COGR

Council On Governmental Relations

An Association of Research Institutions

August 19, 2020

Via Electronic Submission to https://grants.nih.gov/grants/rfi/rfi.cfm?ID=108

National Institutes of Health
Office of the Director

RE: Comments Submitted in Response to Notice Number NOT-OD-20-130, Request for Information

To Whom It May Concern:

The Council on Governmental Relations (COGR) is an association of 190 public and private U.S. research universities and affiliated academic medical centers and research institutes. COGR concerns itself with the impact of federal regulations, policies, and practices on the performance of research conducted at its member institutions. One area of significant interest and expertise among COGR member institutions is ensuring the integrity of basic and applied animal research.

COGR appreciates the opportunity afforded by the National Institutes of Health (NIH) to provide information in response to the June 16, 2020, Request for Information (RFI): Enhancing Rigor, Transparency, and Translatability to Improve Biomedical Research Involving Animal Models, Notice Number: NOT-OD-20-130.

The RFI states that it is critical for NIH to "focus on ways to ensure the value, rigor, and transparency of animal studies, while considering the impact on the overall funding landscape." It seeks input on the following three themes concerning animal research and lists specific questions/issues under each: (a) rigor and transparency; (b) optimizing the relevance of animal research to human biology and disease; and (c) research culture. This letter does not seek to address each specific question/issue set forth in the RFI, but rather provides general comments on areas where COGR can provide expertise, as set forth below.

Comments Regarding Rigor and Transparency

Pre-Registration: The complexities associated with using live animals as a research model inherently pose reproducibility challenges that researchers consistently seek to address. The RFI raises the possibility of pre-registering research protocols as a means for improving rigor and transparency. At its heart, however, a pre-registration system is basically another means for peer review. It may be more efficient to improve the already strong scientific peer review system that forms the backbone of the current animal research review process. Steps could be taken to better systematize the review process and to ensure that information bearing on research reproducibility is methodically collected, analyzed, and shared. Although efforts toward this end such as the implementation of the ARRIVE guidelines have not been as successful in improving reproducibility as hoped,[1] the literature suggests that stronger

[1] Leung V, Rousseau-Blass F, Beauchamp G, Pang DSJ (2018) ARRIVE has not ARRIVEd: Support for the ARRIVE (Animal Research: Reporting of *in vivo* Experiments) guidelines does not improve the reporting quality of papers in animal welfare, analgesia or anesthesia. PLOS ONE 13(5): e0197882. https://doi.org/10.1371/journal.pone.0197882

enforcement of such guidelines by journals may result in better compliance,[2] and NIH efforts that support such enforcement may help. Additionally, methods that encourage use and enforcement of standards for the proper planning and preparation of studies (e.g., the PREPARE guidelines[3] and the Experimental Design Assistant [EDA][4]) should be considered.

Prior to implementing any study pre-registration system, the concept should be sufficiently piloted within the research community to determine if it would truly add value, or merely be an additional step in an already labor-intensive research approval process. In this regard, any discussion of pilot projects should consider pre-registration not only in the area of animal research, but also as a means of strengthening aspects of and approaches to all research questions. Pilot projects should ensure that any contemplated pre-registration system is sufficiently socialized among groups of researchers and appropriate data is collected to quantify improvements. In this respect, piloting of pre-registration systems will need to address concerns from scientists regarding pre-registration of unique ideas and the possibility of being 'scooped'.

In considering pre-registration and how it can benefit transparency efforts, comparisons are often made with the use of pre-registration in clinical research. In the context of animal research however, there is a distinct possibility that a small subset of unscrupulous actors may improperly employ pre-registration by taking the research information provided out of context and inappropriately using it to malign researchers and research institutes. Accordingly, development of pre-registration systems must address this issue and give thoughtful consideration as to how proper support will be provided for researchers who become the subject of such improper attacks.

Transparency: The RFI seeks steps that NIH can take to support transparency of animal research, along with ways in which NIH "can partner with the academic community, professional societies, and the private sector to enhance animal research quality though scientific rigor and transparency." Many members of the public do not fully appreciate the importance of animal research, and frequently, the research is taken out of context or misconstrued. These public misperceptions hamper efforts at transparency.

One simple means by which NIH could promote transparency is to work with partners in the research community to educate the public about the need for the use of animal models in research, particularly with respect to the use of large animal models. Such educational efforts could include information about the current research review system and its safeguards, as well as the extensive vetting and oversight that animal research receives. Funding agencies, research institutes and professional societies who make up the animal research community must unite and support one another publicly so that scientists can feel confident doing outreach in the community and carrying out their research.

Large Animal Models: The RFI includes a question about ways in which NIH can address the complexity and expense of large animal models. As the current COVID-19 pandemic has demonstrated, there is a continued need for the use of large animal models in drug and vaccine development and other research endeavors, and the U.S. must remain prepared to execute this research if it intends to remain competitive in these areas. One possible mechanism is the establishment and use of a national research network to share control animals, provide access to model organisms, and implement standardization across studies conducted at multiple locations. The National Primate Research Centers offer an example

[2]See, Percie du Sert, N., Hurst, V., Ahluwalia, A. *et al.* The ARRIVE guidelines 2.0: Updated guidelines for reporting animal research. *BMC Vet Res* **16,** 242 (2020). https://doi.org/10.1186/s12917-020-02451-y
[3] Smith, A.J. Guidelines for planning and conducting high-quality research and testing on animals. *Lab Anim Res* **36,** 21 (2020). https://doi.org/10.1186/s42826-020-00054-0
[4] National Centre for the Replacement, Refinement & Reduction of Animals in Research, The Experimental Design Assistant – EDA, available at https://eda.nc3rs.org.uk/ (accessed Aug. 18, 2020).

of such a mechanism that could be expanded to other large animal models. Successful implementation of this structure, however, requires both financial and cultural support, including elimination of barriers to the use of large animal resources (e.g., difficulties in securing transportation for research animals, absence of a nation-wide strategy to address access to large animals, and lack of demonstrated support for the use of animal models in research).

Comments Regarding Optimizing the Relevance of Animal Research to Human Biology and Disease ("Translatability Issues")

The desire to move quickly from bench to bedside may actually harm translatability because it drives researchers to push the limits of basic animal research models. In an ideal research progression, a hypothesis is tested at the cellular level and/or through computational models, then progresses into a whole animal model, and finally includes testing of different interventions in multiple animal models. More frequently, however, research has become a "one-shot" project that leaps from a basic animal research model to translational research as soon as anything promising is found. Too often, these models fall flat because they were never intended to be used as the sole support for translational research in the first place.

Somewhat paradoxically, NIH might best be able to support the translatability of animal research by providing more support to basic animal research models and education in their use. For example, NIH could provide additional support for experiments in which researchers undertake to demonstrate a hypothesis in a second species before moving an intervention into research involving human participants. As noted above, support for the use of larger animal research models is critical in this regard. Given the expense and difficulties in using large animal models, researchers are often driven to using rodent models, but such models may not provide the data needed to ensure accurate translation to human biology and disease. Nevertheless, support of basic research on how best to increase the utility of small mammals and efforts to educate researchers about when the use of small mammals is appropriate could produce gains in translatability.

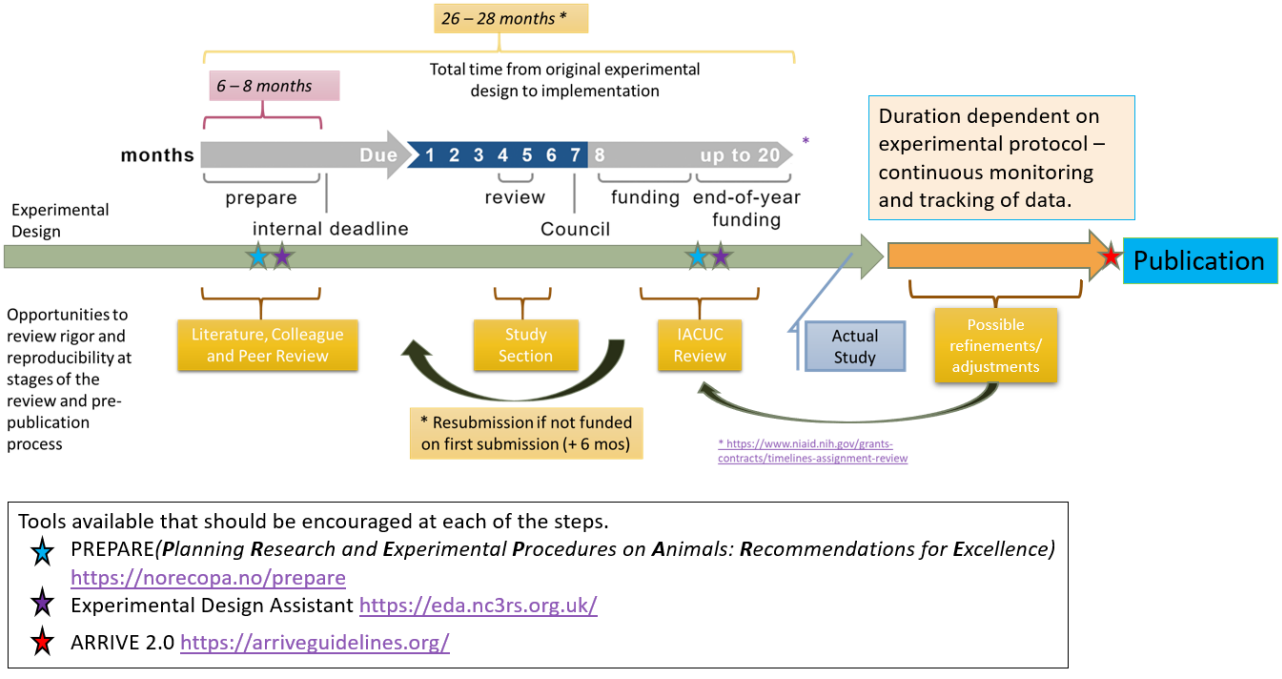
Comments Regarding Research Culture

Research in general, and more particularly animal research, tends to be very risk averse. Researchers frequently stick with animal models with which they have experienced success, and hesitate to move to other models, particularly if those models involve additional costs or controversial studies. Further, as is common in all areas of research, there is extensive pressure to produce positive, as opposed to "negative" results. NIH's efforts in this area may be an opportunity to reframe the way that scientists are looking at data and using terminology. "Negative" results answer scientific questions, and NIH could support a shift in focus to publishing results (whether they support the hypothesis or negate it) and not defining results as positive vs. negative. By viewing all results as essential to improving research rigor, and ultimately translatability, NIH can positively influence choices in animal research by encouraging well-designed studies that produce *results* that can be used to answer future questions and develop new hypotheses.

Although researchers have become better educated about the use of animal models, increased emphasis on statistical training and training in basic disease processes would assist in producing rigorous research design. As researchers become more specialized and work at the molecular levels in so many areas, it is important to step back and look at the macro levels of organ systems and basic physiology to ensure that there is good understanding of how everything works together. NIH, institutions, and professional associations could partner in developing educational initiatives along these lines. Additionally, training programs and professional societies should focus on how experimental design can be strengthened to make the scientific process more rigorous.

Finally, in examining the timeline of grant submission, review, funding and implementation it becomes apparent that there are major gaps in the opportunity for review of rigor and reproducibility prior to the time that potential publication is submitted to a journal for consideration. As *Figure 1* depicts, the original hypothesis is generated and grant preparation takes several months, followed by several additional months for study section review and ranking. The grant often must be resubmitted, the funding notice and transfer of funds can take up to a year, and the protocol must undergo the IACUC review and approval process before the study can start. Accordingly, thought must be given to the stage at which the experimental design and statistics are reviewed because by the time the funding is received the original submission has likely significantly changed.

Figure 1



This timeline becomes even more drawn out when time necessary to complete the journal's peer review process is considered.

Conclusion

COGR and the institutions that it represents recognize the importance of animal research to basic and applied research and support changes that improve the integrity, reproducibility and translatability of that research. In considering whether specific modifications should be adopted, however, it is critical to carefully weigh the benefit of the change against any administrative burden it imposes to ensure that implementation is truly a value-added proposition. Additionally, recognition should be given to the many processes within the animal research review system that currently work well, with an eye toward using and improving these existing components, as opposed to adding additional mechanisms.

We appreciate NIH's solicitation of stakeholder input that should be considered in issuing any guidance or making funding decisions in this area. We hope that the information provided herein is useful to NIH. If you have any questions regarding these comments, please contact Kris West, Director of Research Ethics and Compliance, at kwest@cogr.edu.

Sincerely,

Wendy D. Streitz
President