43rd Meeting of the NIH Advisory Committee on Research on Women's Health

Office of Research on Women's Health
National Institutes of Health

April 4, 2017

National Institutes of Health
Office of Research on Women's Health

Reminder: Special Government Employees

- Subject to the same ethics rules that apply to government employees
- Rules located in “Standards of Ethical Conduct for Employees of the Executive Branch”
- Real, potential, or apparent conflict of interest

43rd Meeting of the NIH Advisory Committee on Research on Women's Health

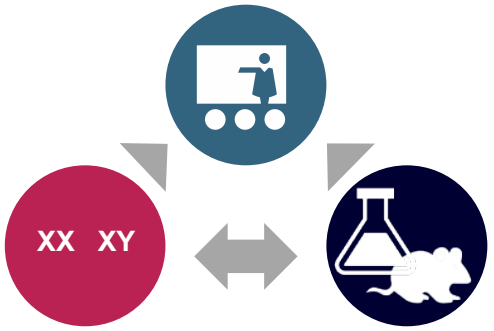
Janine Austin Clayton, M.D.
NIH Associate Director for Research on Women's Health
Director, Office of Research on Women's Health
National Institutes of Health

Director's Report

April 4, 2017

National Institutes of Health
Office of Research on Women's Health

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

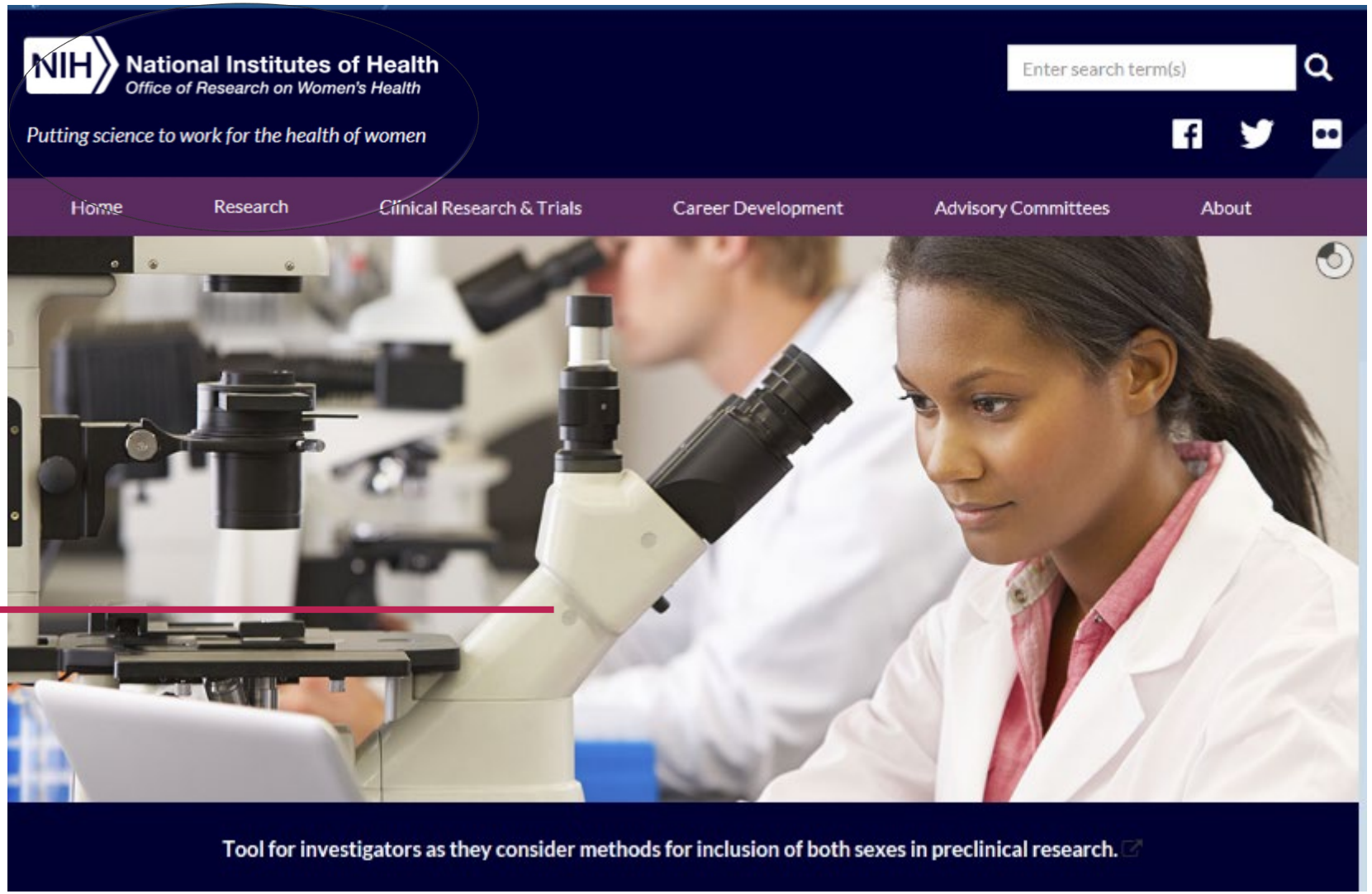


Our Mission:

- Enhance and expand women's health research
- Include women and minority groups in clinical research
- Promote career advancement

National Institutes of Health
Office of Research on Women's Health

ORWH Purpose



New ORWH Staff

Monica Ramirez Basco, PhD
Associate Director,
Science, Policy, Planning,
and Analysis

Victoria Cargill, MD, PhD
Associate Director,
Interdisciplinary Research

Chyren Hunter, PhD
Associate Director,
Basic and Translational Research

National Institutes of Health
Office of Research on Women's Health

Team ORWH

National Institutes of Health
Office of Research on Women's Health

SABV Policy Announcement

"NIH expects that sex as a biological variable will be factored into research designs, analyses, and reporting in vertebrate animal and human studies."

January 25, 2016 (effective date)

NOT-OD-15-102: Consideration of Sex as a Biological Variable in NIH-funded Research
https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-102.html

SABV Gets Recognized

Growing Interest in SABV

American Chemical Society

ENDOCRINE SOCIETY

VA HEALTH CARE Defining EXCELLENCE in the 21st Century

AMSUS The Society of Federal Health Professionals

NIH National Institutes of Health
Office of Research on Women's Health

Implementation is a Team Sport

How Did We Get Here?

SABV Phase II: Intentional Integration

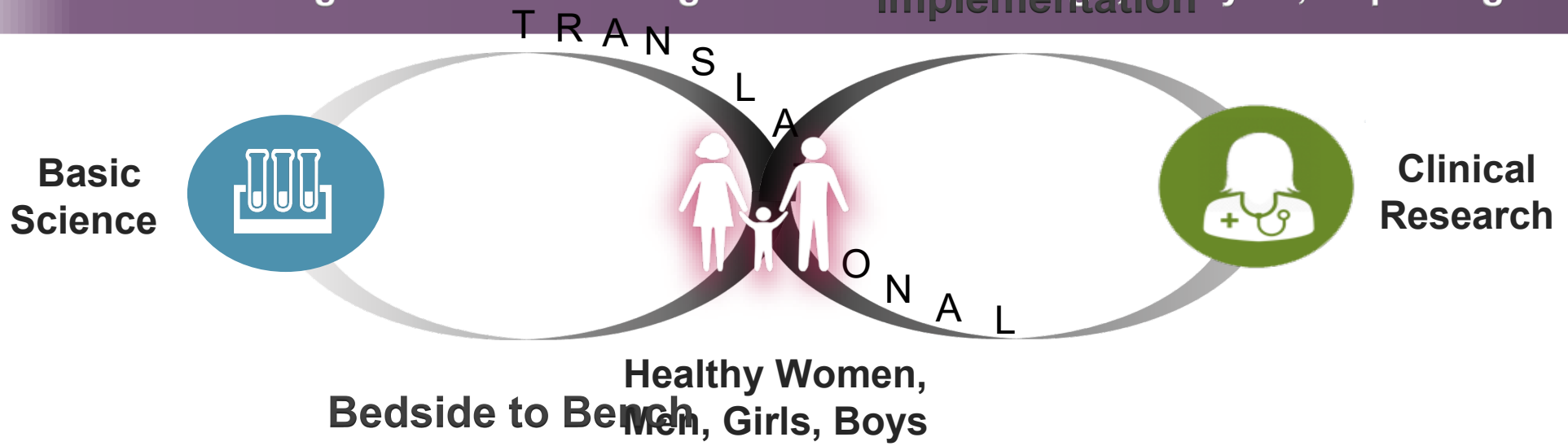
Sex/Gender Influences on Health and Disease

Preclinical Studies

Phase I, II, III, IV
Clinical Trials

Accounting for Sex as a Biological Variable in Design, Analysis, Reporting

Implementation



Education | **Health Policy** | **Health Care**

National Institutes of Health
Office of Research on Women's Health

Guidelines Facilitate SABV Application in Scientific Publication

Sex and Gender Equity in Research: rationale for the SAGER guidelines and recommended use

May 3, 2016

Heidari, Shirin, et al. "Sex and Gender Equity in Research: rationale for the SAGER guidelines and recommended use." *Research Integrity and Peer Review* 1.1 (2016): 1.

Accessed close to 5,500 times
(a/o 04.03.2017)

European Association of Science Editors

EASE

www.ease.org.uk/

National Institutes of Health
Office of Research on Women's Health

Er

SABV POLICY

THE FASEB JOURNAL
The Official Journal of the Federation of American Societies for Experimental Biology

Studying both sexes: a guiding principle for biomedicine

Janine Austin Clayton

Author Affiliations

Correspondence: Correspondence: Office of Research on Women's Health, National Institutes of Health, 6707 Democracy Blvd., Suite 400, Bethesda, MD 20892, USA. E-mail: janine.clayton@nih.gov

Abstract

In May 2014, the U.S. National Institutes of Health (NIH) announced that it will ensure that investigators account for sex as a biological variable (SABV) in NIH-funded preclinical research as part of the agency's rigor and transparency initiative. Herein, I describe in more detail the rationale behind the SABV policy component and provide additional detail about policy goals. In short, studying both sexes is a guiding principle in biomedical research that will expand knowledge toward turning discovery into health. NIH expects that considering SABV in preclinical research will help to build a knowledge base that better informs the design of clinical research and trials in humans. Integrating the practice of studying both sexes in preclinical research will, over time, expand our currently incomplete knowledge base that plays a critical role in informing the development of sex- and gender-appropriate medical care for women and men. —Clayton, J. A. Studying both sexes: a guiding principle for biomedicine.

gender NIH sex-based biology inclusion SABV

THE FASEB JOURNAL
The Official Journal of the Federation of American Societies for Experimental Biology

Considering sex as a biological variable in preclinical research

Leah R. Miller*,[1], Cheryl Marks[†], Jill B. Becker[‡], Patricia D. Hurn[§], Wei-Jung Chen[¶], Teresa Woodruff[||], Margaret M. McCarthy[#], Farida Sohrabji[¶], Londa Schiebinger**, Cora Lee Wetherington[††], Susan Makris[‡‡], Arthur P. Arnold[§§,¶¶], Gillian Einstein[|||,##,***], Virginia M. Miller[†††,‡‡‡], Kathryn Sandberg[§§§,¶¶¶], Susan Maier*, Terri L. Cornelison* and Janine A. Clayton*

Author Affiliations

[1]Correspondence: Office of Research on Women's Health, National Institutes of Health, 6707 Democracy Blvd., Suite #400, Bethesda, MD 20892, USA. E-mail: leah.miller@nih.gov

Abstract

In June 2015, the National Institutes of Health (NIH) released a *Guide* notice (NOT-OD-15-102) that highlighted the expectation of the NIH that the possible role of sex as a biologic variable be factored into research design, analyses, and reporting of vertebrate animal and human studies. Anticipating these guidelines, the NIH Office of Research on Women's Health, in October 2014, convened key stakeholders to discuss methods and techniques for integrating sex as a biologic variable in preclinical research. The workshop focused on practical methods, experimental design, and approaches to statistical analyses in the use of both male and female animals, cells, and tissues in preclinical research. Workshop participants also considered gender as a modifier of biology. This article builds on the workshop and is meant as a guide to preclinical investigators as they consider methods and techniques for inclusion of both sexes in preclinical research and is not intended to prescribe exhaustive/specific approaches for compliance with the new NIH policy.—Miller, L. R., Marks, C., Becker, J. B., Hurn, P. D., Chen, W.-J., Woodruff, T., McCarthy, M. M., Sohrabji, F., Schiebinger, L., Wetherington, C. L., Makris, S., Arnold, A. P., Einstein, G., Miller, V. M., Sandberg, K., Maier, S., Cornelison, T. L., Clayton, J. A. Considering sex as a biological variable in preclinical research.

Ann Ist Super Sanità 2016 | Vol. 52, No. 2: 154-157
DOI: 10.4415/ANN_16_02_05

MONOGRAPHIC SECTION

COMMENTARY

Sex And Gender Equity in Research (SAGER): reporting guidelines as a framework of innovation for an equitable approach to gender medicine

Paola De Castro[1], Shirin Heidari[2] and Thomas F. Babor[3]

[1]*Settore Attività Editoriali, Istituto Superiore di Sanità, Rome, Italy*
[2]*Reproductive Health Matters, London, UK*
[3]*Department of Community Medicine, University of Connecticut, School of Medicine, Farmington, CT, USA*

Abstract

Sex and gender are important determinants of health and influence research findings in a variety of ways, yet they are often overlooked and underreported. This oversight limits the generalizability of research findings and their applicability to clinical practice. The objective of this paper is to point out how journal editors can influence better reporting of sex and gender in research by establishing a methodological framework directly addressing authors of scientific publications as well as referees, and indirectly affecting all the stakeholders in the research cycle, from funders to policy makers and clinicians. Such a framework is represented by the Sex And Gender Equity in Research (SAGER) guidelines, developed by the European Association of Science Editors (EASE) to encourage a more systematic approach to the reporting of sex and gender in research across disciplines. The paper includes the rationale and basic principles of the SAGER guidelines.

Key words

- sex
- gender
- guidelines
- SAGER
- scientific publishing
- gender bias
- equity

SEX AND GENDER ARE OVERLOOKED AND UNDERREPORTED, WHERE DOES RESPONSIBILITY LIE?

Sex and gender and their interactions play a very important role for the health and wellbeing of individuals and, subsequently, impact public health. Sex and gender are in fact important determinants of health, and influence research findings in a variety of ways. Yet, sex and gender are generally overlooked and underreported in research across disciplines. This oversight limits the generalizability of research findings and their applicability to clinical practice, in particular for women, but also for men.

Drugs, for example, are metabolised differently in men and women, and can result in different adverse event profiles, treatment responses and treatment outcomes. Lack of gender balance in drug trials and the failure to consider sex and gender in design of these trials result in insufficient information being available prior to approval and marketing. Safety tests of car seats, often based on male standards, show different risk for injuries among females; the effect of chemicals in the environment have been studied predominantly in men, although they can have deleterious effects on women's reproductive health. These are but a few examples that demonstrate that the needs, behaviours and attitudes of women as well as men are important determinants of health and well-being, yet they are often underestimated [1]. Sex- and gender-blind reporting presents a serious threat that limits the generalizability of research and causes an avoidable waste of resources [2]. Any research effort which does not take into consideration sex and gender dimensions (whenever applicable, in the study design, data analyses, results and interpretation of findings) is incomplete and in some cases can harm the "planetary health", a new science that takes into account the interdependence of human and natural systems [3]. The research community needs to become aware of their responsibilities in this regard and this issue should be taken more seriously also in science communication to the general public [4].

Disparities in research participation are well documented (see, for example, the recent article on women

Address for correspondence: Paola De Castro, Settore Attività Editoriali, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy. E-mail: paola.decastro@iss.it.

VIEWPOINT

Reporting Sex, Gender, or Both in Clinical Research?

Janine Austin Clayton, MD
Office of Research on Women's Health, National Institutes of Health, Bethesda, Maryland.

Cara Tannenbaum, MD, MS
Institute of Gender and Health, Canadian Institute of Health Research, Montréal.

Viewpoint page 1865

Should the sex or the gender of the study participants be reported? What is the correct term for designating males and females or men and women?

Virtually every clinical research report includes basic demographic characteristics about the study participants, such as age, and how many participants were male/men or female/women. Some research articles refer to this latter variable as sex, others refer to it as gender. As one of the first pieces of data reported, the importance of including sex appears undisputed. But what does the sex-gender category really entail, and how should it be reported?

With emerging evidence that both sex and gender have an effect, for instance, on how an individual selects, responds to, metabolizes, and adheres to a particular drug regimen,[1] there is an ethical and scientific imperative to report to whom research results apply. This Viewpoint explains the contexts in which sex and gender are relevant and provides suggestions for improving reporting of this characteristic.

Terminology

Two common questions asked by clinical researchers are (1) Should the sex or gender of the study participants be reported? and (2) What is the correct term for designating males and females or men and women? The answers depend on whether biological or psychosocial factors are under study. Sex and gender are not mutually exclusive. They are integrally related and influence health in different ways. According to the National Institutes of Health (NIH)[2] and the Canadian Institutes of Health Research (CIHR),[3] sex is considered a biological component, defined via the genetic complement of chromosomes, including cellular and molecular differences.[4] Karyotype at birth is nearly equal for 46XX and 46XY. Sex is reflected physiologically by the gonads, sex hormones, external genitalia, and internal reproductive organs. The terms male and female should be used when describing the sex of human participants or other sex-related biological or physiological factors. Descriptions of differences between males and females should carefully refer to "sex differences" rather than "gender differences."

Gender comprises the social, environmental, cultural, and behavioral factors and choices that influence a person's self-identity and health.[3,4] Gender includes gender identity (how individuals and groups perceive and present themselves), gender norms (unspoken rules in the family, workplace, institutional, or global culture that influence individual attitudes and behaviors), and gender relations (the power relations between individuals of different gender identities).[5] At present, there are no agreed-upon, validated tools for assessing gender. A 2-step approach to questioning has been proposed, whereby participants are asked both their sex assigned at birth and their current gender identity.[6] Authors should consider appropriate use of the words sex and gender to avoid confusing both terms.[4]

Transparency

NIH policies to enhance reproducibility through rigor and transparency require that researchers address and report relevant biological variables, such as sex, in human and vertebrate animal studies.[2] The Sex and Gender Equity in Research (SAGER) guidelines reinforce that authors should provide an explanation in the methods section whether the sex of human research participants was defined based on self-report or was assigned following external or internal examination of body characteristics or through genetic testing or other means.[4] When sex is based on self-report, it will be incorrect in a very small percentage of individuals because some individuals will not be 46XX or 46XY. However, in most research studies, it is not possible to conduct detailed genetic evaluation to determine the genetic make-up of all participants.

Authors reporting the results of clinical trials should analyze and report data separately for male and female study participants.[3,4] Three compelling reasons drive the recommendation to stratify and report outcome data by sex, gender, or both. One reason is to avoid drawing incorrect conclusions. When results for male and female participants are combined, the average of aggregated male and female participants' results may mask differences between them. The effects of an intervention in one sex might be greater than in the other; toxicity might differ; symptom profiles might differ; or one sex might experience more adverse effects.[1] Failing to account for gender can also lead to spurious results. For example, gender, independent of sex, predicts poor outcomes after acute coronary syndrome.[7]

Another reason to report data by sex, gender, or both is to facilitate meta-analysis. When no differences exist, and even when studies are underpowered, the raw data should be presented to allow for meta-analysis by sex, gender, or both and can inform sample size calculations for future studies. A third reason is to reduce waste in research. Repeating a trial because previous

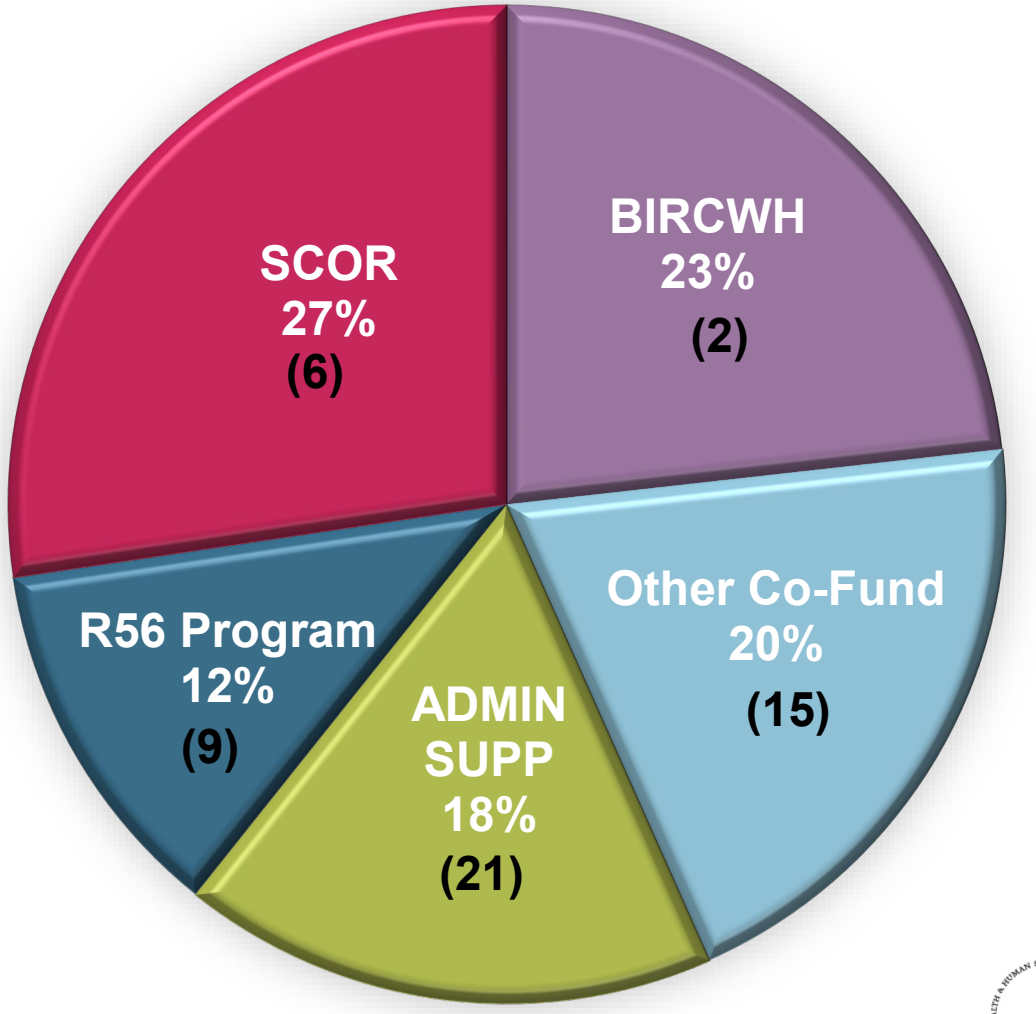
Corresponding Author: Janine Austin Clayton, MD, Office of Research on Women's Health, National Institutes of Health, 6707 Democracy Blvd, Bethesda, MD 20817 (janine.clayton@nih.gov).

Enhancing Science and Health with SABV

Supplemental Data

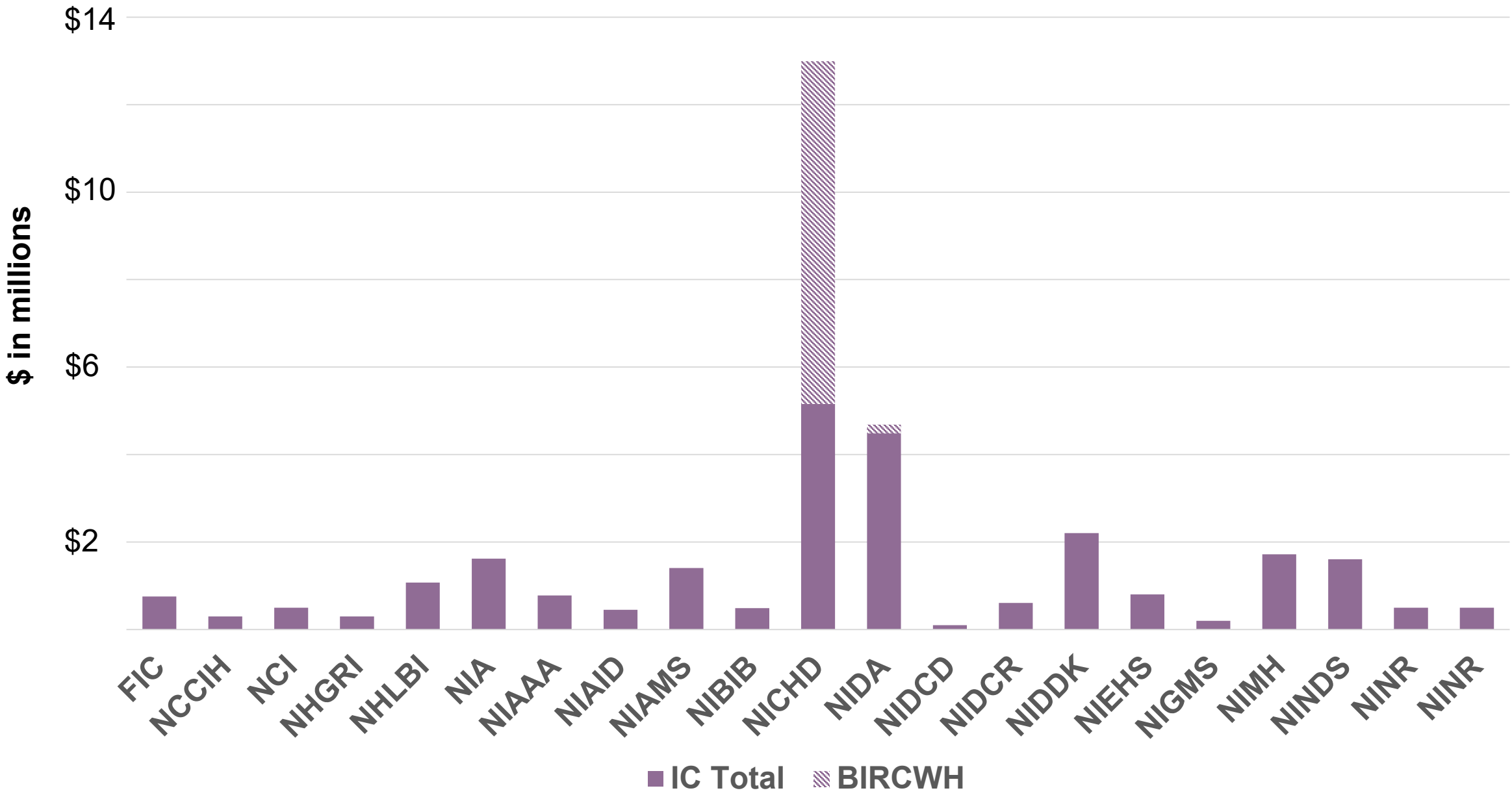
National Institutes of Health
Office of Research on Women's Health

FY16 ORWH Research Funding (%) by Program



(#) Participating ICs

ORWH FY2016 Extramural Awards, By IC



The Incorporation of Sex and Gender Influences
FY2016 ORWH Administrative Supplements

Study Type

Description	Percent
Propose preclinical research	55%
Propose clinical research	27%
Propose both clinical and preclinical	18%

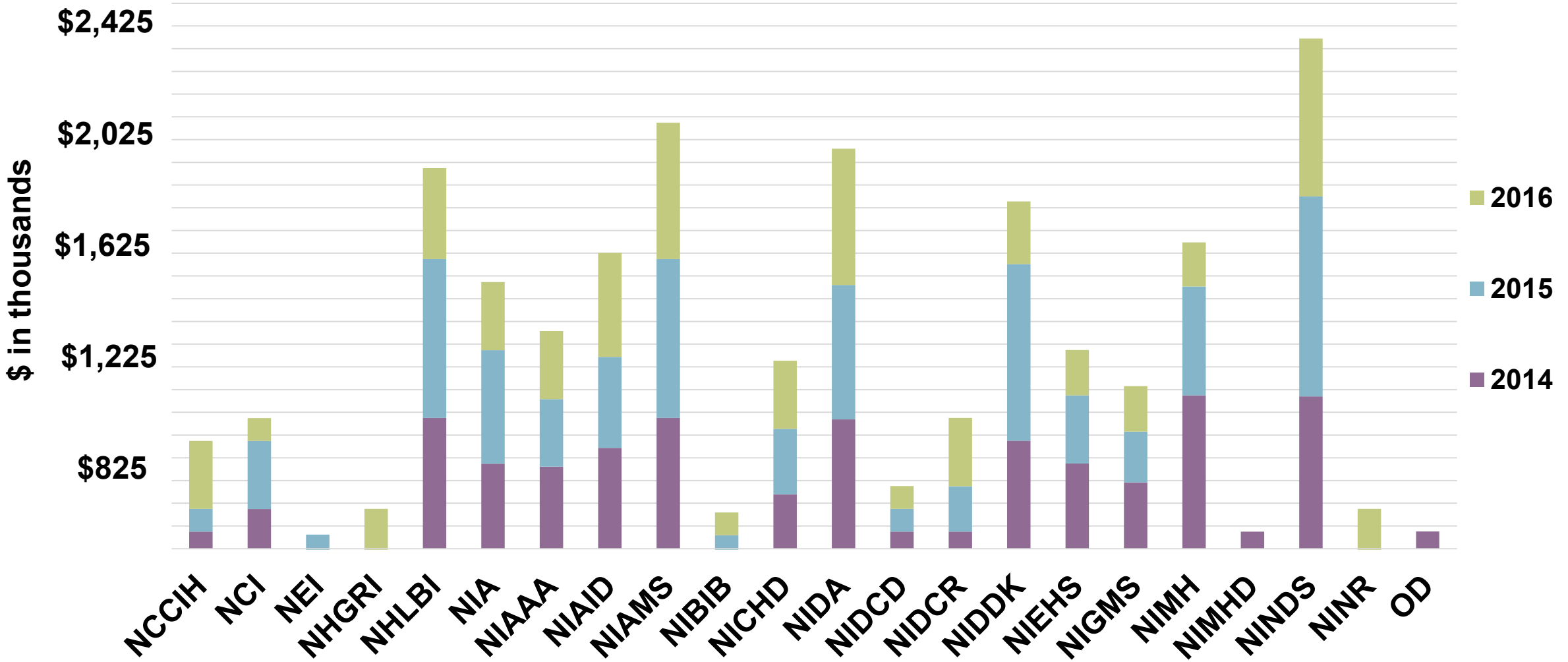
Approach

Description	Percent
Add new sex to single sex research	47%
Add subjects to existing study to increase power	36%
Analyze existing samples/data sets	17%

(N=60)

National Institutes of Health
Office of Research on Women's Health

ORWH Invests in 191* Sex and Gender Influences (SGI) Supplements



*over 3 years

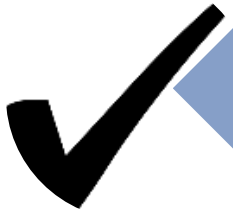
National Institutes of Health
Office of Research on Women's Health

Executing the NIH Strategic Plan for Women's Health Research Goals

Examples

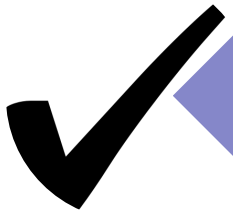
GOAL 1: Increase sex differences research in basic science studies

IC: NIBIB
Title: *Preclinical Investigation of a Bioengineered Vascular Graft*



GOAL 2: Incorporate findings of sex/gender differences in the design and application of new technologies, medical devices, and therapeutic drugs

IC: NIA
Title: *Wisconsin Registry for Alzheimer's prevention*



GOAL 3: Actualize personalized prevention, diagnostics, and therapeutics for girls and women

IC: NIGMS
Title: *Integrative informatics approach to develop safe glucocorticoid therapies*

ORWH R56 Program for FY 2016

14 apps | **10** ICs

- Internal Applicants
- Short-Term
- High-Priority

NIH National Institutes of Health
Office of AIDS Research

NIH National Institutes of Health
Office of Dietary Supplements

Partnership with OAR and ODS

NIH National Institutes of Health
Office of Research on Women's Health

Specialized Centers of Research on Sex Differences (SCOR), FY16

- 11 Awards
- 6 ICs

National Institute on Aging

National Institute of Arthritis and Musculoskeletal and Skin Diseases

National Institute of Diabetes and Digestive and Kidney Diseases

National Institute of Mental Health

Eunice Kennedy Shriver National Institute of Child Health and Human Development
Health research throughout the lifespan

National Institute on Drug Abuse
Advancing Addiction Science

- Interdisciplinary collaborations
- Research on sex and gender factors underlying a priority women's health issue
- Bridges basic and clinical research
- Partner with FDA

National Institutes of Health
Office of Research on Women's Health

Women in Biomedical Careers

National Institutes of Health
Office of Research on Women's Health

BIRCWH

Building Interdisciplinary Research Careers in Women's Health

- Annual meeting: October 25, 2017
- NIH Main Campus
- "IC mentoring", plenary sessions, etc.

Contributing ICs

NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases

NIH National Institute on Drug Abuse
Advancing Addiction Science

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
Health research throughout the lifespan

NIH National Institute of Environmental Health Sciences

NIH National Institute of Allergy and Infectious Diseases

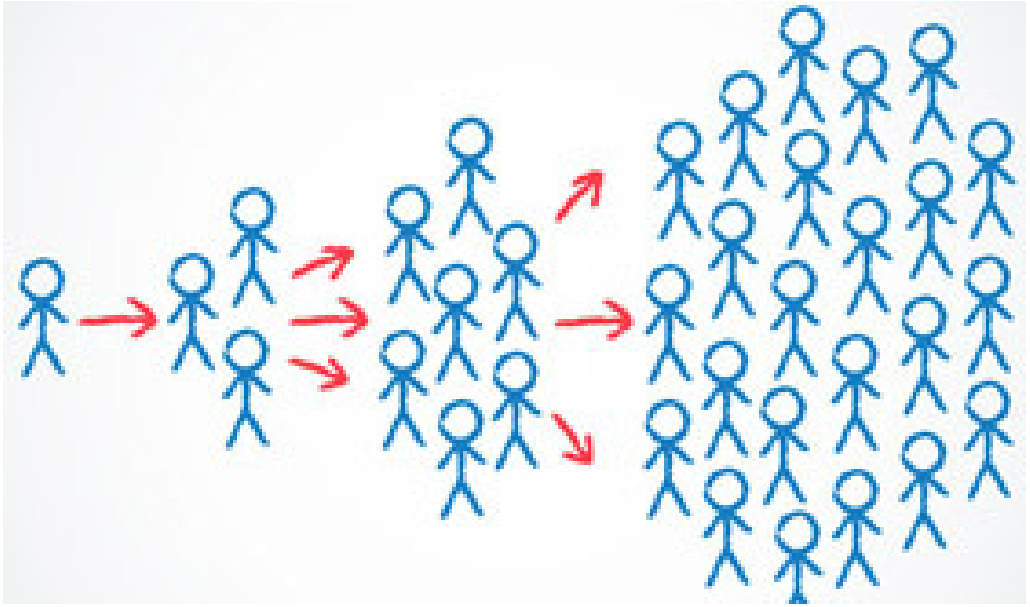
NIH National Institute of Dental and Craniofacial Research

NIH National Institute on Aging

NIH National Institutes of Health
Office of Research on Women's Health

ORWH

Amplifying the Message



National Institutes of Health
Office of Research on Women's Health

ORWH: Amplifying the Message

WOMEN'S HISTORY MONTH

STONE SYMPOSIA™
olecular and Cellular Biology
Accelerating Life Science Discovery

ROSALIND FRANKLIN UNIVERSITY of MEDICINE AND SCIENCE
EST 1912

NIH National Institutes of Health
Office of Research on Women's Health

2nd Annual NIH Vivian W. Pinn Symposium

Putting Science to Work for the Health of Women

HEALTHY WOMEN MAKE HEALTHY COMMUNITIES: WOMEN AS MAKERS

Wednesday, May 17, 2017, 2:00pm
NIH Main Campus

#NWHW

Ana Langer, M.D.
Harvard T.H. Chan School of Public Health

Afaf Meleis, Ph.D., Dr.P.S., FAAN
University of Pennsylvania School of Nursing

Stephen Woolf, M.D., M.P.H
Virginia Commonwealth University,

NIH National Institutes of Health
Office of Research on Women's Health

ORWH: Looking Ahead

DATE	EVENT
April 27th	NIH-FDA Pre-Conference Symposium at the 25th Anniversary Women's Health Congress
May 17th	2nd Annual NIH Vivian W. Pinn, M.D. Symposium
June 1st-2nd	Inclusion Across the Lifespan
September 13th	ACRWH Fall Meeting
October 25th	BIRCWH Meeting
October 26th-27th	ORWH-Common Fund Symposium

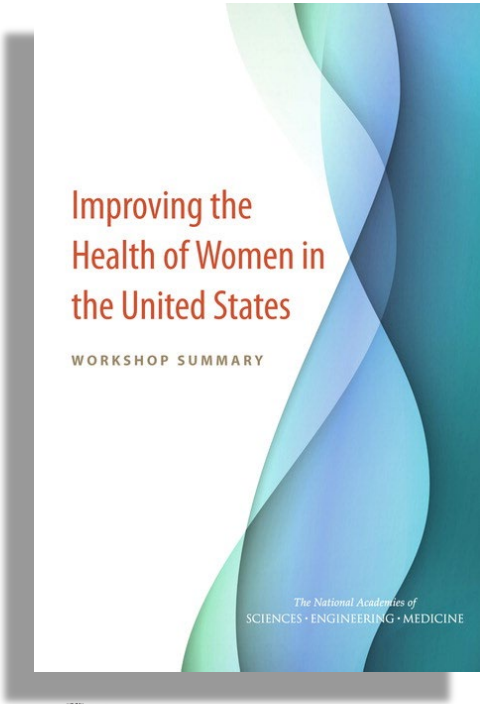
Later Today . . .

NIH National Institutes of Health
Turning Discovery Into Health

Perelman School of Medicine
University of Pennsylvania

NIH Center for Scientific Review

All of Us
THE FUTURE OF HEALTH BEGINS WITH YOU



NIH National Institutes of Health
Office of Research on Women's Health

THANK YOU

National Institutes of Health
Office of Research on Women's Health

Enhancing Science and Health with SABV

IMPLEMENT SABV POLICY

WHO: NIH COMMUNITY

- Program Officials
- IRGs/Reviewers
- Grantees/Trainees

WHAT: TOOLS/CHECKLISTS

- IRG Checklists
- PGM Checklists
- Online tools

Improving the Health of Women in the US

Outline the Challenge

The Health of Women in the United States is:

- Poorer than peer countries
- Indicating new areas of worsening health
- Affected by prevailing societal context
- In need of multi-sector *AND* interdisciplinary solutions

National Institutes of Health
Office of Research on Women's Health

Improving the Health of Women in the US

Outline the Challenge:

The Health of Women in the United States is:

- Poorer than peer countries
- Indicating new areas of worsening health
- Affected by prevailing societal context
- In need of multi-sector *AND* interdisciplinary solutions

Search for the Solution:

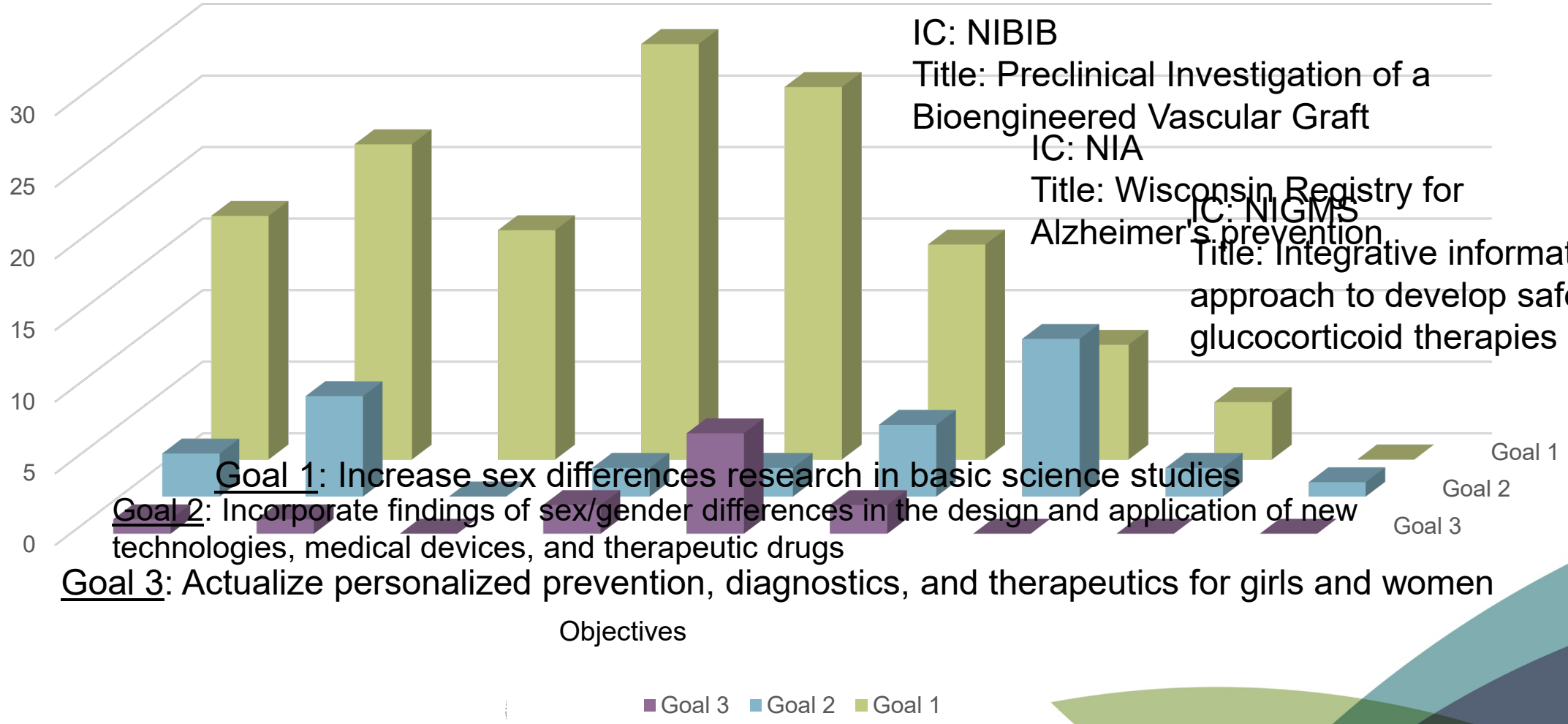
- Develop a strategy to set expectations for and facilitate “raising the bar” for the health of women
- Improve health through integrated/collaborative and coordinated framework for:
    - Study / research
    - Communities of practices and care
    - Sharing with partners and stakeholders

National Institutes of Health
Office of Research on Women's Health

Sex and Gender Influences Across Institutes and Centers by Research Programs

ORWH Program	Collaborating ICs
Specialized Centers of Research on Sex Differences Program (SCOR)	NIA, NIAMS, NICHD, NIDA, NIDDK, and NIMH
Building Interdisciplinary Research Careers in Women's Health Program (BIRCWH)	NICHD and NIDA
Sex/Gender Administrative Supplements	All *except* FIC, NCATS, NEI, NIMHD, NLM, and OD
Other Co-Funds	All *except* NCATS, NCCIH, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMHD, NINR, NEI, NLM, and OD
R56 Program	NCI, NIA, NIAAA, NICHD, NIDA, NIDCR, NIEHS, NIMH, and NINR
Conferences and Scientific Meetings	NICHD, NIDA, and NIDCR

Executing the NIH Strategic Plan for Women's Health Research:
Goals and Objectives



IC: NIBIB
Title: Preclinical Investigation of a Bioengineered Vascular Graft

IC: NIA
Title: Wisconsin Registry for Alzheimer's prevention

IC: NIGMS
Title: Integrative informatics approach to develop safe glucocorticoid therapies

Goal 1: Increase sex differences research in basic science studies

Goal 2: Incorporate findings of sex/gender differences in the design and application of new technologies, medical devices, and therapeutic drugs

Goal 3: Actualize personalized prevention, diagnostics, and therapeutics for girls and women