



Veterans Administration - HSR&D Cyberseminar

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

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October 14, 2014





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

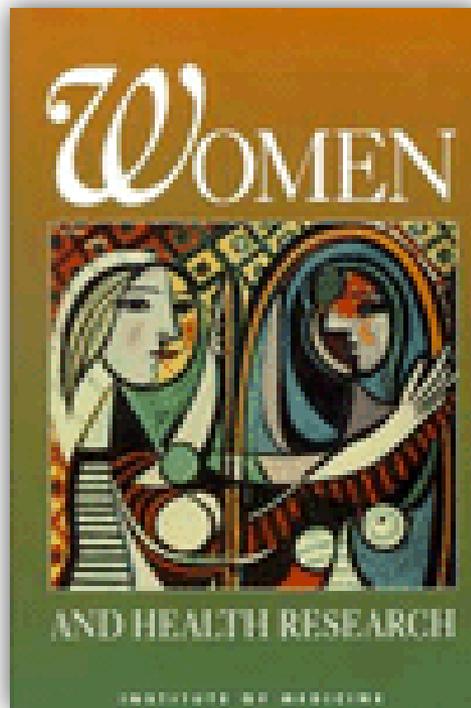
- Examine sex/gender influences in health and disease to inform women's health and women's health research, across NIH
- Ensure that women and minorities are included in all NIH-funded clinical research studies
- Promote recruitment, retention, reentry, and sustained advancement of women in biomedical 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





Audience Poll

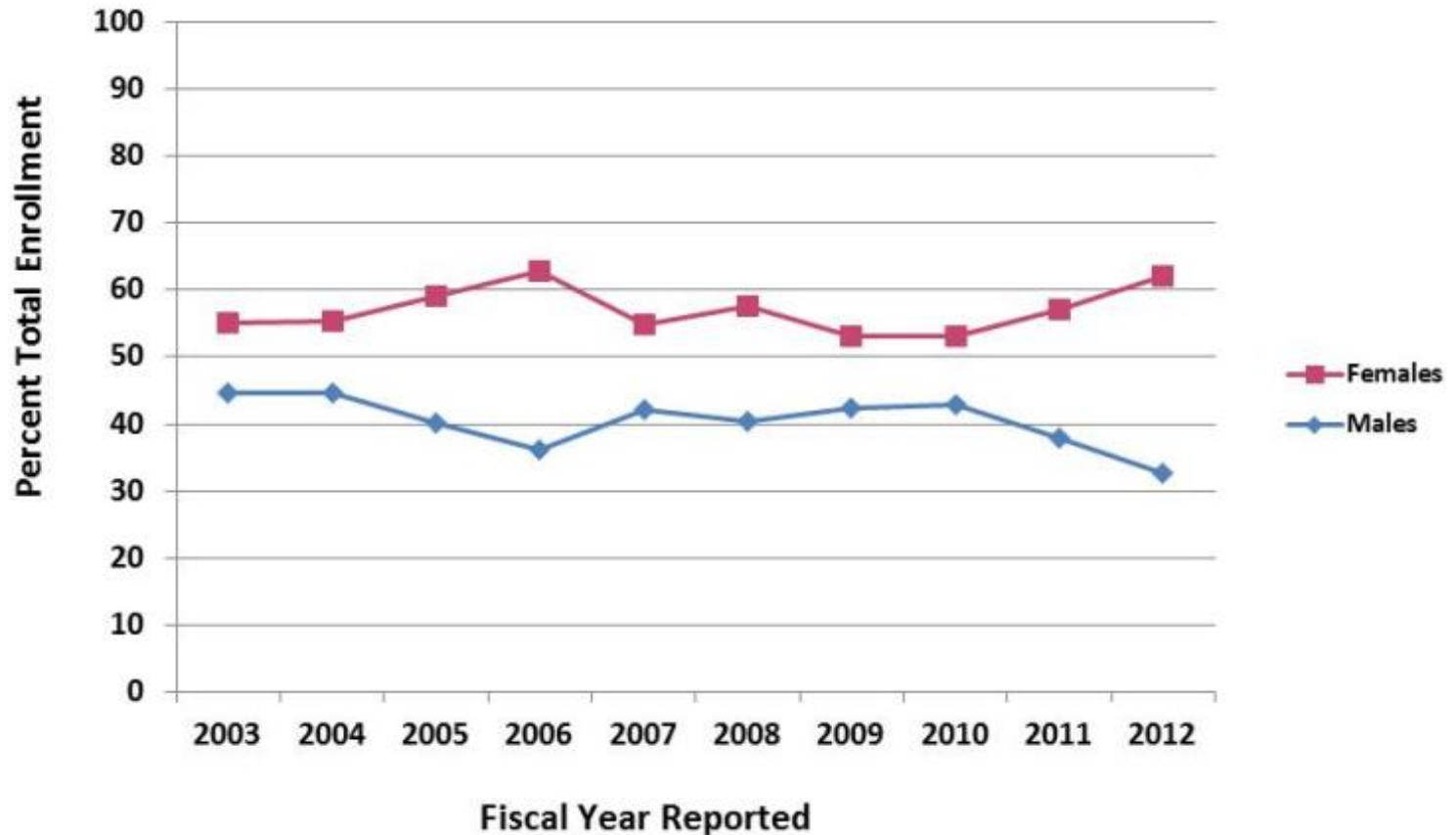
Do you know the difference between **clinical research** and **Phase III clinical trials**?

- Yes
- No



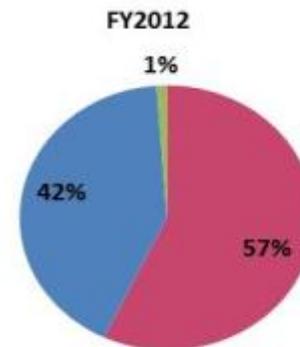
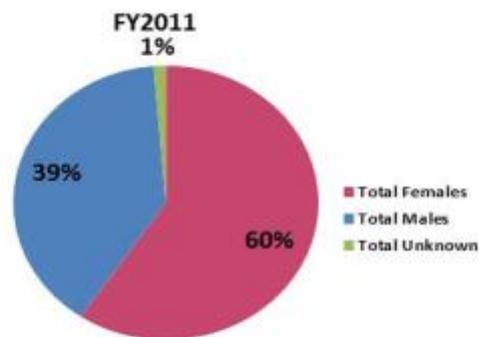


Enrollment by Sex/Gender: NIH-Defined Phase III Clinical Trials

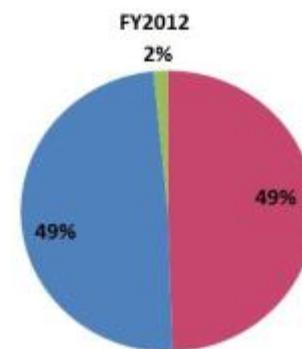
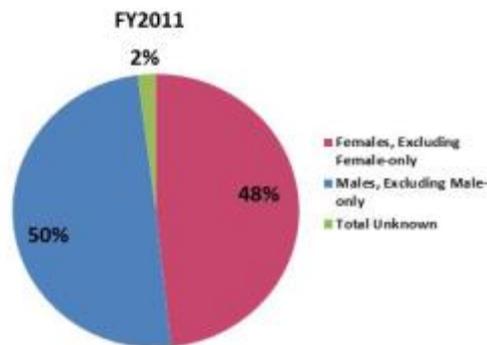




Percent Enrollment by Sex/Gender: NIH Clinical Research FY 2011, FY 2012

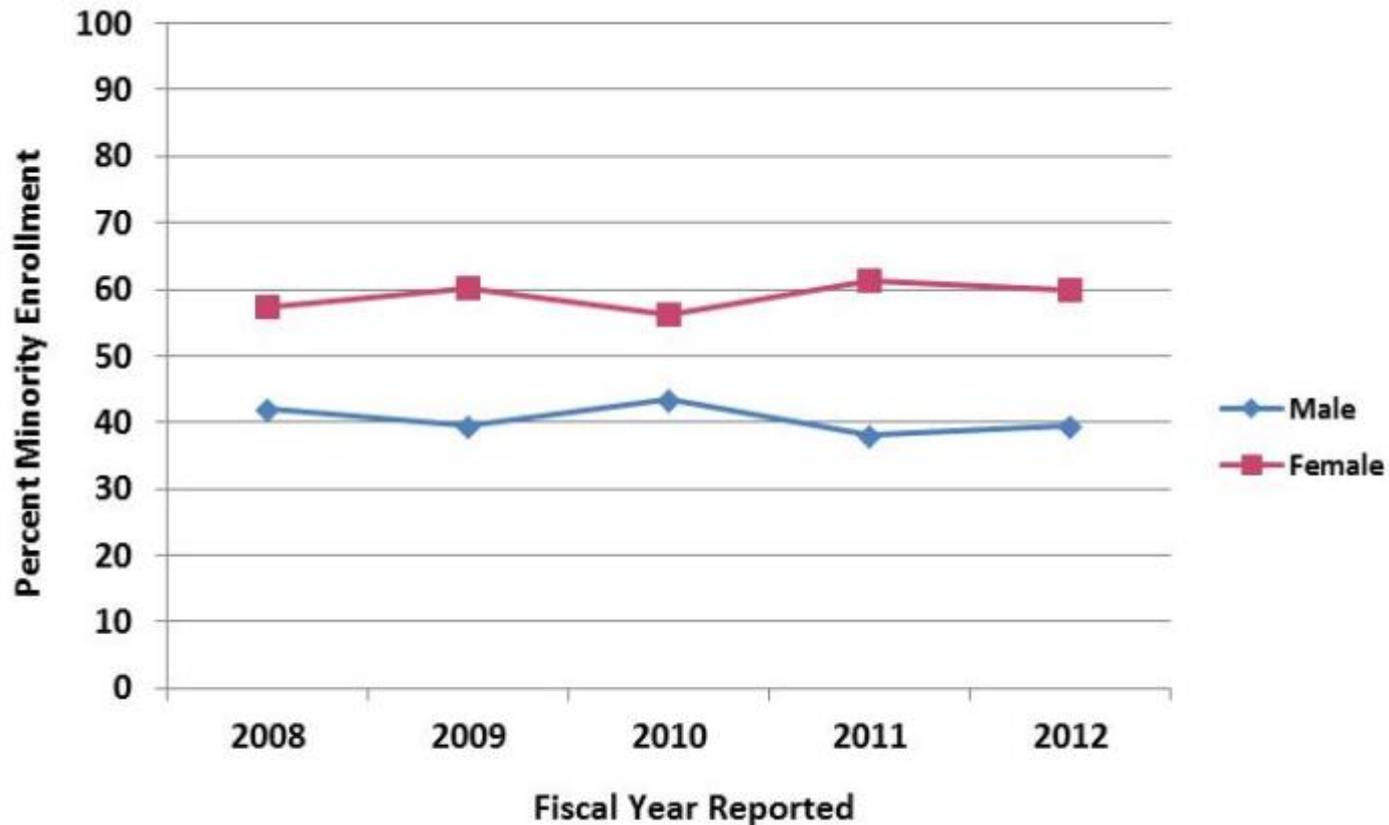


Excluding Male-Only
and Female-Only
Studies





Percent Minority Enrollment by Sex/Gender: Domestic NIH-Defined Phase III Clinical Trials





Barriers to Recruitment and Retention of Women and Minorities in Clinical Trials

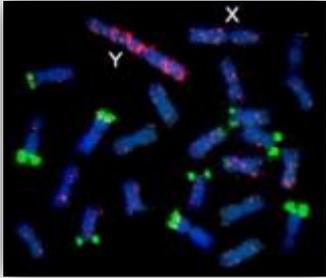
- Fear and distrust of research enterprise
- Lack of knowledge
- Lack of transportation
- Interference with work and/or family responsibilities
- Burden as a result of participation
- Financial costs

Outreach notebook for the inclusion, recruitment and retention of women and minority subjects in clinical research: principal investigators' notebook. National Institutes of Health (U.S.); National Institutes of Health (U.S.). Office of Research on Women's Health., 2002. NIH publication, no. 03-7036.





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

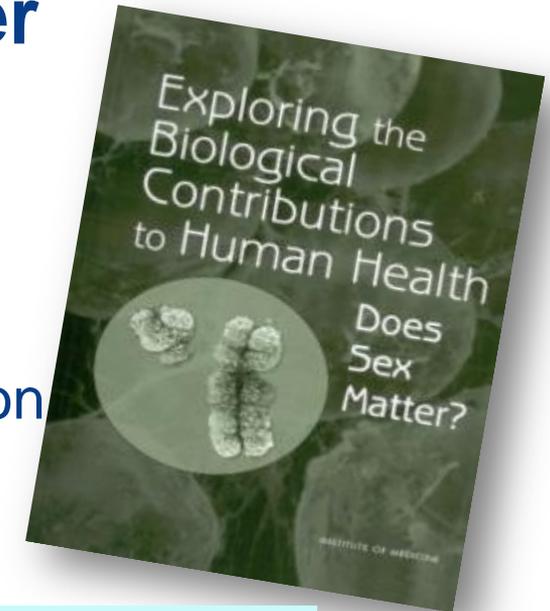
Do you know the difference between sex and gender?

1. Yes
2. No
3. Trick question: It's the same thing.



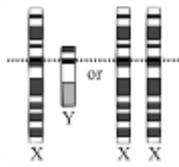
Sex is Not the Same as Gender

- 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



Why Sex/Gender Matters: Drug Effects

The New York Times

Health

THE CONSUMER | JANUARY 28, 2013, 6:32 PM | 30 Comments

The Drug-Dose Gender Gap

By RONI CARYN RABIN



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

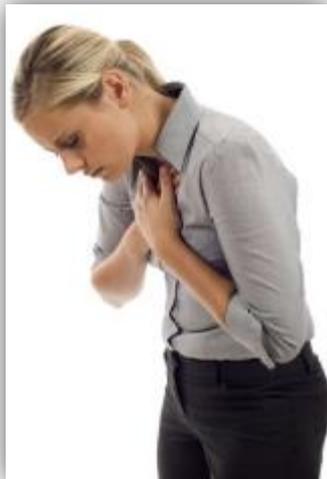
What's going on?

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





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

Yale SCHOOL OF MEDICINE

Education Patient Care Research Faculty News Library A-Z Index Search

PSYCHIATRY

Patient Care Research Education & Training Faculty

Gender-Sensitive Treatment for Tobacco Dependence

1Bhat VM, et al. Dose-response relationship between cigarette smoking and risk of ischemic stroke in young women. *Stroke*. 2008;39:2439-43; 2Thun MJ, et al. 50-year trends in smoking-related mortality in the United States. *N Engl J Med*. 2013 Jan 24;368(4):351-64; 3Cox B, et al. Impact of a stepwise introduction of smoke-free legislation on the rate of preterm births: analysis of routinely collected birth data. *BMJ* 2013; April 2013 *American J Public Health*; 4Gaudet MM, Gapstur SM, Sun J, Diver WR, Hannan LM, Thun MJ. Active Smoking and Breast Cancer Risk: Original Cohort Data and Meta-Analysis. *J Natl Cancer Inst*. 2013 Feb 28.; 5Young-Wolff KC, Hyland AJ, Desai R, Sindelar J, Pilver CE, McKee SA. Smoke-free policies in drinking venues predict transitions in alcohol use disorders in a longitudinal U.S. sample. *Drug Alcohol Depend*. 2013 Mar 1;128(3):214-21.

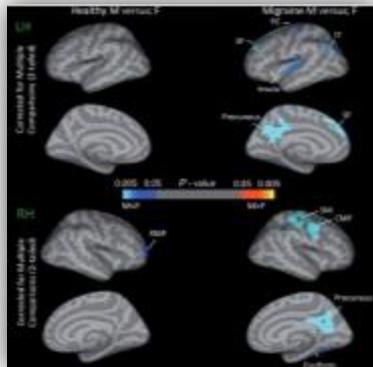


Why Sex/Gender Matters: Pain



- 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)



Brains of female and male migraine sufferers differ

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

Berkley J. Sex differences in pain. Behavioral and Brain Sciences 1997;20:371–380; 2 Miaskowski, C. et al. Sex-related differences in analgesic responses 2000., pp. 209–230. In: Sex, Gender, and Pain. R. B. Fillingim, ed. Seattle: IASP Press.; 3 Mogil JS, Bailey AL. Progress in Brain Research Volume 186, 2010, Chapter 9 – Sex and gender differences in pain and analgesia

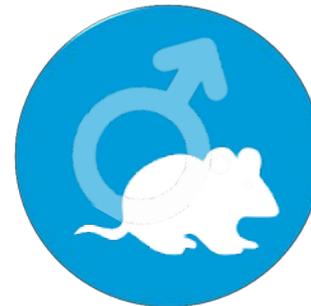


But ... Males Still Dominate Animal Studies



nature

Males still
dominate
animal
studies

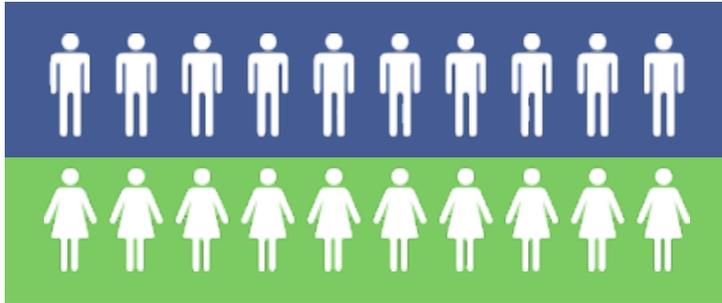


Male Emphasis In **8 of 10** Biological Disciplines



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

Source: Zucker I, Beery AK. Males still dominate animal studies. *Nature*. 2010;465:690.



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)

Beyond Inclusion: Sex-Specific Reporting

Source: Foulkes MA. After inclusion, information and inference: reporting on clinical trials results after 15 years of monitoring inclusion of women. *J Womens Health*. 2011;20:829-36

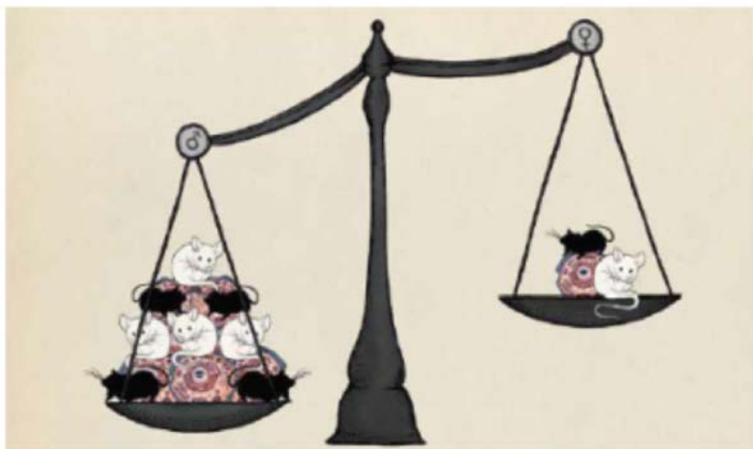




nature

May 15, 2014

COMMENT



NIH to balance sex in cell and animal studies

Janine A. Clayton and Francis S. Collins unveil policies to ensure that preclinical research funded by the US National Institutes of Health considers females and males.

Director's Page

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.



Janine Austin Clayton, M.D.

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

The New York Times
 HEALTH
 Labs Are Told to Start Including a Neglected Variable: Females
 By ROSE CARTY KARNI MAY 14, 2014

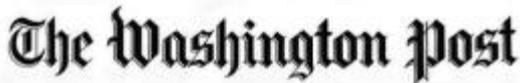


Slate
 THE X-FACTOR WHAT WOMEN REALLY THINK JULY 15, 2014 12:18 PM
Why Are All the Lab Rats Boys? NIH Tells Drug Researchers to Stop Being Sexist Pigs.
 By Amanda Marcotte

Science
 NEWS & ANALYSIS
 NATIONAL INSTITUTES OF HEALTH
Needed: More Females in Animal and Cell Studies
 Jennifer Couzin-Frankel

Vox 0000
 US government to require affirmative action for female lab mice

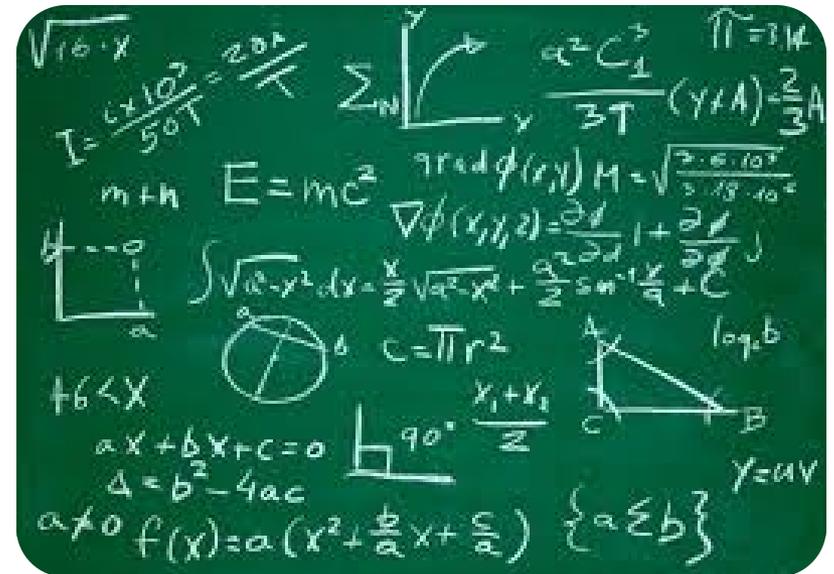
NATURE NEWS BLOG
 NIH to require sex-reporting in preclinical studies
 14 May 2014 | 18:00 BST | Posted by Sara Reardon | Category: Biology & Biotechnology, Drug discovery, Institutions, Policy, Publishing





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



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





Diverse Stakeholders

**NIH &
Extramural
Champions**

**Congress &
GAO**

**NIH
Leadership**

**NIH &
Extramural
Doubters**

Media

**NIH
Systems &
Policies**

**Publishers
&
Journal
Editors**

Advocacy

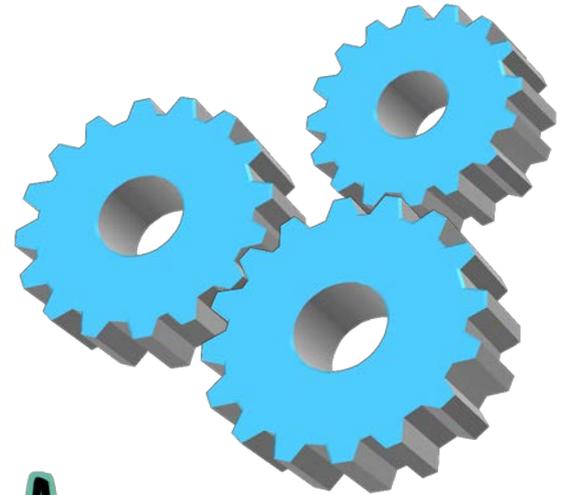
**Federal
Agencies**





What should the policy look like?

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

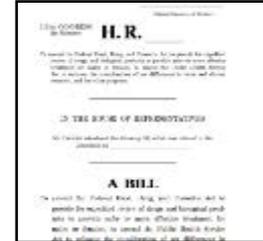




The Landscape

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

OPEN ACCESS Freely available online



Does a Change in Health Research Funding Policy Related to the Integration of Sex and Gender Have an Impact?

Joy Johnson¹, Zena Sharman^{1*}, Bilkis Vissandjée², Donna E. Stewart³

joy.johnson, zena.sharman, Bilkis Vissandjée, Donna E. Stewart

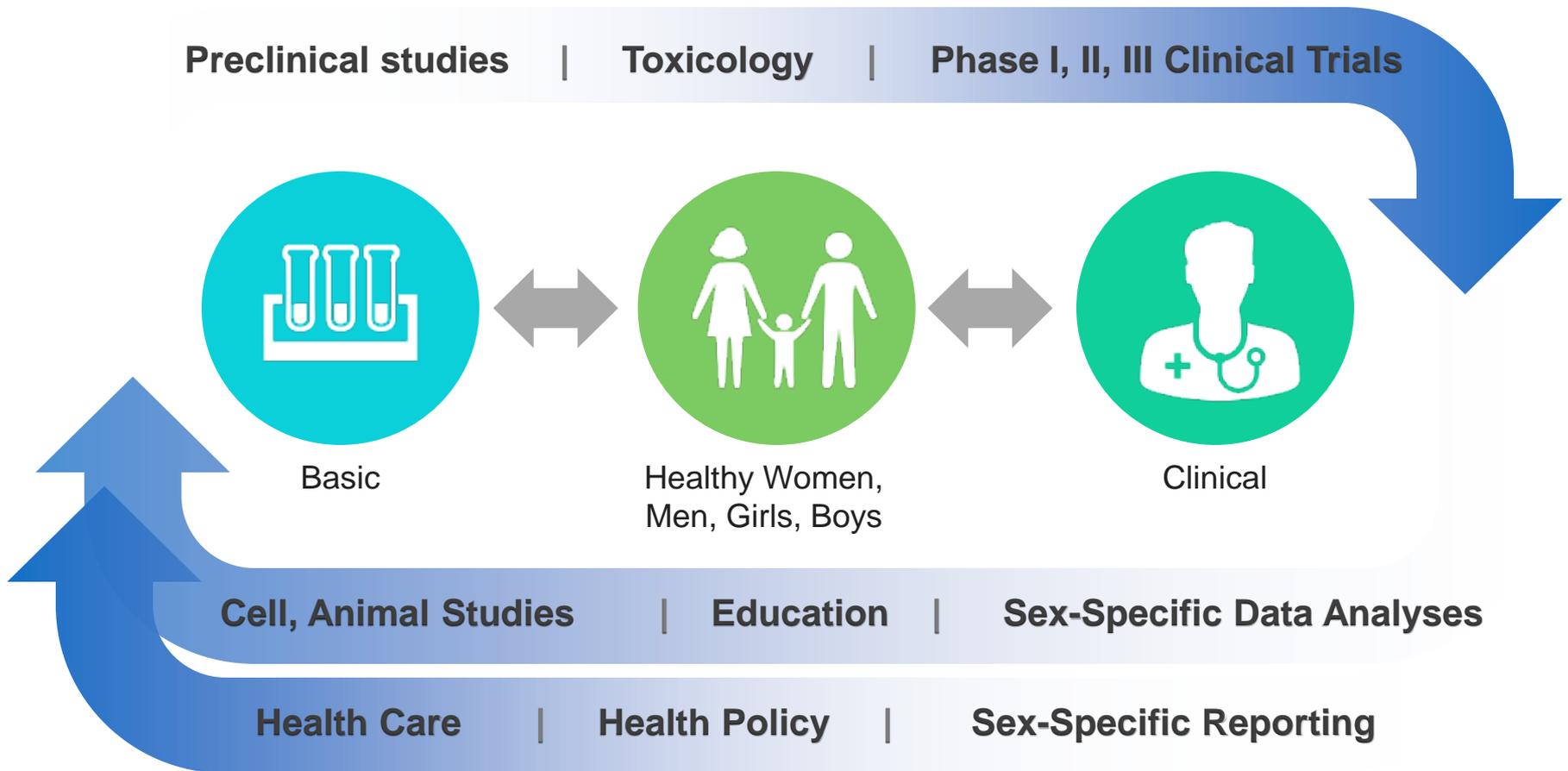
Abstract

- 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, Vissandjée 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





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

NIH Comprehensive reports on Inclusion of Women and Minorities in Clinical Research, <http://orwh.od.nih.gov/research/inclusion/reports.asp>





Questions/Comments?

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