NIH’s Inclusion Policy and Beyond: Including Women and Minorities in Clinical Research

Juliana M. Blome, Ph.D., M.P.H.
Associate Director for Science Policy, Planning and Analysis
NIH Office of Research on Women’s Health

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Audience Poll

What is your primary role in the Veterans Health Administration?

• VA researcher
• Non-VA researcher
• Clinician
• Management/policy maker
• Other
ORWH: Improving the Health of Women Through Biomedical and Behavioral Research

- Examine sex/gender influences in health and disease to inform women’s health and women’s health research, across NIH
- Ensure that women and minorities are included in all NIH-funded clinical research studies
- Promote recruitment, retention, reentry, and sustained advancement of women in biomedical careers
NIH Revitalization Act 1993 (PL 103-43)

NIH Inclusion Guidelines

- Women and Minorities **must be included** in all clinical research studies
- Women and Minorities **must be included** in Phase III clinical trials, and the trial must be designed to permit *valid analysis*
- Cost is **not allowed** as an acceptable reason for exclusion
- NIH to support outreach efforts to recruit and retain women, minorities, and their subpopulations in clinical studies

Do you know the difference between clinical research and Phase III clinical trials?

- Yes
- No
Enrollment by Sex/Gender: NIH-Defined Phase III Clinical Trials
Percent Enrollment by Sex/Gender: NIH Clinical Research FY 2011, FY 2012

Excluding Male-Only and Female-Only Studies
Percent Minority Enrollment by Sex/Gender: Domestic NIH-Defined Phase III Clinical Trials

![Graph showing percent minority enrollment by sex/gender for domestic NIH-defined Phase III clinical trials from 2008 to 2012.](chart.png)
Barriers to Recruitment and Retention of Women and Minorities in Clinical Trials

- Fear and distrust of research enterprise
- Lack of knowledge
- Lack of transportation
- Interference with work and/or family responsibilities
- Burden as a result of participation
- Financial costs
Why Research Sex/Gender Influences?

- Many significant sex factors in diseases/organs *related* to reproduction
- Many significant sex factors in diseases/organs *unrelated* to reproduction
- Sex differences not always differences: "sex factors"
- *What are we missing* by not including sex and gender in investigations at all levels?
- *What harm are we doing* by not including sex and gender in investigations at all levels?
Audience Poll

Do you know the difference between sex and gender?

1. Yes
2. No
3. Trick question: It’s the same thing.
Sex is Not the Same as Gender

- Every cell has a sex
- Sex begins *in utero*
- Sex affects behavior and perception
  - Gender also affects behavior and perception
- Sex affects health
  - Gender also affects health

“Sex”: classification derived from the chromosomal complement (reproductive organs and functions)

“Gender”: a person’s self-representation as male or female

Source: Exploring the Biological Contributions to Human Health: Does Sex Matter, IOM Report, 2001
Why Sex/Gender Matters: Drug Effects

What’s going on?

- Liver is sexually dimorphic:
  - Male rats: higher hydroxylating activity than females
  - Females: express higher 5α-reductase than males
  - Growth hormone release differences
- P450s sexually dimorphic
  - Female: CYP2C12 (15β-hydroxylase)
  - Male: CYP2C11 (16α-hydroxylase)
- Sex significantly influences how the body metabolizes zolpidem
- Details remain unclear

January 2013: FDA issues sex-specific dosage recommendations for zolpidem (Ambien)

May 2013: FDA approves new label changes and dosing for zolpidem products and a recommendation to avoid driving the day after using Ambien CR

Why Sex/Gender Matters: Heart Attacks

• Women often have early symptoms within the weeks prior to their heart attack

• At time of attack, women have:
  • shortness of breath, weakness, and fatigue
  • only half of women have chest pain

• 1997 awareness: 30 percent of all women
  • only 15 percent of black women

• 2012 awareness: 56 percent of all women
  • only 36 percent of black women

Why Sex/Gender Matters: Smoking

- Second-hand smoke affects birth outcomes (pre-term births)
- Women more susceptible than men to smoking sensory triggers as well as to social cues
- Nicotine patches and gums don’t work as well in women as they do in men

Why Sex/Gender Matters: Pain

- Different clinical features of pain in women and men
- Chronic pain much more prevalent in women (~70 percent)
- μ-opioid analgesics more effective in human females than in human males (Morphine, fentanyl, methadone)

... Why did 79 percent of all published papers in journal Pain only test male subjects?

But … Males Still Dominate Animal Studies

Male Emphasis In \textbf{8 of 10} Biological Disciplines

\begin{itemize}
  \item Neuroscience (5.5/1)
  \item Pharmacology (5/1)
  \item Physiology (3.7/1)
\end{itemize}

Animal Studies: Six fields relied on rodents in \textbf{80\%} or more of animal studies (general biology, immunology, neuroscience, physiology, pharmacology, and endocrinology)

Beyond Inclusion: Sex-Specific Reporting

U.S. population

NIH-funded clinical trial sex/gender inclusion (average enrollment of women): 37 percent

NIH-funded clinical trial sex/gender reporting: 28 percent (of the above group)

Filling the Gaps: NIH Enacts New Policies to Address Sex Differences

Posted May 14, 2014

Today in Nature, National Institutes of Health (NIH) Director Dr. Francis Collins and I announce that NIH will be requiring applicants to report their cell and animal inclusion plans as part of preclinical experimental design. By developing this policy, we are promoting a balanced approach to addressing male and female differences in cells and animals — just as we did years ago with women and men in NIH-funded clinical trials.

NIH Takes Steps to Address Sex Differences in Preclinical Research

May 14, 2014

Over the past two decades, we have learned a great deal about how men and women respond differently to medications. This knowledge came after a concerted effort in the early ‘90s to increase the number of women in NIH-funded clinical research. Today, just over half of NIH-funded clinical research participants are women. Unfortunately, experimental design in cell and animal research has not always followed suit. An over-reliance on male animals, and neglect of attention to the sex of cells, can lead to neglect of key sex differences that should be guiding clinical studies, and ultimately, clinical practice. NIH is taking action to address this shortfall as outlined by Janine A. Clayton, M.D., Director of the NIH Office of Research on Women’s Health, and me in the Nature Comment below.

Francis S. Collins, M.D., Ph.D.
Director, National Institutes of Health
Labs Are Told to Start Including a Neglected Variable: Females

By ROSE CARLISLE ARRISON | MAY 18, 2021

NATIONAL INSTITUTES OF HEALTH
Needed: More Females in Animal and Cell Studies

Jennifer Couzin-Frankel

US government to require affirmative action for female lab mice

NIH to require sex-reporting in preclinical studies

18 May 2014 | 18:30 BST | Posted by Sara Reardon | Category: Biology & Biotechnology, Drug discovery, Institutions, Policy, Publishing
Sex is One of Many Biological Variables

- Size
- Age
- Genetic strain
- Source of origin (animal, cell)
- Passage number
- Serum
- Group housing
- Lighting conditions
- Temperature
- Time
- Order of experimentation
- Sex
- And so on …
Connecting the Dots: The Research Continuum

Basic | Preclinical | Clinical Research & Trials | Regulatory Review (if needed) | Clinical Practice

Cell models, samples of human or animal tissues, computer-assisted testing, animal models

Healthy volunteers and patients
Audience Poll

How familiar are you with the process of developing public policy?

- Not at all familiar
- Slightly familiar
- Somewhat familiar
- Moderately familiar
- Extremely familiar
Developing Policy: Considerations and Outcomes

Data and Policies

Public Trust

Best Science for Better Health

Safety

Taxpayer Funds
What should the policy look like?

- Scope
- Breadth
- Penalty for non-compliance
- Peer review criteria
- Educational resources and tools
The Landscape

Congressional interest
- H.R. 4879 Research for All Act (June 2014)
- GAO inquiry on women in clinical trials (April 2014)
- Hill Briefing to enhance understanding (July 2014)

NIH developing policies for deliberate approach to considering sex in preclinical research:
- Trans-NIH Sex Differences in Research Working Group
- RFI released (Sept 2014)

Journal editors and publishers guidelines
- Increasingly reference requirements to report sex
Good Business: The Best NIH Investment Is Solid, Rigorous Research Design

Considering both sexes of animals early in research continuum:

The rest of the world is far ahead of NIH in considering sex as a variable in biomedical research, toward personalized medicine that is gender-appropriate
Our Neighbors to the North

December 2010: all Canadian Institute for Health Research applicants must indicate whether their research designs accounted for sex or gender.

Proportion of applicants responding "yes" to the questions on sex and gender increased from 26% in December 2010 to 48% in December 2011.

Citation: Johnson J, Sharman Z, Vissandje B, Stewart DE (2014) Does a Change in Health Research Funding Policy Related to the Integration of Sex and Gender Have an Impact? PLoS ONE 9(6): e99900. doi:10.1371/journal.pone.0099900
NIH in 2014: Beyond Inclusion
Sex/Gender Influences on Health and Disease

Preclinical studies | Toxicology | Phase I, II, III Clinical Trials

Basic

Healthy Women, Men, Girls, Boys

Clinical

Cell, Animal Studies | Education | Sex-Specific Data Analyses

Health Care | Health Policy | Sex-Specific Reporting

NIH in 2014: Beyond Inclusion
Sex/Gender Influences on Health and Disease
Resources

NIH Office of Research on Women’s Health http://orwh.od.nih.gov/
--To learn more about studying sex to strengthen science, go to http://orwh.od.nih.gov/sexinscience/index.asp.

NIH ORWH Workshop - Methods and Techniques for Integrating the Biological Variable Sex in Preclinical Research - October 20, 2014, 7:45 a.m.-5:30 p.m. To view a draft agenda and link to live videocast, got to: http://orwh.od.nih.gov/news/scientificseminars.asp

NIH Grants Policy on Inclusion of Women and Minorities as Participants in Research http://grants.nih.gov/grants/funding/women_min/women_min.htm

Questions/Comments?

Contact Information
Juliana M. Blome, PhD, MPH
(blomeju@od.nih.gov)