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NORTHWESTERN UNIVERSITY

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Francis S. Collins, MD, PhD
Director, National Institutes of Health
Bethesda, Maryland

Dear Dr. Collins:

The Women's Health Research Institute at Northwestern University and its Leadership Council are committed to the full inclusion of both sexes in basic, translational, and clinical research as reflected in our motto, *Science to Care* (http://www.womenshealth.northwestern.edu).

It is clear that much progress has been made in female inclusion since the passage of the NIH Revitalization Act of 1993 (PL103-43) mandating full NIH implementation of earlier policies for inclusion of women and minorities in clinical studies. We recognize and appreciate the efforts that the NIH made to advance women's health research; namely, the funding of SCOR Centers, Administrative Supplements for Sex/Gender, REAP and ANSWHR projects, and ongoing support for the Office of Research in Women's Health under the leadership of Dr. Janine Clayton who has demonstrated strong passion for creating a "new lens for sex and gender research."

We applaud your recent announcement of an unprecedented partnership that unites government, industry, and the non-profit community in order to transform the current competitive models used to develop new therapeutics. The conditions targeted in this new initiative---Alzheimer's disease, Type 2 diabetes mellitus, rheumatoid arthritis and lupus---are of particular concern to advocates for women's health[1],[2]. Indeed, nearly two-thirds of Americans with Alzheimer's disease are women[3], 90% of adults with lupus are women[4], and women are three times more likely than men to suffer from rheumatoid arthritis[5]. It is therefore essential that the drug development pipeline—from bench to bedside, from *in vitro* studies with cells and model

[1] http://www.nytimes.com/2014/02/05/health/nih-joins-drug-makers

[2] PNAS editorial, in press

[3] Alzheimer's Association (2012) Alzheimer's Disease Facts and Figures. http://www.alz.org/downloads/facts_figures_2012.pdf. Accessed February 24, 2014.

[4] Office on Women's Health US Department of Health and Human Services (2014) Lupus fact sheet. http://www.womenshealth.gov/publications/our-publications/fact-sheet/lupus.html. Accessed February 24, 2014.

[5] Centers for Disease Control and Prevention (2010). NHIS Arthritis Surveillance. Arthritis prevalence in women and men. http://www.cdc.gov/arthritis/data_statistics/national_nhis.htm. Accessed February 24, 2014.

systems to clinical trial design—include women. NIH insists that grantees report the sex of human subjects; the next step is to ask that the same attention to sex be placed on animal research.

We were equally encouraged by your statement published in *Nature* that "crucial experimental design elements are all too frequently ignored including…the effect of sex differences". [6] This deliberate attention to sex differences by the NIH will go a long way towards encouraging the basic science community to focus attention on sex as an important variable in the earliest steps of the discovery process. If we can learn where and how sex matters during the initial developmental phases of the scientific research pipeline, we will not only reduce costs in the later testing phases, but also reduce the risk of adverse events and improve the efficacy of drugs based on a 'personalized' approach to medicine.

We, the undersigned, believe that the XX-XY knowledge gap, which remains in basic science, preclinical, and even clinical research, must be eliminated. Filling this gap will include **assurance that cell and animal studies include both sexes, that clinical studies are designed to include sex and gender variables with outcomes reported accordingly, and that resulting publications require outcomes be analyzed and reported by sex.** If both sexes are not included in a study, the rationale for exclusion should be stated.

In 2010, an opinion paper published in *Nature* advocated for animal studies to include both sexes and for clinical trials to include a sufficient numbers of males and females to evaluate whether sex matters[7]. Since then, little progress has been made. Outcomes by sex are not reported in 64% of clinical studies, and sex-specific analysis remains low[8]. A survey of more than 1,200 neuroscience papers published in five high impact journals (*Science*, *Nature*, *Nature Neuroscience*, *Neuron*, and *The Journal of Neuroscience*) from June 2011 through May 2012 showed that studies using rodents reported the sex of the animals in their analyses only 42% of the time. Of the studies that did report on sex, females were studied only 24% of the time. Comparable studies reported in cardiology reflect similar male bias orientation in basic research studies. Journals that are now requiring sex reporting still fall short of mentioning whether or not sex influenced the results.

Finally, the January 2014 issue of the *Journal of Women's Health* published an analysis of the inclusion of women in post-approval medical device studies based on FDA draft guidelines[9]. Their study revealed that only 14% of device studies included sex as a key outcome measure, and only 4% included a subgroup analysis for female participants. This information may seem

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[6] Collins F, Tabak L (2014). NIH Plans to Enhance Reproducibility. *Nature*. 505:612-613.

[7] Kim AM, Tingen CM, & Woodruff TK (2010). Sex bias in trials and treatment must end. *Nature* 465(7299):688-689.

[8] Geller SE, Koch A, Pelletieri B, Carnes M. (2010) Inclusion, Analysis, and Reporting of Sex and Race/Ethnicity in Clinical Trials "Have We Made Progress." *Journal of Women's Health.* Vol 20:3.

[9] Pinnow E, Herz, Loyo-Berrios N, and Tarver M. (2014). Enrollment and Monitoring of Women in Post-Approval Studies for Medical Devices Mandated by the Food and Drug Administration. *Journal of Women's Health.* Vol 23:3

shocking, but the lack of sex-based analysis has been documented for many years despite repeated efforts to advocate for its inclusion in study design. While no formal mandates have yet been issued, the FDA is now drafting an Action Plan to be released this year that emphasizes the importance of recognizing the unique clinical needs of women by the medical device industry. The news on devices is in the context of the well-known problems with the FDA drug pipeline and the associated adverse events that impact one sex more than another. Zolpidem (Ambien®) is one example of a drug that harms women at the same dose found to be efficacious for men. This issue was highlighted by *60 Minutes (http://www.cbsnews.com/news/sex-matters-drugs-can-affect-sexes-differently/).*

We believe that it is time to reignite the advocacy that created the NIH Revitalization Act of 1993 so that inclusion will go beyond just numbers to include study design, analysis, and reporting. In both preclinical and clinical research, some of the consequences of not acting now include:

- An increased number of adverse drug reports especially in women
- A missed opportunity to better understand the sex-based biology needed to develop more personalized diagnostics, prevention strategies, and treatment options
- Exacerbation of the real and alarming rise in U.S. female mortality[10]
- Increased long-term costs associated with exclusion of one sex in cell and animal research

The IOM 2013 Report, *Shorter Lives, Poorer Health,* found that Americans may be wealthy compared to the rest of the world, but we are not particularly healthy compared to peer nations. This finding, along with the increasing trend in female mortality, raises a red flag that necessitates inclusion of sex and gender dimorphisms in future research.

In 2010, the Canadian Institutes of Health added the following mandatory questions about sex and gender in their research funding applications:

- Are biological sex considerations taken into account in this study? (Y/N)
- Are gender (socio-cultural) considerations taken into account in this study? (Y/N)
- If Yes, please describe how sex and/or gender considerations will be considered in your research design.
- If No, please explain why sex and/or gender are not applicable in your research design.

We respectfully request that as a consequence of your actions to target diseases that impact women, your interest in ensuring that the scientific process is as robust as possible, and the preponderance of evidence that sex matters in biological processes and health, you initiate steps at NIH to require that 1) sex be included in basic science studies using animals as it is in clinical studies funded by NIH; 2) authors report the outcomes of their work by sex in any

[10] Kindig DA, Cheng ER. (2013) Even as mortality fell in most US counties, female mortality nonetheless rose in 42.8 percent of counties from 1992 to 2006. *Health Aff.* 32(3):451-8

publications that result from NIH-funded research; and, 3) any sex differences or lack of sex disparities be included in study reports.

We would be delighted to follow up with your office on the implementation of these inclusion instructions to our basic science studies.

Sincerely,

Teresa K. Woodruff, PhD
Director, Women's Health Research Institute
Thomas J. Watkins Professor of OB/GYN
Northwestern University

Co-Signed WHRI Leadership Council members:

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