**Report:** Individuals can report any type of inappropriate conduct and the Civil Program Office will intervene.

**Resolve:** The Civil Program Office reviews evidence to determine if an Administrative Inquiry is necessary. Beginning in 2019, the Civil Program will provide data regularly on the aggregate number of allegations received and the outcomes.

**Discussion:** Kimberly Gregory, M.D., asked if the Civil Program is tracking the number of people who file vs those wish to discuss their options. Ms. Hawkins responded that a script outlining options is provided to the contractor that is staffing the hotline, and that the Employee Assistance Program and the Office of the Ombudsman know how to explain benefits and protections. Dr. Valentine interjected that the issue of reporting has been identified as an important one, since the extramural community is interested in replicating the NIH system. Ms. Hawkins noted that when people goes to the Civil website, they will be able to indicate if what they want to report happened at NIH or at an NIH-supported institution.

Noel Bairey Merz, M.D., inquired about strategies for transparency, noting that when a harassment issue is raised in academic medicine, there's a lot of "lawyering up" and further information is not available to faculty and victims. She asked if the federal government could take leadership on this issue. Dr. Valentine replied that by opening up new avenues for reporting, NIH is attempting to do this. Ms. Hawkins said that the only time there is a gag order in a federal setting is if there's a settlement. She explained that the Civil Program Office conducts the inquiry and then provides its findings to the Office of General Counsel, which advises the manager. Dr. Valentine expressed interest in hearing from ACRWH members about how this issue should be handled. She acknowledged limitations on what the federal government can do, stressing that all individuals and institutions need to work together to solve the problem. Susan F. Wood, Ph.D., asked Dr. Valentine if data from the survey, e.g., response rates, has been disaggregated by sex. Dr. Valentine responded that findings from the survey, including response rates, will be analyzed soon and reported in the future.

#### **NIH Institute Update: National Institute on Drug Abuse (NIDA)**

Nora D. Volkow, M.D., NIDA Director, addressed the topic of Gender in Opioid Research: Basic, Clinical, and Translational Implications. Dr. Volkow began by highlighting the massive increase in opioid deaths from fewer than 10,000 deaths per year in 1999 to almost 50,000 per year in 2016. She stated that more men than women are dying of opioid overdoses, but the death rates between the two are close in many areas, and the increase in overdose fatalities is driven largely, but not completely, by over-prescription of opioid drugs by the health system. Other factors include the introduction of high purity, low price heroin from Mexico beginning in 2011 and the 2013 introduction of the synthetic opioid fentanyl- and the much stronger carfentanyl-laced drugs including heroin, prescription opioids, cocaine, or methamphetamine. The higher potency of carfentanyl requires a much smaller volume to have the same effect as fentanyl. This has led to changes in the way drugs enter the country, increasingly through the mail.

The rate of women's overdose death is equivalent to that of men for prescription drugs, especially for older women, and the rate is accelerating more rapidly for women than for men. Men are more likely to die of a heroin overdose than are women, but there's been significant increases in the number of women experimenting with heroin and overdosing. Similarly, men are more likely to overdose from synthetic opioids than women are, but the rate among women is increasing. Women are more likely than men to be prescribed an opioid; thus, they are placed in a more vulnerable position for becoming addicted and overdosing. They are also more likely to be prescribed a benzodiazepine drug that, in combination with an opioid, places them at greater risk. Dr. Volkow suggested that educating clinicians to follow evidence-based prescription recommendation is the low-hanging fruit.

Dr. Volkow reported that women are more likely to be prescribed opioids because they are more sensitive to pain than men, due to differences in the opioid receptors in men and women.

Dr. Volkow pointed out some of the unique challenges in applying this information to the development of medications for opioid use disorder (MOD). MOD decreases opioid use, opioid-related overdose deaths, criminal activity, and infectious disease transmission, while increasing social functioning and retention in

treatment. There are two classes of medications for addiction: agonist (e.g., methadone) and antagonist (e.g., naltrexone); buprenorphine is a partial agonist. Because mortality is high, there is a need to treat Opioid Use Disorder (OUD) aggressively and medications are the best approach. However, she explained, because of the stigma toward addiction, many believe that medication-assisted treatment (MAT) is just trading one drug for another. This has resulted in a low rate of administration of MOD and closing this gap is one of NIDA's highest priorities.

Priority research areas (for NIDA and HEAL) include expanding therapeutic options that make it easier for a patient to stay on medication; optimizing new treatment strategies, such as expanding the number of places where drugs can be administered beyond the medical office; developing new treatment strategies and improved prevention; and enhancing treatments for infants with neonatal abstinence syndrome (NAS)/neonatal opioid withdrawal syndrome (NOWS).

**Challenges for Women:** Women (25.8 percent) are less likely than men (54.3 percent) to receive naloxone during an overdose. Dr. Volkow continued, since naloxone works equally well on both sexes to reverse the effects of the drug, there is a need to understand why this disparity exists. Another issue is the best strategy for treating opioid addiction among pregnant women. Outcomes for women treated with medications are better than for those not offered medications. However, an analysis conducted in four Appalachian states revealed that opioid agonist treatment (OAT) providers were less likely to treat pregnant women, especially those who couldn't afford to pay for treatment. The number of neonatal intensive care unit admissions for NAS is skyrocketing. The optimal treatment strategy for these infants is buprenorphine, which results in a shorter duration of NAS and length of hospital stay than treatment with morphine.

NIDA is launching a multi-site, longitudinal Healthy Brain and Child Development (HBCD) initiative with multiple ICs to learn more about how the human brain develops cognitively, behaviorally, socially and emotionally, using imaging studies. To understand how drug use in pregnancy affects brain development, the study will oversample for prenatal opioid exposure.

**Discussion:** Roger Fillingim, Ph.D., suggested that finding alternative pain treatments for women is important. Dr. Volkow concurred, pointing out that women are more likely to experience chronic pain, more likely to become addicted to opioids, and more likely to commit suicide, than men are. Thus, there is a need for tailored interventions. However, there are also specific challenges, e.g., women are more likely than men to relapse while on opioid medications, most likely due to their family support responsibilities which make it more difficult for them to adhere to a regular treatment routine.

Carolyn Mazure, Ph.D., emphasized the greater stigma attached to women's drug use which is a significant barrier to providing woman-based services that also address the needs of children; she urged NIDA to draw more attention to this issue. Dr. Volkow agreed, citing the fact that in some states, women won't come into treatment because Child Protective Services will take their children away. This reflects the high degree of stigma women face. She stated that NIDA can respond by demonstrating that a woman in treatment has better outcomes for herself and her family.

Alyson McGregor, M.D., pointed out that there is a regulatory framework that affects how doctors practice that could benefit from NIDA's research, coupled with drug companies' previous statements that opioids were safe. Emergency room (ER) physicians now need to take eight hours of training in MAT. Dr. Volkow responded that physicians have to question what drug companies say and should not follow the rules blindly. Now the pendulum is swinging in the other direction and patients in pain are suffering. It is heartening to see ER doctors bringing forth new strategies for care.

Marcia L. Stefanick, Ph.D., asked that data about naloxone be separated by fentanyl and carfentanyl. One of the big sex differences is how large a person is and their ability to handle carfentanyl; thus, women may be affected more than men. There needs to be more public awareness about drugs being laced with carfentanyl and people overdosing from them. Dr. Volkow agreed, noting that synthetic opioids are driving the mortality rate. NIDA is very interested in understanding the best way of reversing an overdose from these drugs because both fentanyl and carefentanyl get into the brain very rapidly so that there is almost no time to administer naloxone before death. When opioids are ingested, the rate of respiration decreases, muscular rigidity increases so the lungs cannot expand, and hypertension occurs, reducing circulation and inhibiting naloxone's ability to reach the brain. Thus, NIDA is trying to encourage researchers and drug companies to develop medications to stimulate respiration and increase circulation so that these drugs can be combined with naloxone to help it move more quickly through the body to increase the likelihood of reversing overdoses.

Rachel Jones, Ph.D., R.N., encouraged increased attention to acupuncture as a treatment for pain. Dr. Volkow replied that integrative treatments such as acupuncture, meditation, and improving sleep are emerging areas of treatment that HEAL will address. This research is likely to be particularly valuable for women.

### **National Academies Video Recap**

A short video was shown with highlights from the National Academies Symposium Highlighting Evidence-Based Interventions to Address the Underrepresentation of Women in Science.

### **Inclusion of Women, Minorities, and Individuals Across the Lifespan**

Dawn Corbett, M.P.H., NIH Inclusion Policy Officer, Office of Extramural Programs, reviewed the goals for her presentation: To understand recent changes to NIH policies and procedures regarding inclusion of women, minorities, and individuals across the lifespan in NIH-funded clinical research; review the status of Government Accountability Office (GAO) recommendations related to inclusion of women and minorities; review FY 2016-FY 2018 data on the inclusion of women and minorities in NIH-funded clinical research; and learn about recent changes to the Federal Policy for the Protection of Human Subjects (Common Rule).

**Recent Changes to Policies and Procedures:** Ms. Corbett reviewed the timeline of inclusion at the NIH beginning in 1986 with a policy encouraging researchers to include women in studies. This policy became law with the Revitalization Act of 1993 and in December 2016, the 21<sup>st</sup> Century Cures Act was passed which included new requirements for inclusion and reporting of participants, based on sex or gender, race, ethnicity, and age. Finally, in January 2019, NIH's Inclusion Across the Lifespan policy became effective which requires the inclusion of individuals of all ages in NIH clinical research, unless there is a scientific reason for their exclusion.

The 21<sup>st</sup> Century Cures Act required NIH to convene a workshop on age grouping and exclusions (Inclusion Across the Lifespan Workshop, June 2017); examine inclusion guidelines on age and publish data on the age of participants in NIH clinical research; assemble participant inclusion data, disaggregated by research area, condition, and disease category; and a requirement that all applicable clinical trials report results of valid analyses by sex or gender, and race and ethnicity at ClinicalTrials.gov.

**Status of GAO Recommendations:** In 2015, GAO published a report entitled *Better Oversight Needed to Help Ensure Continued Progress Including Women in Health Research*. Since then, NIH has been working on implementing the recommendations in the report. Two of the recommendations—"make IC-level enrollment data readily available through public means" and "ensure that program officers have a means of recording their monitoring of awardees plans for and progress in conducting analysis of potential sex differences" have been

implemented. Three additional recommendations remain in progress including “the ability to report inclusion data by research, condition, and disease category.

**Data on the Inclusion of Women and Minorities:** Inclusion by research, condition, and disease categories (RCDC) may be found on the NIH RCDC Inclusion Statistics Report website, which contains data, by IC, number of, and characteristics of participants according to 281 RCDC categories. Ms. Corbett provided a summary of NIH enrollment data by sex/gender, race, and ethnicity.

**Common Rule:** The Common Rule refers to HHS regulations used in Human Subjects research. A revised Rule was published in 2017; implementation was delayed until July 19, 2018 and was voluntary until January 21, 2019 when compliance became mandatory. The revisions addressed changes in informed consent, Institutional Review Board (IRB) review, definitions of human subjects and research, and an expansion of the exempt categories of research from six to eight, including three new exemptions. The revised Common Rule required use of a single Institutional Review Board (IRB) as of January 20, 2020. However, NIH’s single IRB policy has already been in effect for domestic, multi-site studies since 2018.

**Discussion:** Dr. Gregory asked if a PI in a multi-site study would be penalized if an institution required the use of its own IRB. Ms. Corbett noted that the policy represents a big culture change for institutions; NIH will provide guidance on setting up reliance agreements and gaining cooperation. The use of multiple IRBs after the compliance date would be considered non-compliant.

Dr. McGregor inquired why NIH is collecting data by gender unknown and if biological and social gender information will be considered. Ms. Corbett responded that data collection is voluntary; if an individual chooses not to disclose the information, s/he will be identified as unknown/not identified. NIH leaves it up to PIs to collect the data as they want to define it. Dr. Clayton commented that because the measurement of gender is more nuanced and complicated than sex, ORWH believes there are methodological barriers to moving forward on this issue without validated instruments and tools. Under the trans-NIH strategic plan, there is a specific goal focused on methods. Under that goal would be development of measures of gender.

Dr. Bairey Merz inquired about the use of large datasets that were collected before implementation of the revised Common Rule. Ms. Corbett replied that such use would be subject to all non-exempt human subjects research, e.g., IRB approval, unless broad consent was obtained. NIH has not yet seen guidance for exemptions 7 and 8, which may help in this regard. Dr. Bairey Merz also asked what happens to the patterns of enrollment in NIH-funded clinical health studies if reproductive health studies are removed. Ms. Corbett responded that the statistics on single sex studies look fairly similar. Overall, the statistics are not organized with reproductive health studies removed. The aforementioned website includes a category for reproductive health and allows the user to exclude male-only or female-only studies for a more granular view.

#### **Sex as a Biological Variable (SABV) Program Update**

Chyren Hunter, Ph.D., ORWH Associate Director for Basic and Translational Research, reported on the status of SABV policy uptake and implementation; new impetus for assessment of SABV policy uptake; new partnerships for SABV resource development; other SABV resources; and SABV application to the science.

**SABV policy uptake and adoption:** Dr. Hunter reviewed the policy that went into effect on January 25, 2016. Adoption, however, remains incomplete. A study in the *Journal of Women’s Health* (2019) surveyed NIH study section members from 2016-2017 via email about their perception of SABV consideration by applicants; study section members are supposed to downgrade applications if SABV is not addressed. The study section members who responded to the survey (10-15 percent, depending on year) perceived an increase in the

consideration of SABV by applicants. At least 30 percent, however, felt that half or fewer applications addressed SABV in their experimental design, analysis, and reporting. More research and evaluation on this issue is needed.

**New impetus for assessment of SABV policy uptake:** Further assessment of SABV policy intake was included in the 21<sup>st</sup> Century Cures Act (2016). The Cures Act focused on enhancing rigor and reproducibility of scientific research; the Trans-NIH SABV Working Group, accordingly, has focused on rigor and outcomes evaluation. Public Law 115-135, Foundations of Evidence-based Policy Making of 2018, was signed into law on January 14, 2019. It seeks to improve evidence-based policy making through increasing the evaluation capacity of federal agencies. In response, NIH created an Office of Evaluation, Performance and Reporting within the Office of the Director. Its mission is to better capture, communicate, and enhance the value of NIH research through strategic planning, performance monitoring, evaluation, and reporting.

**New partnerships:** ORWH and the National Institute of General Medical Sciences (NIGMS) established a new partnership to develop a primer on SABV. The goal of the primer is to enhance the consideration of SABV in the context of conducting rigorous research to improve the reproducibility of data by clarifying the SABV policy, achieving buy-in and compliance, and helping investigators to apply the policy to their research, whether it is basic science, preclinical, clinical, or population health. The primer will be an interactive, e-learning course designed as independent, interrelated modules, with an instructor guide, glossary and references.

**Other SABV resources:** ORWH has co-funded field-specific training on SABV, e.g., RFA GM-18-002, Training Modules to Enhance the Rigor and Reproducibility of Biomedical Research to include Addressing Sex as a Biological Variable in Preclinical Pharmacology and Neuroscience Research: Accounting for Neglected Factors and Applying Practical Solutions to Enhance Rigor and Reproducibility.

**Spotlighting SABV in science:** George F. Koob, Ph.D., Director of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) gave a presentation on “Emerging Research on Alcohol and Women’s Health: What Do We Know and Where Do We Go from Here?” to the NIH Coordinating Committee on Research on Women’s Health on March 13, 2019 ORWH hosted a GWAS, Sex & Chromosomes Think Tank on February 27, 2019, attended by 15 NIH ICOs. The meeting explored issues related to under-representation of sex chromosomes in GWAS results.

**Discussion:** In reference to the SABV primer, Dr. Stefanick observed that it’s important that environmental factors be considered because environmental conditions in preclinical studies are very different for male and female rodents

Geert J. de Vries, Ph.D., commented that neuroscientists are aware of differences in brain and body size; there are many sex differences that researchers identify, but often not much of a difference between men and women, e.g., in the opioid receptors in the brain. The field doesn’t yet know much about the implications. Dr. Bairey Merz said that while the survey of study section reviewers was useful, its 15 percent response rate was inadequate. Dr. Clayton noted that ORWH has had preliminary discussion with the new Office of Evaluation about this and is working with the governance group and other officials to orient everyone to the SABV policy, trying to address the issue at multiple levels.

Sabra Klein, Ph.D., observed that lip service is paid to the SABV policy in grant writing, but resulting publications don’t report on the data. Dr. Clayton said that NIH has had three workshops with journal editors; journal policies are improving but it’s an ongoing battle. She encouraged ACRWH members to influence policies at journals with which they are associated.

Dr. Clayton cited a paper by member Stacie Geller, Ph.D. Dr. Geller observed that less than one-third of NIH Phase III clinical trials have any SABV data reported in publications. In compliance with the 21<sup>st</sup> C. Cures act, they will now have to put the data into ClinicalTrials.gov within a year of the primary completion date.

Dr. Jones reported that her experience reviewing manuscripts indicates that the use of male-only subjects has been justified because an HIV study is focusing on men having sex with men. However, these men may also be having sex with women, thereby overlooking an important aspect of HIV transmission in women. Her concern is that the argument for a single-sex study is one that should be probed more deeply.

As part of researchers' accountability, Dr. Gregory suggested that adherence to the SABV policy be mandated, e.g., its application described in the final report or written into milestones with further funding denied unless the milestone had been met. Dr. Clayton responded that NIH has not had a final progress report requirement.

Dr. Mazure suggested implementing a policy that if the researcher does not publish the SABV information, s/he will not be successful when pursuing a renewal; a question about this could be added to the final progress report. Dr. Clayton responded that as part of the 21<sup>st</sup> Century Cures Act, if a researcher does not report applicable results in ClinicalTrials.gov, the NIH Director has the ability to withhold funding to the institutional grantee.

**Access and Analysis of Large Datasets:** Dr. Bairey Merz offered a practical suggestion for overcoming public access barriers to using large public NIH-funded Phase III datasets, i.e., pay for sex-specific meta-analyses by outside groups that have the capacity to analyze large amount of data. Dr. Mazure commented that the concept is that the taxpayer has paid for this research and should have open access after a number of years. Dr. Hunter commented that NIH is now requiring open access to data sets as described in the notice of grant award. Margaret Bevans, Ph.D., reiterated NIH's public access to data policies, including for GWAS, and suggested the ACRWH make comments on those policies based on the present conversation. Dr. Stefanick suggested that expertise in big data can be found at Stanford University which has created an academic department on this topic; Dr. Mazure said her program uses graduate students that want to learn to do this. She encouraged researchers to plan who is going to get to know a dataset well so that it can be used effectively.

#### **ACRWH Discussion**

Dr. Clayton invited comments and suggestions for future meetings. Dr. de Vries suggested that a future topic be gender as seen through a sex lens. Gender influences issues like housing of rodents in preclinical studies, as well as face-to-face data collection in clinical research. There have been previous discussions about issuing a call for research in this area; he would like to see that reactivated.

Michelle Robinson, D.M.D., suggested future discussions about the intersection between gender, race, and ethnicity, noting, for example, that prescription patterns are different for people of color. Dr. Clayton acknowledged the importance of the intersection of race, gender and ethnicity, as well as context. She asked Vicki Cargill, M.D., ORWH, to describe how ORWH is thinking about these issues in the U3 program. Dr. Cargill explained that because underrepresented women often have multiple other factors that are co-occurring; therefore, the U3 program is interdisciplinary, requiring expertise that is often not included in biomedical research.

Dr. Klein commented that many researchers, including those at her SCORE program at Johns Hopkins University (JHU), are exploring new ways to measure the intersection of race, gender, and ethnicity.

Dr. Stefanick reiterated the need for continued discussion on the intersection of race, gender, and ethnicity, but encouraged the addition of age and social structure to the mix.

Dr. McGregor reinforced Dr. Stefanick's comments about studying women across the lifespan, noting that there are biological issues that change with increasing age. Dr. Clayton encouraged everyone to pay attention to page 7 of the *Trans-NIH Strategic Plan for Women's Health Research*. It incorporates internal and external factors that influence women's health across the lifespan. She asked for ACRWH members' help disseminating the vision to the field.

Dr. Fillingim suggested discussing the role of male mentors to promote women's career development in the sciences, noting that men are stepping back from this role yet there are an insufficient number of senior women to serve as mentors.

Dr. Bairey Merz encouraged revisiting journal policies about reporting on sex differences at a future meeting.

Dr. Wood commented that page limits used to be cited by editors as a reason for restricting full reporting, but that is no longer a consideration now that everything is online.

Dr. Jones encouraged the continuation of translational research, and the use of social media and development of mobile applications to reach both men and women. In response to a request from Dr. Clayton, she explained her success in recruiting study subjects through social media.

Dr. Regensteiner commented positively on the depth of information presented at ORWH meeting, while acknowledging that much more research is needed.

Dr. Gregory expressed appreciation for the references shared and opportunities to follow up.

Dr. Page observed that awareness of the need to study women's health issues and SABV have increased dramatically over the past 16 years, but expressed disappointment that the resources to address the issues have not kept pace. Dr. Clayton responded that Team ORWH has done a fantastic job leveraging available resources and making tough decisions.

Dr. Mazure commented that the rate of change in the field is increasing in a positive direction due to changes in NIH's requirements. She also noted that her institution is dealing with climate, harassment, and other issues discussed at this meeting.

Dr. Wood noted that while it's good to consider how to analyze the data in an intersectional way, it's often difficult to get the basic data. She encouraged the field to focus on the basics of collecting demographics and then to think about ways to visualize the data to share with others.

Louise D. McCullough, M.D., Ph.D., expressed hope that the momentum begun by the GWAS Think Tank will continue because it is an important issue in both preclinical studies and GWAS studies. Dr. McCullough commented that she is starting to see some pushback about new requirements and worries that the field will waste time debating them.

Dr. Bairey Merz commented that if a clearinghouse could be created and then publish sex-stratified analyses on the web, a requirement related to this could be placed in FOAs. This would spur researchers to publish the desired data.

Dr. Page asked Dr. Clayton to provide more "color commentary" on where ORWH's strongest partners or champions are emerging. Dr. Clayton responded that ORWH has been building relationships via the CCRWH. In the past, some of ORWH's biggest partners have been NIDDK, NIDA, NIAAA, NHLBI, and NICHD. ORWH is starting to work with NICHD in a new way, e.g., working to address MMM synergistically across ICS. The Cures

Act includes a mandated annual meeting between each IC director and Dr. Clayton, and a specification of how the IC will address women's health, including metrics, in its annual strategic plan. All of these new requirements should support more progress for women's health research.

Dr. Klein suggested working with the Center for Scientific Review to learn how sections within specific disciplines are adopting SABV.

Bairey

Ms. Spencer concluded the discussion by thanking ACRWH members for their comments on biennial report. It will be published in the near future. ORWH also welcomes members' feedback on the meeting, as well as suggestions for future meetings. She encouraged members to email their ideas to her.

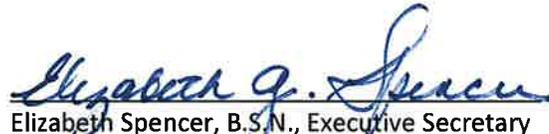
**Closing Remarks**

Dr. Clayton reminded ACRWH members that the next meeting is October 22-23, 2019. She adjourned the meeting at 3:24 pm.

**Certification**

We certify that the contents above are accurate and complete.

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

  
\_\_\_\_\_  
Elizabeth Spencer, B.S.N., Executive Secretary  
Advisory Committee on Research on Women's Health

Date 9.26.19

Date 9.25.19