Association of
American Medical Colleges
655 K Street, N.W., Suite 100, Washington, D.C. 20001-2399
T 202 828 0400 F 202 828 1125
www.aamc.org

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National Institutes of Health
9000 Rockville Pike
Bethesda, Maryland 20892

Re: Request for Information- Enhancing Rigor, Transparency, and Translatability to Improve Biomedical Research Involving Animal Models (NOT-OD-20-130)

The Association of American Medical Colleges (AAMC) appreciates the opportunity to comment to the National Institutes of Health (NIH) on enhancing scientific rigor in biomedical research involving animal models. The AAMC is a not-for-profit association dedicated to transforming health care through medical education, patient care, medical research, and community collaborations. Its members are all 155 accredited U.S. and 17 accredited Canadian medical schools; more than 400 teaching hospitals and health systems, including Department of Veterans Affairs medical centers; and more than 70 academic societies. Through these institutions and organizations, the AAMC leads and serves America's medical schools and teaching hospitals and their more than 179,000 full-time faculty members, 92,000 medical students, 115,000 resident physicians, and 60,000 graduate students and postdoctoral researchers in the biomedical sciences.

The AAMC strongly supports the ethical use of animals in research as critical to understanding human and animal disease and as a necessary element in the development of diagnostics, treatments, and cures. In collaboration with other organizations, AAMC has previously released recommendations[1] and commented[2] to the NIH on reforming animal research regulations, with a goal of streamlining requirements for researchers while maintaining the highest standards in animal use and care. AAMC also shares the NIH's commitment to improving the rigor and reproducibility of

[1] Reforming Animal Research Regulations: Workshop Recommendations to Reduce Regulatory Burden
Report of an April 17, 2017 workshop organized by FASEB, AAMC, and COGR, with assistance from NABR.
https://www.aamc.org/system/files/c/1/485962-reforminganimalresearchregulations.pdf

[2] AAMC Comments to NIH on RFI: Animal Care and Use in Research (NOT-OD-18-152). June 7, 2018.
https://www.aamc.org/system/files/c/1/489596-nihrfi-animalresearch.pdf

biomedical research and appreciates the agency's focus on animal studies in this effort. We are pleased to offer the following comments in response to the questions posed in the RFI.

Rigor and Transparency

As compared to research using in vitro systems, ensuring rigor in animal studies presents considerable challenges and differences. These include defining the sample size necessary to establish statistical significance for each animal model and setting, identifying optimal study design, and ensuring that a study is both efficient and still adequately powered. Rigor and transparency can also be enhanced by ensuring that key experimental methods are recorded and that the study protocol and all data analyses are interpreted and reported without selectivity or bias. Elements specific to animal research methodology to enhance rigor and replicability include using proper and consistent nomenclature and reporting: the strain and species of animals; the source of the animals; a description of animal housing conditions and feeding regimens; controls used in the study; and details of experimental procedures, such as reagents or drugs.

The NIH should provide guidance around the standards and details necessary when proposing, conducting, and evaluating animal studies funded by the agency, and ensure that investigators provide this information in grant applications and progress reports. The ARRIVE (Animals in Research: Reporting *In Vivo* Experiments) Guidelines, initially published in 2010[3] and updated this year[4], outline a growing consensus around improving the rigor and reporting of animal research. The NIH can utilize these guidelines as a basis for developing expectations for researchers.

The costs involved in recording and managing this additional experimental information are not insignificant and require additional expertise, staff time, and infrastructure. The agency should fund the collection and storage of this additional data and develop and manage resources and a platform specifically for this purpose.

Any new requirements must be carefully evaluated prior to implementation for their ability to enhance the quality of animal research without compounding the research regulatory burden in this field, in which needed reform efforts have met with only modest success. When considering any additional steps, such as preregistration of a research plan, the NIH should be clear about the specific

[3] Kilkenny C, et al. (2010) Improving Bioscience Research Reporting: The ARRIVE Guidelines for Reporting Animal Research. PLoS Biol 8(6): e1000412. https://doi.org/10.1371/journal.pbio.1000412
[4] Percie du Sert N, et al. (2020) The ARRIVE guidelines 2.0: Updated guidelines for reporting animal research. PLoS Biol 18(7): e3000410. https://doi.org/10.1371/journal.pbio.3000410

information needed from investigators and carefully balance the potential benefits of preregistration requirements with any increased burdens or concerns for researchers' safety. Particularly, given the relatively recent emergence of preregistration, we recommend the NIH solicit additional public input on this issue and undertake a pilot study on a smaller level before establishing any new agency-wide requirements.

The AAMC encourages the NIH to continue to partner with the academic medical community and professional societies to improve rigor and transparency in animal research, particularly to ensure that there is clarity in expectations and requirements for investigators, as well as sufficient funding and support to enable investigators to comply with agency guidelines and conduct the highest quality animal research. The NIH will need to provide resources to institutions as they continue to expand appropriate domain and statistical expertise. Additionally, many scientific societies have animal issues committees, an ideal source of information on animal models. These societies could also engage their members to develop and promulgate discipline-specific guidelines for research data quality. Finally, the NIH should work with institutions to understand other needs specific to animal research, such as the costs inherent to maintaining regional primate centers, and the potential for the agency to increase capacity by further supplementing the institutional investment in these centers.

Optimizing the Relevance to Human Biology and Disease

In considering actions to facilitate the translatability of animal research to human biology and disease, the NIH should recognize that there are inherent limitations in the translatability of some research and that it can be very difficult to mimic biology and disease pathogenesis across species. It is also key to note that animal research can be conducted in a very rigorous and reproducible manner but still end up untranslatable—and this aspect in and of itself should not diminish the value and scientific validity of the work.

The NIH could create a database of known, published animal models with a description of what aspect of the human disease it covers to promote open discussion about which models fit a specific disease, disease state, or some other narrower aspect of disease, as it is relevant to the research question being asked. This may involve the agency setting up working groups to draw from expertise in the research community and should include a thorough review of the literature. Understanding the pathophysiology of a disease is also essential in selecting the correct animal model, and researchers in the basic sciences may benefit from increased collaboration with clinicians on these issues.

Encouraging researchers to select or develop animal models with high utility and design experiments that have external validity to the clinical populations is a complex task. As a general principle, NIH

can improve translatability by making funds available to confirm the findings of promising studies, validate animal models currently in use, and identify and characterize potential new models.

Research Culture

The greatest incentive to using the most appropriate animal model is finding a model that can be replicated and produces consistent results when responding to therapeutic interventions. However, the current "publish or perish" incentive structure of the research enterprise also rewards quick production of results and publications, which can discourage researchers from working with less established models or conducting additional experiments to identify the most suitable model. Lack of clear guidelines, limited funding, and significant regulatory burden also function as barriers to achieving rigor in animal research. Reducing the funding level of a grant involving animal research may force researchers to change their research plans and/or experimental designs such that it may be difficult to meet necessary standards, for example, by having to reduce the number of animals used.

NIH review processes and policies are important drivers in influencing research culture. The NIH should include the funding of statisticians in project teams and instruct and provide support for reviewers to consider the strength of statistical methods in the review process. Study section review holds researchers accountable by requiring rigorous research plans in order to get funded, and the NIH should continue to use this leverage point to ensure high quality research.

The NIH can also help ensure an optimal research culture by contextualizing rigor and reproducibility in animal research in terms of broader agency efforts in this area across all research. Harmonizing requirements across the research portfolio by defining terms such as 'translatability' and integrating expectations for animal research into the existing agency framework for NIH-funded studies will provide a useful background for investigators. Like all other research, applications and reporting for animal studies should address rigor of the prior research and current experimental design, consideration of relevant biological variables, and authentication of key resources.

The AAMC recommends that the NIH collect and make available existing courses and training modules, including specific modules on study design and statistical analysis as they apply to animal research, as well as work with the extramural community to fill any gaps in these materials. These topics can also be built into the requirements for training grants, and the agency should require that all trainees who work with animals, regardless of funding mechanism, undergo rigor and reproducibility training with the same level of standardization, specificity, and gravity currently applied to responsible conduct of research training. Any training resources and funding opportunities

specific to rigor in animal research should also be listed under the main NIH site on rigor and reproducibility to allow investigators to access these items in one place.

The AAMC appreciates the NIH's engagement with the community as it works to improve biomedical research involving animal models. Please feel free to contact me or my colleagues Anurupa Dev, PhD, Lead Specialist for Science Policy (adev@aamc.org) and Amanda Field, PhD, Senior Specialist for Science Policy (afield@aamc.org) with any questions about these comments.

Sincerely,

Ross McKinney, Jr., MD
Chief Scientific Officer