

Office of Research on Women's Health (ORWH)  
National Institutes of Health (NIH)

## 43rd Meeting of the NIH Advisory Committee on Research on Women's Health (ACRWH)

NIH Main Campus, Building 31  
Conference Room 6C10  
Bethesda, MD  
April 4, 2017

### SUMMARY

#### ACRWH Members Present

Janine A. Clayton, M.D. (Chair)  
Jill Becker, Ph.D.  
Wei-Jung Chen, Ph.D.  
Geert de Vries, Ph.D. (via telephone)  
Carmen Green, M.D.  
Angela Kashuba, Pharm.D.  
Ana Maria Lopez, M.D., M.P.H.  
Carolyn Mazure, Ph.D.  
Mary Palmer, Ph.D., R.N.C.  
Judith Regensteiner, Ph.D.  
Elizabeth Spencer, R.N.  
Connie Weaver, Ph.D.  
Teresa Woodruff, Ph.D.

#### Guests Present

Wendy Brewster, M.D., Ph.D.  
Kimberly Gregory, M.D.  
Rachel Jones, Ph.D., R.N.  
Emeran Mayer, M.D.  
Louise McCullough, M.D., Ph.D.  
Susan Wood, Ph.D.

#### Presenters Present

Monica Basco, Ph.D.  
John Burklow  
Eric Dishman  
Neill Epperson, M.D.  
Richard Nakamura, Ph.D.

### CALL TO ORDER, INTRODUCTION OF MEMBERS AND STAFF, APPROVAL OF SEPTEMBER 2016, MINUTES

*Janine A. Clayton, M.D., Director of ORWH, Associate Director for Research on Women's Health*

Dr. Janine Clayton called the group to order at 9:00 a.m., welcoming the attendees to the 43rd meeting of the Advisory Council on Research on Women's Health. She noted that the meeting was open to the public and was being broadcast on the NIH videocast network. She referred to the rules for ethics regarding conflicts of interest, asking meeting participants to recuse

themselves in any cases where conflicts of interest might arise during the day. The participants introduced themselves.

Dr. Clayton asked the members to consider the draft minutes of the previous meeting of the Advisory Committee. The minutes of the September 2016 meeting were approved unanimously.

Carmen Green, M.D., encouraged the members to applaud the awards given to Dr. Clayton in recent months. Recognition of Dr. Clayton's efforts has helped to publicize and strengthen the work of the ORWH.

## **DIRECTOR'S REPORT**

*Janine A. Clayton, M.D., Director of ORWH*

Dr. Clayton stated that the mission of the ORWH features the enhancement and expansion of women's health research, the inclusion of women and minority groups in clinical research, and the advancement of careers of women scientists. She cited the historical efforts of leaders, including Dr. Ruth Kirschstein, Dr. Bernardine Healy, Senator Barbara Mikulski, and Dr. Vivian Pinn, to advance the Office. The ORWH seeks to put science to work for the health of all women.

Dr. Clayton introduced three new ORWH associate directors: Monica Basco, Ph.D. (Science Policy, Planning, and Analysis), Victoria Cargill, M.D., (Interdisciplinary Research), and Chyren Hunter, Ph.D. (Basic and Translational Research).

Dr. Clayton reviewed the Office's work in implementing the new Sex as a Biological Variable (SABV) policy and the recognition the policy has received. She cited examples of articles that were published Federation of American Societies for Experimental Biology (FASEB) and The Journal of the American Medical Association (JAMA). In addition, Dr. Clayton mentioned she accepted the Woman's Day Red Dress Award and the American Medical Association's Nathan A. Davis Award. SABV is receiving media attention with articles in The Washington Post, Chemical & Engineering News, The Scientist, and future articles in The Huffington Post and Stanford Medical News. Dr. Clayton reported that there is growing interest in SABV through partnerships with the American Chemical Society, the Endocrine Society and AMSUS, The Society of Federal Health Professionals.

Today the NIH expects that sex will be factored as a biological variable into research design, analysis, and reporting. Recognition of the ORWH and this policy has grown, especially because of recent publications, and the Office has been receiving awards. One recent meeting/publication focused on the use of terms regarding sex and gender. The Office has played a significant role in the advancement of SABV issues, for example, by partnering with academia and societies and spreading the word that ignoring sex-differences in research outcomes represents a missed opportunity to maximize returns on the research investment. As a result, the knowledge base remains incomplete.

As the NIH advances the policy to a new phase, the NIH's SABV policy efforts focus on turning policy into practice. It is addressing the entire research continuum, starting with basic science,

designing the research question, and creating the study design. This includes the preclinical arena. Sex and gender also need to be considered in the clinical arena, in factors such as safety and dosage and in efforts to bring issues from the bedside back to early research. The overall goal is to offer sex/gender appropriate care. ORWH advocates for research that is rigorous, reproducible, and relevant. Both sex and gender are important for health. We must be using the terms correctly. We must disseminate information.

Dr. Clayton presented how a phased approach science and health is enhanced with SABV. It began with the drafting of the SABV policy. Next, she discussed the implementation of the policy, citing the FASEB paper, *Studying both sexes: a guiding principle for biomedicine*. Dr. Clayton continued by saying that SABV is currently in the intentional integration stage, referencing the FASEB paper *Considering sex as a biological variable in pre-clinical research*. The next step is the outcome: translating SABV for public health, using the supporting document *Reporting Sex, Gender, or Both in Clinical Research*, published in JAMA. Finally, researchers must publish the results and reference the resource, specifically by referencing the *Sex and Gender Equity in Research* guidelines.

The funding mechanisms of NIH turn policy into practice and feature institutional collaboration. Issues surrounding sex and gender influences in health and health research were evident in the FY2016 ORWH administrative supplements (additional funds for grantees who are already funded). Grants that add sex and gender considerations have been growing across the scope of NIH institutes, realizing the ORWH strategic plan. One large ongoing funding effort is the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) program for career development. The program has trained more than 600 scholars.

ORWH has presented at a variety of specific scientific research events around the country. It will host the second annual NIH Vivian W. Pinn symposium ("Healthy Women Make Healthy Communities") on women's health and research in May 17, 2017 on the NIH main campus. This month (April) the Office partnering with the FDA in presenting the Pre-conference Symposium for the 25<sup>th</sup> anniversary of the Women's Health Congress. June 1-2, ORWH will participate in the Inclusion Across the Lifespan workshop, in alignment with the 21<sup>st</sup> Century Cures Act. In October, ORWH will collaborate with the Office of Strategic Coordination, DPCPSI, which oversees the NIH Common Fund, to offer a symposium focusing on scientific advances from the ORWH sex and gender differences administrative supplement recipients and Common Fund supplement grantees.

## **ACCELERATING PRECISION HEALTH FOR ALL**

*Eric Dishman, Director, All of Us Research Program*

Mr. Eric Dishman, Director of the All of Us Research Program, which addresses individual, precision health care, described his background as survivor of a rare form of cancer and his experiences leading to an understanding of the benefit of focusing on the needs of the individual patient. He stated that no person is the average person. Mr. Dishman recounted some of his past experiences studying social aspects of medicine. The All of Us Research Program encourages customized, precision care. It recognizes the need to determine what the individual patient is

going through. For that, we need more science and data. One barrier to reaching the goal of precision medicine is the small sample sizes of most studies, which feature low diversity.

The All of Us Research Program has a mission to accelerate health research and medical breakthroughs, with its large sample sizes enabling individualized prevention, treatment, and care. It will create a national resource of clinical, environmental, lifestyle, and genetic data. It will represent diverse patients, providers, and researchers and will feature a focus on those who are under-represented in biomedical research. It seeks to support breakthroughs and what might be called “knowledge turns”, and it supports development of large data sets to support research and breakthroughs. It supports the development of tools and capabilities for researchers.

The Program has a 10-year plan and is working with NIH. There is a focus on the life process rather than recruitment based on particular diseases. There is a focus on minorities. Core values of the Program include diversity, use of partners, engagement, transparency, and accessible data. It features a data repository, a biobank, a participant center, technology systems, links to health care provider organizations, and local and national organizations as partners.

Mr. Dishman noted the Program’s current awardees and consortiums (a network), which are scattered around the United States. The Program has completed pilot-testing of language, concepts, and interfaces. A version 1 protocol for data collection has been submitted to an IRB. Enrollment and data collection using electronic health records and survey modules will begin soon. Workshops will serve to identify research questions as the program moves forward.

#### *Discussion*

Rachel Jones, Ph.D., R.N., noted the value of using Facebook for activities such as recruitment. As an example of its power for research, Facebook has presented clusters of new recruits at times. Mr. Dishman was encouraged to incorporate social network analysis. He stressed that the All of Us program will over-recruit women participants. Mr. Dishman also was encouraged to consider phenotype in addition to genotype when studying aspects of exposure to drugs.

Regarding the All of Us program’s levels of research to be supported, Mr. Dishman stated that it is accepting proposals with data access and biosamples in three tiers, spanning a spectrum of risk. Alpha and beta phases of data collection will begin in May 2017. The national phase will begin in September or October.

### **PEER REVIEW: FAIRNESS OF CSR PEER REVIEW AND REVIEW OF SEX AS A BIOLOGICAL VARIABLE**

*Richard Nakamura, Ph.D., Director, NIH Center for Scientific Review*

Dr. Richard Nakamura spoke about the NIH peer review process for funding research. The NIH mission is to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability. It focuses on both basic science and public health. The mission is achieved mainly through the use of extramural research grants, which are awarded by a peer review process.

Dr. Nakamura noted the occurrence of sex disparities in the process and presented data showing rates for research grant recipients. More men apply for grants, hence there is a gap between the total amounts of grants awarded to men and women (about 30 percent go to women). However, the success rates for obtaining awards are nearly identical for men and women researchers who apply. There may be disparities in numbers of applicants caused by the environments surrounding the decision to apply for grants. The NIH has been studying its process of peer reviewing, seeking any evidence for bias. Female reviewers of grant proposals are a little more than 30 percent of the total.

Dr. Nakamura referred to a recent anonymization study that will consider potential implicit biases for race (in particular, African American/White), sex, and more in the peer review process. The study features the masking of personal identifications for 1,200 previously reviewed applications. It will attempt to determine whether differences are the result of reviewer bias or quality of applications. A minority-owned organization outside NIH is running the study. Dr. Nakamura suggested that we try to change the conscious decisions that we make rather than change the unconscious decisions that we make.

In recent times, there has been a suggestion of flaws in research—flaws relating to the rigor and reproducibility of scientific studies. In response, NIH is working to clarify expectations and highlight the following areas in need of attention: scientific premise, scientific rigor, relevant biological variables (including sex), and authentication of key biological and chemical resources. Dr. Nakamura listed some common problems, such as insufficient reporting of methodological approaches in preclinical studies, the small size of many studies (hence underpowered), and selective reporting.

Dr. Nakamura stated that the NIH is working with publishers and others to address the problems. He also called on researchers themselves to consider the issues, to increase transparency, and to promote training. Various publication venues should offer information about negative results. NIH continues to encourage exploratory studies.

### *Discussion*

Kimberly Gregory, M.D., noted that one drawback of the NIH review study sections is the pressure to keep scores within a modest range. Often a strong personality will win the discussion, and there will be a bias in favor of the majority. Sometimes a very good researcher will submit a proposal that is weak. Dr. Nakamura responded that there is an argument between those who feel it is helpful to know the track record of an applying scientist and those who feel that has an effect of maintaining the dominance of very well-known scientists. The NIH should address such issues.

Dr. Nakamura noted a NIH study that compared preliminary scores and final scores of applications and found no change in scores because of the addition, during the discussion phase, of knowledge about minority or female status of the applicant. He stated that his personal review of younger applicants found that even those who failed to achieve significant NIH funding for bench research achieved gratifying careers eventually in industry and other businesses.

Carmen Green, M.D., encouraged the Center for Scientific Review to delve deeper into the review model as it addresses researchers who are women and minority women, to examine the interplay of factors and biases. Are there advocates in the room? Dr. Nakamura noted that studies are underway.

Connie Weaver, Ph.D., asked whether there is evidence of greater scientific rigor and reproducibility outside the NIH extramural program. Does the NIH program sort biological variability or the use of different-sized cohorts? Dr. Nakamura stated that there is interest in the causes of variability in studies—causes such as stress and rearing among those studied. Researchers need to consider more aspects of the microenvironment to get to a robustness.

Jill Becker, Ph.D., wondered about the capability of study sections to include people with expertise that can evaluate the need for males and females in particular studies. The Center for Scientific Review was encouraged to include reviewers with such expertise.

## **NIH LEGISLATIVE AND POLICY UPDATE**

*Monica Basco, Ph.D., Associate Director for Science Policy, Planning, and Analysis, ORWH*

Dr. Monica Basco reported that her team at ORWH is working to develop the next NIH strategic plan for women's health research on behalf of ORWH. It will be seeking input in the upcoming months and will present a draft report on progress at the September ACRWH meeting. The final plan will be released in early 2018. The ACRWH Biennial Report for years 2015-2016 also is being written. It will include research progress, sex and minority inclusion data, and reports from NIH institutes and centers.

Dr. Basco gave a brief overview on the 21st Century Cures Act and how it will affect the activities at ORWH. Section 2031 requires IC directors to consult annually with directors of National Institute of Minority Health and Health Disparities and ORWH to make sure their IC and individual missions and goals take into consideration women and underrepresented racial and ethnic groups as well as focus on reducing health disparities.

Section 2032 changes biennial report to triennial report, but did not specifically mention ORWH. Currently the Office is still working out the details what will be required and how they will receive the data.

Section 2083 requires that the NIH Director update guidelines for the inclusion of women in research and hold a workshop to solicit input on appropriate age groups for research. On June 1-2, 2017, NIH will offer, on the main campus, a workshop titled "Inclusion Across the Lifespan." It will focus on the inclusion of children and older adults in clinical research. This workshop will feature subject-matter experts and is open to the public.

A NIH Working Group on Women in Biomedical Careers has established a newsletter and a Web presence [[womeninscience.nih.gov](http://womeninscience.nih.gov)]. A subcomponent of the working group is the research partnership of principle investigators (PIs) that responded to the earlier request-for-applications (RFA) on causal factors and interventions for understanding and improving recruitment, retention, and advancement of women in science. This group continues to be active together;

they will do a panel together at AAMC: Advancing Women in STEM and they will continue to try to do more research together as a group of PIs.

Another subgroup is the Women of Color Committee. One big success of this group is they have worked with the Special Populations Research Forum to get more women and members of under-represented racial ethnic groups as speakers in the very prominent NIH Director's lecture series (WALS), including most recently Nobel Prize Winner Dr. Linda Buck. Another component of the working group is the women of color online research network, now with a LinkedIn group and four regional chapters: North Carolina, Indiana, Washington, D.C., and Baltimore. . One goal of the subgroup is to create a venue at NIH for young scientists who have had success as Steadman scholars or who have had other experiences at the NIH as part of the intramural research staff.

### **MAKING THE CONNECTION: COMMUNICATING ABOUT NIH**

*John Burklow, Associate Director, NIH Office of Communications and Public Liaison*

Mr. John Burklow presented an overview of the work of the NIH Office of Communications and Public Liaison. The Office supports the communications of NIH Director Francis Collins and other NIH leaders. It coordinates across the NIH's Institutes and Centers and across U.S. agencies and departments. It also engages with constituency organizations and media reporters, editors, and producers to disseminate information. In the past year, the Office produced about 5,000 press releases. It responds to the public and handles freedom-of-information requests.

Key messages that guide the Office include the following: the value of investing in medical research, the health impact of NIH research, the economic impact of NIH research globally and locally, the importance of basic, clinical, and translational research, and the broad footprint or impact of NIH.

Mr. Burklow noted that NIH adopted a logo that lends a consistent identification to its products. NIH-related work is in the news every day, yet a connection back to itself is not always clear. Dr. Clayton has helped to promote NIH. The NIH Director's communication efforts include media interviews, social media information, speeches/presentations, scholarly papers, commentaries, interactions with congress, and scientific initiatives. Dr. Collins made 117 presentations in 2016. He has represented the NIH on a variety of televised programs and has engaged modestly in issues of a political nature, especially regarding the NIH budget. He has a widely read Director's Blog and many followers on Twitter.

The Office produces publications such as "NIH News in Health" which has 210,000 Email subscribers and 32,000 print-copy recipients. Another publication, "NIH Research Matters", has 100,000 subscribers. The Office supports a Spanish-language Website at <https://salud.nih.gov>. It is part of a panoply of NIH Websites with strong viewership.

Mr. Burklow announced that the Discovery Channel recently developed a documentary focused on four patients in the NIH clinical center (its research hospital). The story follows the patients over a long period of time. Titled "First In Human: The Trials of Building 10", it will be broadcast in August. It documents the challenges in diagnosing and treating difficult illnesses and reveals the reality of experimental medicine.

## *Discussion*

Judith Regensteiner, Ph.D., encouraged the Office to inform the U.S. population about of the manner in which NIH distributes money for research throughout the nation. Perhaps the NIH could humanize the sciences by presenting individual scientists and their links to NIH. Mr. Burklow noted a recent Twitter campaign that cited research links in the states.

Teresa Woodruff, Ph.D., suggested that the NIH is doing a disservice by stressing what are called basic and translational research rather than touting good work in very difficult science and medicine. Many people equate “basic” science with “easy” science.

Dr. Green stated that many people are confused about medical and NIH research issues and might benefit from a greater stress on health literacy.

## **EXAMPLES OF BENCH-TO-BEDSIDE-TO-COMMUNITY HEALTH RESEARCH**

*Neill Epperson, M.D., Director, Penn Center for Women’s Behavioral Wellness, University of Pennsylvania*

Dr. Neill Epperson described research at the University of Pennsylvania and one particular research program that includes a focus on the roles of sex and gender in medicine and health. The *Penn PROMOTES Research on Sex and Gender in Health* program at the university has benefited greatly from funding from the ORWH’s BIRCWH and SCOR programs.

The *Penn PROMOTES* program is a “whole school” initiative which promotes a consideration of sex and gender as critical variables in health research across the lifespan. It features multi-principal-investigator, multi-cycle, program grants that will be effective in fostering translational research. *Penn PROMOTES* was established in 2012 with a grant from the National Institute of Mental Health and ORWH initially to study mood disorders across the female lifespan.

The *Penn PROMOTES* program has assessed the status of considering SABV and gender in clinical research at the University of Pennsylvania. It has trained Institutional Review Board (IRB) members about NIH guidelines regarding SABV and changed the language of templates to include discussion of SABV in all IRB submissions.

Dr. Epperson focused on important investigations of the effects of Adverse Childhood Events (ACE) in the pre-pubertal window on later health. Early adverse events were found to be associated with later risk in areas such as depression, verbal memory performance during menopause, other brain functions, and fetal stress when the mother gives birth. One chemical culprit may be enduring alterations in the cytokines in the woman’s body. The studies enrolled women as well as male and female animal models. Dr. Epperson concluded that animal models of stress can mimic human stressors. To determine mechanisms, we will need to identify ecologically relevant stressors. The research will need close collaborations among investigators to successfully link bench to bedside to community.

## *Discussion*

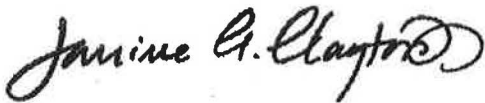


Dr. Gregory asked about the need to control for hormonal birth control in such studies, as there may be overlap with the effects of ACE. Dr. Jones added the need to investigate the capacities for neuroplasticity. Of course, one way to reduce effects of ACE is to prevent the occurrence of ACE to begin with. That would come about by improving the mental health and economic health of parents.

Emeran Mayer, M.D., noted that the cited studies involve mental health effects in western societies. Might such effects be found to be greater in societies where stress, or adverse events, are more prevalent? Dr. Epperson stated that the women studied by her group are at the top of their intellectual game and they notice the changes in themselves. Expectations about mental activities at various ages can differ among the many cultures of the world.

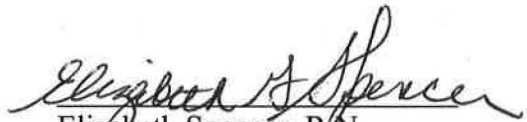
### **CLOSING REMARKS**

Dr. Clayton concluded that we need to develop strategies and trial designs that lead to efficacy of studies for both women and men. She thanked the ACRWH members, speakers, and other attendees and adjourned the meeting at 2:30 p.m.



---

Janine Austin Clayton, M.D.  
Director, ORWH



---

Elizabeth Spencer, R.N.  
Executive Secretary, ACRWH