October 13, 2014

Dr. Francis Collins  
Director, National Institutes of Health  
9000 Rockville Pike  
Bethesda, Maryland 20892

RE: NOT-OD-14-128, Request for Information: Consideration of Sex As a Biological Variable in Biomedical Research  
Submitted via http://grants.nih.gov

Dear Dr. Collins:

The Association of American Medical Colleges (AAMC) appreciates the opportunity to comment on the National Institutes of Health (NIH) request for information related to its intention to develop and implement policies for NIH-funded investigators regarding the consideration of sex as a biological variable in the design and analysis of biomedical research.

The AAMC is a not-for-profit organization representing all 141 U.S. allopathic medical schools, nearly 400 teaching hospitals and health systems, and 90 academic societies. Through these institutions, the AAMC represents 128,000 faculty members, 75,000 medical students, 110,000 resident physicians, and thousands of graduate students and post-doctoral trainees in the biomedical sciences.

In response to the NIH request, the AAMC is pleased to provide comment on specific topics regarding the consideration of sex as a biological variable in preclinical research. The AAMC has also shared this notice widely with research leadership at member institutions, and encouraged them to respond as well.

**Whether consideration of sex as a biological variable is an issue affecting the reproducibility, rigor, and/or generalizability of research findings.**

Reproducibility in biomedical research is currently a major issue of concern, extending beyond the research community. Addressing this issue is indispensable to maintaining public trust in the results of NIH-funded research, and excluding female cells and animals in preclinical research is one of the potential factors in this irreproducibility. The effects of sex differences should be removed as a confounding factor in the reproducibility of scientific studies by the inclusion of both male and female cells and animals. The NIH should work with the scientific community and encourage input to determine how best to achieve both documentation and publication of these results to advance future discovery.
Consideration of sex differences in preclinical research is also a fundamental aspect of experimental rigor. It is not sufficient to consider sex variation only in experimental design; this variable should also be a component of data analysis and reporting, so that researchers can interpret results in a sex-specific, disaggregated manner. The NIH should also encourage reporting of negative results, both in the grant review process or in journal articles through collaboration with publishers. These data should include sex-dependent analyses—information which is valuable even when the sex does not contribute to a differential experimental outcome. Again, not reporting this information also increases the likelihood that attempts to reproduce experiments will lead to different results.

Sex is a critical biological variable, and consideration of sex differences at multiple stages of the experimental process increases the potential that the conclusions we draw from biomedical research are generalizable to a broader population. As the NIH has previously noted, a number of fields of biology rely on male animals over 80% of the time—research which, by nature, is one-sided in its observations and the conclusions it generates.

**Areas of science (e.g., cancer, neuroscience) or phases of research (e.g., basic, translational) conducted with animals that have the greatest opportunity or need for considering sex as a biological variable.**

Balancing sex variation in animal studies is a consideration which should be applied across all areas of biomedical science: using both male and female animals allows for the investigation of two separate and distinct physiologies. Animal studies are also a critical step in translational research/preclinical development and are often the precursor to clinical trials.

Given that the research community is approaching parity in clinical research in the inclusion of both men and women as research subjects, balancing male and female models in preclinical research as well could better inform the decisions and direction of the research. This balance could both provide critical information for clinical trials and also promote preclinical research design that maximizes the relevance of data gained from animal studies. The AAMC supports the ethical use of animal models in scientific research; it is incumbent upon us to ensure that those studies are readily translated to the next phase in the research continuum.

**Areas of science or phases of research conducted with cells and/or tissues that have the greatest opportunity or need for considering sex as a biological variable.**

Cells and tissues which have been isolated from a broader biological system may function differently in experimental settings depending on the sex of derivation. Even at the level of basic research, studies in cells and tissues have potential future applications in advancing human health, making it critical to study and analyze any variability due to sex.

**Main impediments (e.g. scientific, technical, and other) to considering sex as a biological variable in research.**

The perceived impediments include those associated with the complexity of changing current experimental models and design, a need for new training, and additional expenses. The AAMC
appreciates that implementing these changes may require dedicated time, effort and money during a time when all resources are under stress. But scientists are committed to the very best science, and will take the necessary steps to achieve the highest standards. We understand that the NIH plans to implement any new policies in stages, and many of the above mentioned items will be one-time challenges/costs which will diminish as these become standard practices in research.

**Ways in which NIH can facilitate the consideration of sex as a biological variable in NIH-supported research.**

Researchers will need clear guidance from the NIH on how to implement any new policies into their experimental methods and data reporting. We encourage the NIH to implement its plan to incorporate requirements for consideration of sex differences in experimental methodology into grant review—to facilitate this process, both applicants and reviewers should receive training on appropriate methods and new expectations for grant applications.

The NIH should continue to engage with all current grantees through training and education on how their research can reach the highest possible standards of scientific inquiry by inclusion of sex and gender in any ongoing studies. NIH should also interface with researchers and journal publishers to facilitate reporting of results in a sex-specific manner, including negative results. This is a first step which can be taken that should not require significant changes in experimental planning or additional resources.

The NIH should also begin to implement guidelines within the intramural research program, to provide a model for extramural researchers and to better understand potential challenges and opportunities for efficiency.

**Additional comments to NIH about the development of policies for considering sex as a biological variable in research involving animals, tissues, or cells.**

In summary, the AAMC fully supports the goals of the NIH to develop policies that support the balancing of sex in cell and animal studies. The NIH has long incorporated important requirements leading to the consideration of sex differences in clinical research by the inclusion of both male and female subjects. These requirements were partly as a result of legislation but also in response to growing awareness of the need for representative research models in order to facilitate generalizability across the population. The goals to extend this inclusion in clinical trials across the spectrum of biomedical research are in line with and build upon these prior policies.

The recent Nature commentary on this issue (Clayton and Collins. *Nature*. 2014 May 15; 509(7500):282-3) persuasively laid out the case that the evidence supports changing longstanding research practices to consistently include the role of sex variation from cells or animals in influencing results. The AAMC has long been mindful that, given the respective public health missions of the NIH and our member institutions, our organizations should work collaboratively to ensure that research models, data, and repositories upon which medical
advances depend should be constituted to be as relevant and as representative as possible to all populations that may benefit from this research; for example, please see AAMC’s comments in support of NIH’s genomic data sharing policy recently finalized¹. We have also advocated strongly to NIH, FDA, and other agencies that such data or resources—with potential to benefit people of all backgrounds or both sexes—be shared within the research community to maximize the potential of these resources². It is vitally important to ensure that the benefits of medical research be equitably shared across communities, and genders.

It is imperative that the scientific establishment continue to think critically about its own research, its standards and processes, and the effectiveness with which it serves patients and the nation. Advancing our understanding of any sex-specific variability will undoubtedly result in the ability to create more effective health interventions in the future.

The AAMC, therefore, commends NIH for its intention to develop a comprehensive and effective policy for consideration of sex as a biological variable in biomedical research. We recommend that the trans-NIH working group move to implement policies to balance sex in cell and animal studies by mechanisms to include changes in grant review and additional training for researchers, and to issue any resulting policy with sufficient guidance for the medical research community to meet these new objectives.

As the Nature commentary definitively stated, a plan to require the inclusion of sex differences in preclinical research is “essential, potentially very powerful, and need not be difficult or costly…” and “will ensure that the health of the United States is being served by supporting science that meets the highest standards of rigor."

The AAMC is again grateful for this opportunity to comment, and we look forward to working with the NIH as it moves toward a final policy. Please contact me, or my colleagues Heather Pierce, J.D., M.P.H. (hpierce@aamc.org) or Stephen Heinig (sheinig@aamc.org) with any questions about these comments.

Sincerely,

Ann C. Bonham, Ph.D
AAMC Chief Scientific Officer

¹. Nov. 20, 2013, AAMC Comments to NIH on genome data sharing policy, [https://www.aamc.org/download/362234/data/aamccommentsonnihgenomedatasharingpolicy.pdf](https://www.aamc.org/download/362234/data/aamccommentsonnihgenomedatasharingpolicy.pdf)