August 21, 2020

BY ELECTRONIC SUBMISSION

Advisory Committee to the Director
Working Group on Enhancing Rigor, Transparency, and Translatability in Animal Research
National Institutes of Health
Once Center Drive, Rm 126
Bethesda, MD 20892-0147

Response to NIH Request for Information [NOT-OD-20-130]: "Enhancing Rigor, Transparency, and Translatability to Improve Biomedical Research Involving Animal Models"

Dear Working Group Members,

The American Society for Pharmacology and Experimental Therapeutics (ASPET) appreciates the opportunity to provide comments to the National Institutes of Health (NIH) in response to its Request for Information on the topics of rigor and reproducibility, translatability, and research culture related to animal research. ASPET is committed to improving the robustness and transparency of scientific reporting.

ASPET is a 5,000-member scientific society located in Rockville, MD. ASPET's members conduct essential basic and clinical pharmacological research and work for academia, government, large pharmaceutical companies, small biotech companies, and non-profit organizations. Their efforts help to develop new medicines and therapeutic agents to fight existing and emerging diseases.

For the last decade, the biomedical research community has been engaged in identifying the causes of lack of reproducibility of key research findings. The inability to reproduce research stalls scientific progress and squanders valuable (oftentimes public) resources. It also undermines public trust in science. ASPET is appreciative of NIH's efforts to rectify this problem. Nevertheless, while ASPET recognizes NIH has a duty to be a vigilant steward of taxpayer funds and thus has a significant role to play in improving research reliability and translatability, solving this problem requires the collective efforts of the entire biomedical research community. This includes publishers and journals who must raise standards of publication and standards of review.

I. Rigor and Transparency

The challenges of rigor and transparency in animal research and actions NIH can take to improve the quality of animal research including rigor and transparency

Ensuring rigor in the design and performance of scientific research and the ability to reproduce

biomedical research findings are integral to the advancement of science. To improve rigor and transparency in research with animals, NIH can encourage the publication of negative data by journals. For example, ASPET journals accept manuscripts based on the research question they address and the quality of the methods and not based on results. Publishing papers with negative results reduces the incentive to find positive results and encourages the use of robust experimental designs, which have a much greater chance of producing negative outcomes. NIH can assist in the normalizing of the publication of negative results by finding incentives for journals to adopt guidelines for the publication of negative results or providing a venue for the reporting of negative data. Encouraging the publication of negative results may lower the overall number of animals used in a study as researchers will not feel pressured to continue experiments until it yields a positive result. NIH may also consider that negative data could be used as data for pilot studies.

NIH may also consider developing centralized training on animal research, similar in scope and design to the Human Subjects Training and Resources offered by the Office of Extramural Research. The program could have a focus on ethics in animal research and it could be completed online. This would prepare trainees for working with animals and standardize certain practices emphasized in the training.

How preregistration, the process of specifying the research plan in advance of the study and submitting it to a registry, would impact animal research including improving the quality of scientific research.

While preregistration is often considered in the context of hypothesis-testing and confirmatory experiments, would it be useful at other stages of the research process, such as the exploratory and hypothesis generating.

Proponents of preregistration point to its benefits including increased transparency that prevents researchers from tweaking results after studies are initiated (commonly cited as a cause of reproducibility). But for exploratory research, there is concern that preregistration stifles discovery and creates additional burdens on researchers. For example, when completing experiments with novel drugs, researchers identify numerous parameters from previously published work and adapt those for the goals of the study, including drug administration times, drug doses, and routes of administration. However, once the experiment is completed, changes might need to be made if the novel drug shows unexpected effects, such as testing lower drug doses or shorter drug administration times. These changes would be a departure from the preregistered experimental plan, but necessary to fully characterize a novel drug. Preregistration requires experimenters to know all of these possible outcomes prior to completion of an experiment and with exploratory research this is not possible.

There's also a question of whether the additional transparency provided by preregistration is necessary for research using animal models. Animal research is already heavily regulated via Institutional Animal Care and Use Committees (IACUC) that review and approve detailed descriptions of how animal models will be used in a study, including procedures to be performed and experimental endpoints. IACUCs also provide flexibilities more compatible with exploratory research than preregistration. Under the example above, an IACUC will approve a range of doses and administration times for a novel compound so that the researcher can make adjustments without having to document guesswork or delay the experiment to amend a protocol.

Consideration of preregistration must also account for the risk posed to researchers by animal rights groups. Preregistration presents another opportunity for animal rights activists to harass researchers working with animal models. These activists and their affiliated groups use the Freedom of Information Act (FOIA) to obtain information about biomedical research grant projects and then post the information online and to social media. These networks often encourage persecution of researchers. Researchers seeking to work with animal models—especially non-human primates and canines and felines—may feel that the risk of disclosing more information via preregistration is not worth the potential risk to the disruption of their professional and personal lives.

Lastly, If NIH intends to move forward with preregistration, ASPET requests that NIH issue a separate Request for Information on the issue. There is confusion within our community over precisely what preregistration entails, what issues it would address., and how it would be implemented. The issue deserves additional scrutiny and feedback from stakeholders.

How to address the complexity and expense related to use of large animals, including nonhuman primates, that may provide biologically more relevant models.

Animal welfare considerations are important to the conduct of good research. Working with large animals requires extensive training, satisfactory infrastructure, and well-trained personnel to care for the animals. The success of preclinical pharmacology and toxicology studies relies on researchers and their teams using best practices for animal socialization and enrichment. Animals maintained in stressful environments will be less physiologically stable and therefore yield compromised study data. But providing for socialization and enrichment is expensive. Researchers may elect to use less expensive models to avoid funding issues. To encourage researchers to select the more biologically relevant models, NIH can design a separate revenue stream specifically for socialization and enrichment.

How NIH can partner with the academic community, professional societies, and the private sector to enhance animal research quality though scientific rigor and transparency.

There is no single factor that explains the problem of reproducibility in biomedical research. Poor study design and inadequate description of the methods used, lack of standardization, and insufficient training in research methods are all factors that contribute to reproducibility issues. Some of these issues can be addressed by the editors of journals. It is critical that journals raise standards of publication and raise standards of review to enhance rigor and reproducibility. Much of the recently identified reproducible research issues in pharmacology were based on literature reports published in journals that would not be considered leading pharmacology research journals. Journal editorial boards need to be vigilant about what research they accept. As long as there are journals that will accept bad science, then bad science will continue to be produced.

ASPET has taken steps to increase the reliability of scientific reporting in its own journals. Three of ASPET's primary research journals—Drug Metabolism and Disposition, Journal of Pharmacology and Experimental Therapeutics, and Molecular Pharmacology—have updated its instructions to authors. The new instructions focus on data analysis and reporting, including statistical analysis. ASPET journal authors are advised on how to graph data and write methods, results, and figure legends to ensure that data presentation is appropriately granular and harmonized across our journals. For animal experiments in particular, ASPET advises authors intending to submit to its journals that they should report the source, species, strain, sex, age, randomization, blinding, and husbandry of the animals. They should

also report the strain characteristics of genetically engineered animals including generations of back-crossing, or percentage of contributing strains if genetic analysis was performed.

Though these instructions are aimed at investigators in experimental pharmacology, they are applicable to most fields of experimental biology, and can perhaps be used to assist other disciplines in enhancing rigor and transparency. NIH may consider identifying and partnering with journals that have fewer reproducibility issues to develop education, best practices, and training methods that can be shared by NIH or used to develop courses for trainees implemented or endorsed by NIH.

NIH can also improve the rigor and reproducibility of animal studies by ensuring that consideration of sex differences in biomedical research is a priority of professional societies and the academic community. NIH can work with IACUCs and local institutional review boards (IRBs) to provide greater oversight by encouraging researchers to address sex as a biological variable during protocol review.

Finally, NIH can also encourage partnerships between academia and industry to address reproducibility. Standard practices in industry to ensure rigorous research includes counter-signing data points and digitally recording data so that it is timestamped and can be shared more easily.

II. Optimizing the Relevance to Human Biology and Disease

Actions NIH can take to facilitate the translatability of animal research to human biology and disease.

NIH must provide researchers funding for the tools they need to conduct methodologically sound research to improve translatability. Before clinical trials on humans can begin, researchers need to conduct in vivo pre-clinical studies of drugs to examine preliminary efficacy, toxicity, and pharmacokinetics. Researchers performing these studies are often screening for subtle effects and require an appropriate number of animal models to show an effect. But reductions in grant funding mean researchers cannot properly power their studies. This not only produces unreliable results, it wastes resources and raises ethical concerns. Studies with animal models need to be adequately funded to be effective.

Another area where NIH can improve translatability is in funding efforts to validate animal models currently in use and identifying and validating new animal models. The need for new animal models in several research areas where progress has stagnated is paramount. Drug discovery for psychiatric disorders is one area where the validation of new animal models might increase the success rate of developing new therapies. To identify new translational models, NIH can direct scientific review groups to prioritize grants that seek to make explicit comparisons between biological mechanisms in humans and animals. NIH will also need to fund studies to validate translational models in non-rodent species. Relatedly, scientists need to provide assurance that research animals are being used responsibly to make progress in the treatment of human diseases. Reassessment of current models and validation of new, more precise models can provide that reassurance.

How to encourage researchers to select or develop animal models with high utility and design experiments that have external validity to the clinical populations.

NIH can help researchers select or develop animal models that produce useful, empirically valid knowledge that advances our understanding of disease and therapeutics by facilitating interaction

between investigators and animal facilities staff. One way to do this would be to include animal technicians in discussions of relevant aspects of experimental design. Animal techs can provide investigators with information on care, facility capacity, inventory, and reproduction. Knowledge of these variables can help an investigator tailor a study to the capabilities of the vivarium rather than force a researcher to make post-hoc changes to a research plan.

NIH can also expand the Vertebrate Animals Section of grant applications so that researchers can provide additional information on the selection of animal models. Explaining why a particular animal model is necessary to address the research question may help researchers make more thoughtful selections of models. The expansion of this section could also compel researchers to provide information on housing room temperature, animals per enclosure, the type of enclosure, and genetic strain characteristics.

How NIH can partner with the academic community, professional societies, and the private sector to enhance animal research translatability.

Raising awareness and increasing access to resources on research methodology is necessary. NIH can signal-boost Society-specific resources by creating a repository to share information, by highlighting these resources in newsletters, and by partnering with scientific societies to disseminate these resources at annual meetings.

III. Research Culture

How research culture drives the choice of animal models.

How incentives/disincentives in the research enterprise influence research using animals

Laboratory research culture is primarily driven by the lab's principal investigator. Members of the lab will learn and adopt habits from the PI, including preference for animal models.

One incentive that may be impacting selection of animal models is the fear of failure, especially among newer researchers. Researchers may default to using animal models that they are more comfortable with or they know will produce results, even if that model is not best suited for the research question. Failure is an inherent part of the scientific process, and a failed experiment can be as informative and useful as a successful one. Recognizing this, there has to be opportunity for research to fail. Researchers cannot be penalized on their next grant application for taking a risk in selecting a newer, unfamiliar model and then later having to admit that their selection failed. As noted above, having a venue to submit and publish this negative data would not only assist the research community in evaluating the usefulness of this new model, but also would provide a venue for more junior researchers to demonstrate progress on their projects and grants, in spite of the lack of positive findings.

How all researchers, including trainees, are educated in rigorous research design, statistical considerations, transparent research practices, and the role of NIH in this training.

Because trainees will emulate their PIs, it is imperative that PIs remain up to date on new research techniques and technologies within their fields. NIH should consider requiring mid to late career investigators to demonstrate they are maintaining competencies and developing new ones. NIH might

introduce a new section in grant applications and progress reports for a professional development plan emphasizing the goals of the NIH with regards to rigorous research design, statistical consideration, and research practices. It could also include other relevant issues such as mentorship and responsible research conduct.

Respectfully,

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