



# FASEB

Federation of American Societies  
for Experimental Biology

Representing Over 130,000 Researchers

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August 5, 2020

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

**RE: NIH Request for Information (RFI): Enhancing Rigor, Transparency, and Translatability to Improve Biomedical Research Involving Animal Models [NOT-OD-20-130]**

Submitted electronically via portal and e-mail: [Rigor-AnimalModels@od.nih.gov](mailto:Rigor-AnimalModels@od.nih.gov)

Dear Working Group Members,

The Federation of American Societies for Experimental Biology (FASEB) appreciates the opportunity to provide comments in response to the Request for Information (RFI) ([NOT-OD-20-130](#)) seeking input on strategies to enhance rigor, transparency, and translatability of research involving animals. As a federation composed of 29 member societies across a wide array of biology disciplines, we recognize the importance of rigorous science to improve our understanding of the natural world and inform future scientific directions. However, the irregularity of scientific replicability continues to jeopardize the public's trust in basic biomedical research. Acknowledging the complex array of factors that contribute to this issue, in 2016 FASEB issued [formal recommendations](#) that included actions for researchers, institutions, professional societies, journals, and federal agencies to enhance research rigor and reproducibility. We remain committed to strengthening research conduct and look forward to leveraging past and future efforts.

The establishment of the National Institutes of Health (NIH) Advisory Committee to the Director (ACD) Working Group to Enhance Rigor, Transparency, and Translatability will help provide the basis for improved research practices, and FASEB appreciates the Working Group's diligent efforts thus far. As deliberations continue towards final recommendations, we encourage the Working Group to heed the distinction between basic science and pre-clinical animal research, particularly because the former—while foundational for sustained scientific progress—may not demonstrate explicit relevance to human health and disease. Even so, exploratory work remains central to the research enterprise by instructing subsequent clinical studies, and thus merits continued full support. Additionally, we encourage the working group to actively engage stakeholders in discussions of suggested policy changes to ensure implementation is feasible at the institutional and investigator level, with particular respect to administrative burden.

Comments on specific sections of the RFI are provided below.

### ***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*

Rigor and transparency in animal research are fundamental to generating high-quality data while fulfilling the proper stewardship of taxpayer funds. As noted in the FASEB report, [Enhancing Research Reproducibility](#), one of the key challenges in achieving a higher standard of research conduct is insufficient reporting of methods and experimental design. For example, manuscript authors may cite “unpublished data” or “observations” to justify results or discuss potential implications. Additionally, researchers have become accustomed to providing incomplete descriptions of their methodology and other potentially relevant details regarding animal care, typically referring the audience to previous publications to accommodate journal limitations on word count. To address this issue, in 2010, the National Center for Replacement, Refinement, and Reduction of Animals in Research (NC3R’s) developed the [Animal Research: Reporting In Vivo Experiments \(ARRIVE\) Guidelines](#). Although the scientific community endorsed this resource, a [recent study](#) from the University of Edinburgh suggests adherence to the guidelines remains inadequate.

While vague reporting and other strategies may serve as a mechanism for investigators to retain a competitive edge, the lack of enforcement from journals and funding agencies further compounds this critical issue. One possible proactive measure to address this could be to modify the Approach or Vertebrate Animal sections, k of the NIH grant application to explicitly request how investigators will address scientific rigor in each of their Specific Aims —similar to previous efforts in 2015 ([NOT-OD-16-011](#)). However, this may require increasing the allowable page limit for applications.

Secondly, the absence of venues for publishing negative data also poses challenges for strengthening scientific rigor and transparency. Publication of negative data advances scientific progress by enabling researchers to pursue new lines of inquiry with improved methodologies, saving time and resources that would otherwise go towards repeated futile efforts. The lack of support for publishing negative findings is inconsistent with the charge of this Working Group and the community’s overarching goal to strengthen rigor and transparency. To resolve this discrepancy, FASEB urges the Working Group to prioritize this paradigm shift and assist NIH in establishing platforms that highlight these results, perhaps through a public database such as [BioRxiv](#). Another option to consider is developing mechanisms for incentivizing researchers that publish negative findings, as this would mobilize support and encourage transparency. However, the phrase “negative data” is associated with something unnecessary or irrelevant when, in reality, this vital information can potentially inform future experiments. Thus, as an initial step, FASEB recommends the Working Group Vocabulary Subcommittee consider reevaluating the phrase “negative data” and establish an alternative term and definition that emphasizes the positive aspects of such findings.

*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.*

FASEB appreciates the Working Group's efforts to discuss preregistration of animal studies. However, we are concerned that a preregistration requirement may inadvertently create many challenges including increased administrative burden, delayed completion of animal studies, and compromised confidentiality. To address the many nuances associated with this topic and ensure stakeholder feedback is adequately expressed, we encourage the Working Group to issue a separate RFI focused on preregistration and its impact on animal research.

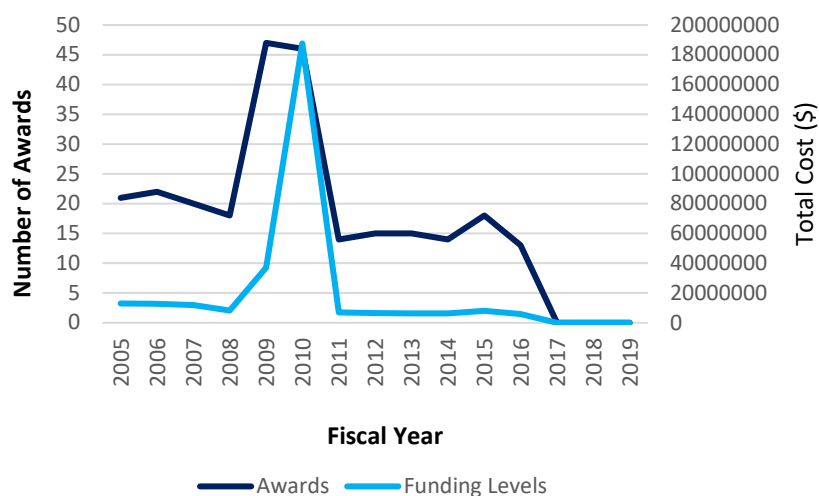
*How to address the complexity and expense related to use of large animals, including nonhuman primates, that may provide biologically more relevant models.*

Research with large animals has been vital to understanding basic biology, and continues to be instrumental in the development of treatments for devastating human and animal diseases such as hepatitis, HIV/AIDS, and cancer. Therefore, it is essential for federal agency funding opportunities to reflect the importance of large animal models in research activities. Increased reliance on large animals will also necessitate additional infrastructure and an expanded veterinary workforce to maintain quality animal care. To this end, FASEB recommends increasing support for infrastructure mechanisms, such as [G20](#), that allow institutions to construct new facilities or renovate current infrastructures to appropriate standards.

FASEB was pleased to see the introduction and approval of a recent [G20 concept clearance](#) from the Office of Research Infrastructure and Programs (ORIP) during the May 15, 2020 Council of Councils meeting and we urge NIH to proactively use this funding mechanism. Between fiscal years 2005-2019, the number of G20 awards declined significantly (*Figure 1, below*). At present, there are no active projects, and data from the NIH RePORTER indicate zero G20 grants were awarded between fiscal years 2017-2019. Thus, FASEB urges renewing and expanding support for infrastructure opportunities to enable optimal animal care with accurate study of disease.

To address increased expenses associated with the use of large animals, an additional option is to provide funding mechanisms to support components unique to large animal research. For example, socialization, environmental enrichment, and potential animal retirement are vital to maintaining optimal large animal welfare while conserving natural species-typical behavior. Creating environments that provide the appropriate amount of space and intellectual stimulation is costly, and deters many researchers from pursuing research with large animals. Furthermore, recent efforts to mandate relocation of post-research animals to sanctuaries is more-so dangerous than beneficial considering the associated costs and negative impacts on animal welfare. Given that this is a recurring issue both on Capitol Hill (e.g., [The Animal Freedom from Testing, Experiments, and Research Act of 2019](#); Fiscal Year 2021 House Appropriations [report language](#)) and at the federal agency level, we encourage NIH to administer resources for institutions to implement "retirement-in-place" for animals following research completion. Rather than relocating animals to sanctuaries that often lack the proper veterinary expertise for appropriate care, funding for retirement-in-place enables facilities to provide high-level, continued animal care through cost-effective mechanisms. Taken together, development of grant opportunities that support socialization, enrichment, and retirement-in-place options for large animal research will concomitantly address overlooked aspects of animal research while enhancing research translatability and animal welfare.

**Figure 1. G20 Award and Funding Levels (FY 2005-2019)**



*Note: Spike between 2009-2011 reflects American Recovery and Reinvestment Act of 2009 funding*

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

FASEB appreciates the Working Group's commitment to collaborate with key stakeholder groups to fulfill its charge. We agree that the first step towards enhancement of rigor, reproducibility, and transparency is development of uniform definitions and were pleased by the establishment of the Vocabulary subcommittee. We particularly appreciated the subcommittee's conclusion that statistical significance alone is insufficient for determining the likelihood of reproducibility. Moving forward, we encourage the subcommittee to consult with institutional and professional societies such as FASEB to ensure definitions are representative of all scientific disciplines, as the level and meaning of uncertainty may vary by field.

Additionally, NIH may want to collaborate with journal editors to create uniform requirements for publishing experimental design and methodologies. To attain visibility for their work, researchers frequently feel pressured to publish results in high-impact, multi-disciplinary journals, many of which limit the number of figures and space available for reporting methods. Other journals permit detailed methods publication but usually as supplementary material, prohibiting the reader from understanding the methodology in the context of study results. Experimental details are valuable for fellow researchers interested in reproducing and building upon previous studies, a process central to rigor enhancement. Establishing a new standard at the publication level that emphasizes details in scientific methodology and design will encourage the biomedical workforce to adopt these practices and mentor trainees to value these aspects of research conduct.

While we recognize NIH is limited in its capacity to enforce publication standards, we encourage convening regular public workshops with journal editors and other research stakeholders to discuss the aforementioned concerns and determine feasible resolutions, similar to the [NIH Workshop on Optimizing Reproducibility in Nonhuman Primate Research Studies by Enhancing Rigor and Transparency](#). Productive meetings such as this permit the community to understand ongoing concerns and refer to examples in its follow-up summary report. In fact, a recurring theme during the most recent workshop

that warrants extended discussion, particularly for rodent studies, is statistical study power and effect size. Researchers may propose studies with too few animals due to a lack of understanding about how to design an adequately powered study. Unfortunately, this pattern magnifies ongoing reproducibility difficulties by prohibiting researchers from generating robust data. As one of the most challenging and critical aspects of experimental design, we encourage NIH to take initiative and continue exploring the complexity of this issue by organizing public workshops focused on strategies to utilize the appropriate number of animals within the confines of our scientific commitment to the 3R's.

Finally, FASEB recommends implementing peer review grant training before scientific review group sessions (e.g., study sections). Rigorous peer review is the cornerstone of the scientific enterprise. Unfortunately, while scientists may have the expertise to critically review the science, some investigators require more guidance about the NIH review process. To support this effort, NIH may want to consider aligning its training with the Center for Scientific Review (CSR) as they continue implementing updates to Chair and reviewer training.

### ***Optimizing the Relevance to Human Biology and Disease***

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

Ensuring preclinical research is translatable to human biology and disease remains a fundamental priority to FASEB and numerous animal research stakeholders. Emphasizing translatability at the peer review level can facilitate this goal. Per our comments in the previous section, FASEB encourages NIH to ensure study section composition includes members with specific expertise on proposed topics to enhance both the peer review process as well as the study's predictive value. In several disciplines, research topics range from cellular mechanisms to molecular physiology to behavioral studies. There is a need for experts on study sections to understand the status of the field and whether proposed research addresses its gaps. FASEB would appreciate the opportunity to assist NIH to develop a mechanism for identifying and recruiting candidates for these positions.

Furthermore, we recommend establishing an interagency steering committee with the Food and Drug Administration (FDA) to assess the safety and scientific merit of promising research before clinical trials proceed. This partnership can mirror previous collaborations between the two federal agencies, such as the [Tobacco Centers of Regulatory Science](#) program established in 2012. While this initiative focuses primarily on tobacco product regulations and funds individual investigators across the country, the program outlines targeted research goals to evaluate the state of the science. Similarly, FASEB encourages NIH and FDA to combine respective strengths in preclinical and public health research to re-assess preclinical data and identify steps necessary for human applicability. Another viable option is broader adaptation of the ongoing public-private partnership known as [Accelerating COVID-19 Therapeutic Interventions and Vaccines](#) (ACTIV). This level of coordination between government and industry entities, particularly through ACTIV's third "Fast Track Area" of improving clinical trial effectiveness, serves as a valuable model to enhance cross-disciplinary collaboration and translatability of research beyond COVID-19. Increased efforts to streamline bench to bedside opportunities aligns with the goals of the 21<sup>st</sup> Century Cures Act, and also provides opportunities for current and future researchers to understand the importance of implementing a rigorous experimental design.

Establishment of such partnerships will require a comprehensive review of current data sharing mechanisms. Sharing data facilitates efficient translation of research findings to clinical trials by enabling

researchers to pool results and enhance statistical study power, allowing investigators to draw conclusions that would otherwise require more time and resources if done individually. However, the research community lacks a centralized location to participate in robust data sharing, often creating their own portals. FASEB recognizes and appreciates NIH's efforts to address these challenges by formulating its [Data Sharing Strategic Plan](#) and draft [guidance](#) for data management and sharing. These efforts include the establishment of NIH-funded data repositories such as [Figshare](#) and [STRIDES](#). We strongly encourage the Working Group to utilize lessons learned from these pilot programs to inform future guidance and data repository features necessary for animal researchers. Another model to consider while developing final guidance is [Neuro Data Without Borders](#), a platform that aims to standardize large neurophysiology data sets by allowing researchers to archive, share, and use information on an international scale.

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

FASEB appreciates the Working Group's careful evaluation of how to improve animal model selection and utility, particularly the emphasis on "systems biology" to better represent complex disease. As noted in the 2016 FASEB Rigor and Reproducibility Report, we also encourage the Working Group to consider the effects of the organization, daily operation, environment, and staffing of an animal facility on experimental outcomes. As critical components, animal facilities and staff should be considered extensions of an investigator's laboratory and research team. Therefore, FASEB recommends increasing the interaction between investigators and animal care staff by including these members in discussions of relevant aspects of experimental design.

FASEB also recognizes and appreciates that investigators and animal facility staff ensure humane treatment and care of animal subjects by adhering to existing guidelines and federal regulations. However, environmental factors are frequently overlooked and contribute mightily to reproducibility and ultimate external validity. For example, changes in husbandry conditions particularly affect mouse physiology and behaviors and thus have important implications for experimental design of subsequent trials. To minimize environmental effects on experimental outcomes and continue to improve animal care standards, FASEB encourages institutions, veterinarians, and researchers to identify, understand, and promote the adoption of evidence-based husbandry practices. To accomplish this, we encourage researchers to enhance reporting of provenance and genetic background of animals by including, as applicable, the following in grant applications and publications:

- Type of housing and cage, including bedding materials
- Number of animals housed per cage
- Food, water, and enrichment materials
- Cage temperature
- Timing and duration of light and dark cycles
- Number of generation crossings
- Other biological factors impacting research design, including sex

Admittedly, one of the reasons investigators may fail to include such detailed information is due to a lack of knowledge and communication about the above-mentioned husbandry practices. While we

acknowledge NIH may not be able to mandate increased lab interactions or higher standards for methods reporting, the funding agency should assist in developing guidance for researchers to ensure they adhere to best practices in animal care and husbandry practices. More importantly, this guidance could emphasize how these practices influence both animal welfare and research outcomes. To establish this, we encourage NIH to partner with both the NIH Intramural Facilities Working Group and the Office of Research Infrastructure Programs to harmonize guidance and ensure it sufficiently explains the critical implications of facility conditions and procedures on animal care. Additionally, we recommend the Working Group build upon their efforts to consult with the National Institutes of General Medical Sciences about selecting the appropriate animal model by developing guidance for investigators and trainees whose research may require transition to a separate model or species. Predetermined guidance will facilitate a seamless research transition and mitigate challenges often associated with complicated changeover. NIGMS has also emphasized the importance of selecting the appropriate organism based on the research question rather than adjusting experimental design to accommodate a specific animal model. We encourage the Working Group to continue highlighting this distinction and its impact on research rigor.

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

As previously mentioned, in 2010, NC3Rs published the ARRIVE guidelines to improve the reporting of research using animals in an effort to maximize the utility of published studies while minimizing the need for additional studies. More recently, [Norway's National Consensus Platform for the Advancement of the 3R's](#) (NORECOPA) established the Planning Research and Experimental Procedures on Animals: Recommendations for Excellence ([PREPARE](#)) Checklist aimed at strengthening experimental design prior to initiating studies. In a recent [publication](#) promoting the utilization of this checklist, it is noted that enhanced animal reporting cannot improve research quality retroactively, and therefore encourages researchers to work closely with animal facility staff to integrate the PREPARE checklist before the ARRIVE Guidelines are consulted.

However, while the ARRIVE Guidelines (including the [ARRIVE 2.0](#) “Essential 10 Checklist”), PREPARE Guidelines, and [Guidance for the Description of Animal Research in Scientific Publications](#) serve as useful references, awareness and utilization of these resources remains low. For example, a recent survey of 298 basic science researchers in China revealed that only 9.4 percent of respondents expressed awareness of the ARRIVE guidelines ([Ma et al., 2017](#)). To reverse this trend and promote research design and translatability, FASEB recommends that institutional animal facilities, Institutional Animal Care and Use Committees (IACUCs), and professional societies work together to promote awareness and use—as appropriate—of the PREPARE and ARRIVE checklists in animal research.

One way to encourage the use and adherence to guidelines such as PREPARE and ARRIVE as a comprehensive approach to research design and reporting is requiring researchers to disclose planned deviations from these guidelines in the ‘Methods’ sections of grant applications and publications. To this end, we advise NIH to partner with the academic community and professional societies to ensure this requirement is streamlined and does not pose additional, unnecessary administrative burden for researchers.

## ***Research Culture***

### *How research culture drives the choice of animal models.*

The culture of the laboratory actively shapes research expectations, goals, and methodologies, including the choice of animal models when designing experiments. FASEB appreciates the Working Group's consideration of this critical aspect. Because principal investigators set the tone for a research lab's operations and trainees primarily learn from their peers, it is important to exemplify best research practices from the top-down. Therefore, FASEB encourages investigators to engage with lab members about key characteristics of ongoing research, including experimental design, adequately powered studies, and appropriate statistical tests. In venues such as lab meetings and journal clubs, discussions of experimental design would supplement conversations of new research findings, and we encourage investigators to examine the study methodology with lab members, statisticians, and animal care staff if possible. Such collaborative discussions will reinforce the importance of these elements in animal research and, more importantly, instill best practices for future experiments.

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

An unfortunate reality in biomedical research is the emphasis on the number and citations of publications authored by an investigator. This “publish or perish” mentality is embedded in the research culture and contributes to the ongoing reproducibility crisis. Funding agencies such as NIH have an opportunity to shift scientific priorities towards research quality and rigor by providing grant support specifically for replication studies, similar to a recent National Science Foundation (NSF) initiative. In March 2018, NSF Directorate for Social, Behavioral, and Economic Sciences issued a [Dear Colleague Letter](#) encouraging researchers to submit proposals that use replication, reproduction, and generalization to test new ideas. These funding opportunities allow investigators to focus on data-intensive and real-world applicability of prior findings and thus help establish a new standard and appreciation for research rigor and reproducibility. This mechanism will also benefit trainees as they gain experience in performing sound scientific practices.

FASEB recognizes that meaningful change requires a concerted effort by funding agencies, investigators, professional societies, journal editors, and institutions. In finalizing its recommendations, we encourage the Working Group to incorporate guidelines for leaders at academic institutions such as research deans, department chairs, and animal facility staff as these members are in a unique position to shape institutional norms. For example, faculty evaluation criteria might place less emphasis on the number of publications and journal impact factors, and greater emphasis on data sharing, methodology transparency, and mentoring trainees to employ rigorous research practices.

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

Data presentation and proper statistical analysis are essential elements for reproducible and rigorous research. However, statistical coursework and training are not always required components of PhD-granting programs. FASEB applauds recent efforts from NIH to amend fellowship, training, and career development applications and require descriptions of how the program and faculty will provide training in rigorous design ([NOT-OD-16-034](#), [NOT-OD-20-033](#)). To build on these efforts, we encourage adding



specific expectations in these sections—particularly for training grant applications—to guide investigators on ways to mentor lab members towards enhanced experimental design and statistical analysis. Training items to consider incorporating include avoiding cognitive bias, eliminating p-hacking, and strengthening randomization. Lastly, we recommend NIH partner with academic stakeholders to develop feasible curriculum modifications and require biostatistical courses in the first year of doctoral training. This way, trainees will integrate rigorous methodologies at the start of experiments, rather than applying them after the fact, when prompted by journal reviewers.

Similarly, research team members and animal facility staff may require additional training to understand, implement, and report animal husbandry practices and genetic backgrounds of animal subjects. Access to statisticians or additional statistical training may also be necessary to ensure that animal sample sizes are sufficient for the required analyses. FASEB recommends collaborating with institutions and professional societies to establish training resources and ensure they are made available to the research community on a regular, on-demand basis. Considering that several training resources designed for improving animal research rigor and reproducibility currently exist for a broad range of disciplines, including a [training module](#) created by FASEB member society the American Physiological Society, we encourage the Working Group to aggregate existing resources through a publicly accessible clearinghouse website. To accommodate training gaps that may emerge, NIH may want to consider periodically updating this website with additional guidance where appropriate, preferably in coordination with stakeholder input.

Finally, FASEB appreciates NIH's efforts to develop [resources](#), including infographics and resource charts for investigators to enhance the rigor of grant applications. In particular, we thank NIH for dedicating an e-mail address ([reproducibility@nih.gov](mailto:reproducibility@nih.gov)) for researchers to submit questions pertaining to these topics. Given the particular challenges of fostering rigor and reproducibility in animal research studies, and the consequences of such on research translatability, FASEB encourages NIH to extend these resources and create separate tools for animal researchers. Likewise, it may be beneficial to establish an additional e-mail address specifically for animal research reproducibility inquiries (e.g., [animalresearchreproducibility@nih.gov](mailto:animalresearchreproducibility@nih.gov)). Enhanced communication with funding agencies will raise awareness and enable scientists to make informed decisions.

FASEB appreciates the opportunity to provide feedback on this RFI and looks forward to the Working Group's final recommendations later this year. We commend your work thus far, and encourage continued engagement with research stakeholders regarding possible next steps, as the enhancement of rigor, reproducibility, and translatability is essential for meaningful scientific advancements and bolstering the next generation of researchers.

Sincerely,

A handwritten signature in black ink, appearing to read "Louis B. Justement". The signature is fluid and cursive, with a large, sweeping flourish at the end.

Louis B. Justement, PhD  
FASEB President