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Federation of American Societies for Experimental Biology

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P.O. Box 2288, Rockville, MD 20847 | faseb.org

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Francis Collins, MD, PhD
Director
National Institutes of Health
Building One, Room 126
Bethesda, MD 20814

Lawrence Tabak, DDS, PhD
Principal Deputy Director
National Institutes of Health
Building One, Room 126
Bethesda, MD 20814

Michael Lauer, MD
Deputy Director,
Extramural Research
National Institutes of Health
Building One, Rom 144
Bethesda, MD 20814

RE: ACD Working Group on Enhancing Rigor, Transparency, and Translatability in Animal Research Final Report

Dear Drs. Collins, Tabak, and Lauer,

The Federation of American Societies for Experimental Biology (FASEB) commends the National Institutes of Health (NIH) for prioritizing rigorous animal research by establishing the Advisory Committee to the Director (ACD) Working Group on Enhancing Rigor, Transparency, and Translatability in Animal Research. Representing 30 member societies and over 130,000 individual scientists across a wide array of biology disciplines, FASEB recognizes how research transparency, rigor, and reproducibility are essential for fostering scientific progress, meaningful research collaboration, and clinical success. Furthermore, we appreciate the unique challenges associated with animal studies and the necessity to balance scientific objectives with considerations for animal welfare and the level of administrative burden.

FASEB applauds the Working Group's detailed and substantive final report presented during the June ACD meeting. The recommendations reflect the group's diligent efforts to fulfill its expansive charge on a complex topic, and we appreciate the emphasis on building a strong evidence base to inform future policy changes. Several themes of the report were commensurate with FASEB's recommendations submitted to the Working Group in 2020 and our 2016 report, *Enhancing Research Reproducibility*. As NIH proceeds with implementation of the Working Group's recommendations, we strongly encourage NIH to provide routine updates to the research community and integrate stakeholder feedback where feasible to leverage the full range of diverse perspectives and resources.

To accompany the Working Group's final report, FASEB offers the following comments, organized by recommendation theme.

Theme 1: Improve Study Design and Data Analysis

Flawed experimental design including poor sample size estimation and inappropriate statistical analyses are among the many factors contributing to low reproducibility in animal studies, and FASEB commends

the Working Group's emphasis on expanding statistical training for animal researchers (*Recommendations 1.1-1.2*). Additionally, we concur with the assessment that NIH could play a direct role in enhancing this complex yet essential type of training. For example, in addition to leveraging existing resources such as the National Institute of General Medical Sciences (NIGMS) Clearinghouse for Training Modules to Enhance Data Reproducibility, building partnerships with animal research and statistics stakeholders will ensure that new resources and training curricula adequately address problematic research practices such as p-hacking, cognitive bias, and lack of randomization. One strategy to enhance statistical training for NIH trainees includes amending fellowship, training, and career development applications and awards (e.g., F-, T-, and K mechanisms) to require descriptions of how institutional programs and faculty will emphasize training and mentoring in rigorous experimental design. By cultivating mentoring styles that prioritize rigorous research practices from the outset, trainees can integrate improved methodologies at the start of experiments rather than retroactively, when prompted by journal reviewers.

Secondly, we appreciate the Working Group's inclusion of FASEB's recommendation to add a single page to the NIH Research Strategy section of grant applications for investigators to specifically address critical elements of study design such as inclusion and exclusion criteria, sample size estimation, and data analysis plans (*Recommendation 1.3*). FASEB agrees this change will help level the playing field for early-career investigators who do not yet have the luxury of referring to previously published work when discussing methodological rigor as do established investigators. Accordingly, while many applicants already incorporate considerations for statistical analyses, rigor, and reproducibility throughout a grant proposal, consolidating these critical elements to a one-page section enables efficient identification and evaluation for reviewers while minimizing the administrative burden on investigators. Furthermore, for research studies where certain elements such as blinding or randomization may not to be relevant or appropriate for the proposed scientific objective, this separate page permits researchers to explain the reasoning behind their particular approach. Moving forward, we strongly recommend NIH collaborate with the Center for Scientific Review (CSR) and its Advisory Council to streamline the inclusion and review of this additional page and ensure the Working Group's recommendations align with CSR's recently proposed strategies.

The Working Group's recommendation for NIH to evaluate when in the pre-study research process experts could assess the quality of study design and data plans (*Recommendation 1.4*) is laudable. To this end, FASEB appreciates the idea to first implement pilot studies with evaluation plans to determine which strategy is most effective and feasible. The first and second proposed strategies—encouraging the use of NC3R's Experimental Design Assistant and including one trained statistician in peer review study sections—could serve as valuable mechanisms for strengthening investigator and reviewer attention to critical components of experimental design. Additional scrutiny of these aspects of the proposal by the study section itself would be facilitated to some extent by the one-page section described above.

However, the third suggestion to employ a post-peer review statistical panel for studies receiving the highest score raises numerous, significant concerns. While we recognize the importance of carefully evaluating statistical design, an additional layer of review would unnecessarily delay the peer review process and subsequent allocation of research funds. More importantly, this approach would create

additional burden for CSR, the NIH Center that has diligently worked to streamline the peer review process and reduce delays. To maintain the integrity of the NIH peer review process, FASEB recommends collecting data and assessing the efficacy of only the first two proposed interventions.

Theme 2: Address Incomplete Reporting and Questionable Research Practices

To sustain biomedical research advancements, complete reporting and transparent disclosure of key research methodologies and parameters are essential. FASEB appreciates the Working Group's comprehensive discussion of preregistration of animal studies prior to data collection as a means of strengthening research reporting practices and, more importantly, acknowledging stakeholders' concerns. Overall, FASEB concurs with the suggested initial step to launch an awareness campaign to improve understanding of both preregistration and registered reports (*Recommendation 2.1*), as several questions about the benefits of these two approaches remain unresolved. Articulating mitigation measures such as embargo periods to protect intellectual property and minimize the risk of harassment from animal rights groups is particularly important, and we strongly urge NIH to highlight these critical details in its awareness efforts.

The Working Group's recommendation to collect sufficient evidence about preregistration's effects on animal research rigor through pilot programs (*Recommendation 2.2*) is a necessary step in determining future actions and potential adoption. FASEB also appreciates the Working Group's consideration of methods beyond prospective reporting. For instance, registered reports provide researchers the opportunity to publish negative results, a critically important strategy to enhance research transparency. Communicating negative results is consistent with animal researcher's commitment to the 3R's because it enables investigators to pursue new lines of inquiry with improved methodologies, saving time and valuable resources—including animals—that would otherwise go towards duplicative and futile efforts. Overall, the success of the Working Group's proposed preregistration pilot program and forthcoming evaluation will require frequent engagement with animal research stakeholders. As trends emerge from pilot program data, FASEB encourages transparent reporting and opportunities for public comment to ensure the diverse perspectives of the research community inform the agency's next steps.

Theme 3: Improve Selection, Design, and Relevance of Animal Models

FASEB welcomes the Working Group's emphasis on understanding comparative human and animal biology to improve study design and animal selection in research studies (*Recommendations 3.1-3.3*). The recommendations outlined in Theme 3 present numerous opportunities for NIH to partner with stakeholder organizations, including FASEB, to develop best practices and promote the exchange of information related to animal model characterization and translatability. For example, a recent collaborative webinar with NIGMS explored the distinct differences between leading with the scientific question to inform animal model section and designing one's research according to a model's characteristics. Another strategy to promote greater awareness of this issue is to incentivize

conference organizers for hosting symposia and sessions related to animal research rigor and reproducibility. Leveraging such opportunities and formalizing these conversations through NIH workshops, webinars, and funding opportunities will support the Working Group's recommendation to generate, maintain, and disseminate a knowledge base focused on improving animal selection and research rigor.

Furthermore, FASEB applauds the Working Group's clear support for the value of research using large animal models and concurs with the recommendation for NIH to champion this research and its translational relevance (*Recommendations 3.4-3.5*). We recognize the misconceptions surrounding this issue—both on Capitol Hill and within the general public—and believe a unified message from stakeholders as well as NIH will help bridge existing knowledge gaps and drive more fact-based discussions. In addition to emphasizing the clinical relevance of large animal research for understanding and treating human diseases, we recommend highlighting the historic achievements large animal research has made in improving animal health. Partnerships with stakeholders such as FASEB could amplify NIH's education efforts and enable added recognition about the benefits of animal research in sustaining biomedical progress.

To complement this advocacy strategy and further signal NIH's support for animal research, FASEB encourages establishing policies and funding opportunities that accommodate the longer time frames, increased budgets, and infrastructure requirements unique to large animal research and care. For example, while the five-year grant period, modular budgets, and $500,000 annual direct costs cap for a standard R01 grant is sufficient for rodent research, these limits severely constrain large-animal studies, particularly those involving nonhuman primates. As rodent studies themselves quickly approach the $500,000 cap, it is critically important to adjust policies in accordance with the needs and requirements of research projects to enable investigators to pursue scientific questions with a continuous source of time and resources. As highlighted in our previous comments, FASEB recommends targeted funding for animal socialization, environmental enrichment, and potential animal retirement, as these components are vital for maintaining optimal animal welfare while conserving natural, species-typical behavior. Furthermore, as evidenced by the nation-wide shortage of nonhuman primates during the COVID-19 pandemic, ensuring institutional facilities and existing national resources, such as the National Primate Research Centers (NPRCs), are financially and physically equipped to maintain animal colonies and veterinary expertise is central to continued research success. Increased support for large animal care and research remains a core value for FASEB, and we appreciate the alignment of the Working Group's recommendation with President Biden's recent budget request to bolster NPRC infrastructure investments. Collectively, these recommendations demonstrate the imperative value of large animal studies in research translatability.

FASEB acknowledges that all animal models possess limitations and recognizes the emerging research and potential of non-animal alternatives. However, these models typically mimic only one aspect of human biology and remain ineffective in replicating the complex physiology and molecular mechanisms underlying systems biology and disease. Moreover, given their low predictive power,

alternative methods merit distinct scrutiny in terms of their rigor, reproducibility, and external validity. Therefore, we support the Working Group's recommendation to charter a high-level task force focused on non-animal models in biomedical research (*Recommendation 3.6*), and strongly encourage NIH to ensure the goals and expectations of non-animal alternatives adhere to the same standards as animal studies. This includes requiring non-animal research proposals to specify experimental design details in a separate page of the grant application, including randomization, inclusion/exclusion criteria, sample size estimation, and data analysis, as outlined in Recommendation 1.3. Another key element to take into consideration is ensuring the task force's composition features the appropriate expertise, including large animal models, comparative biology, translational research, and veterinary medicine. Together with stakeholder engagement, this approach will enable both well-balanced, knowledgeable decision-making as well as cooperative accountability.

Theme 4: Improve Methodological Documentation and Results Reporting

The Working Group's detailed justification for strengthening methodological documentation across the lifespan of a research study reveals the need for systematic changes to experimental approach and results reporting. Extrinsic factors related to the animals' environment is particularly significant for experimental outcomes, and FASEB agrees that factors such as lighting levels, ambient temperature, and enclosure density must be appropriately and intentionally reported. We specifically appreciated the Working Group's emphasis on first improving awareness about the role of extrinsic factors in influencing reproducibility (*Recommendation 4.3a*) and encourage NIH to enhance education efforts towards this issue by developing resources and hosting open-discussion forums for the research community.

Regarding strategies to improve methodological documentation, the Working Group's suggestion to disclose relevant extrinsic factors within NIH Research Performance Progress Reports is a viable option. This could facilitate reporting of key elements and, more importantly, strengthen data sharing opportunities. However, while we agree that standardization of extrinsic factor documentation is necessary, FASEB cautions NIH to consider the potential consequences of launching a website or cloud-based resource that publicly shares this information. Similar to the concerns associated with preregistration, open access to experimental data may create opportunities for animal rights groups to weaponize this information and engage in threatening behavior towards investigators.

Finally, FASEB was pleased with the Working Group's recommendation for NIH to establish a dedicated task force (*Recommendation 4.3b*) to evaluate which extrinsic factors should be cataloged and outline strategies for storing, retaining, analyzing, and sharing data. To facilitate the task force's endeavors, we encourage leveraging the expertise of institutional core facility directors and administrators, as these professionals possess the skills and knowledge about collating and analyzing large multi-disciplinary data sets. Partnerships with core facilities is both a time- and cost-effective approach as well, considering these transdisciplinary hubs inherently rely on sophisticated

technology and streamlined data reporting strategies, which could be adapted to meet animal researchers' needs. FASEB also encourages this task force to pursue partnerships with institutional personnel who directly work with animals, as the perspective of veterinary, operational, and animal care staff will be critically important in formulating evidence-based strategies for documenting extrinsic factor data. Collaborative efforts with core facility directors and veterinary staff may also be useful in improving record-keeping of large animals' longitudinal experimental, medical, and husbandry histories (*Recommendation 4.4*).

FASEB appreciates the opportunity to offer comments on the Working Group's final report and looks forward to future updates regarding implementation. With NIH's leadership, these recommendations serve as an opportunity to reshape how scientists apply critical findings from animal research. Recognizing the extensive responsibility to measure improvements in research conduct, we support the Working Group's phased implementation approach outlined in Theme 5 and emphasize the importance of reviewing ongoing progress on a routine basis to integrate adjustments where necessary. More importantly, transparency with the research community remains essential. Improving research efficiency through enhanced rigor, reproducibility, and translatability requires a concerted effort between stakeholders across the biomedical research enterprise, and FASEB encourages NIH to harness these perspectives through frequent public comment opportunities to inform future actions and enable meaningful scientific progress that will benefit researchers—and public health—for decades to come.

Sincerely,

Patricia L. Morris, MS, PhD
FASEB President

Cc: Noni Byrnes (Director, Center for Scientific Review), John Burklow (Chief of Staff to Director Collins, Members of the ACD Working Group on Enhance Reproducibility, Rigor, and Translatability in Animal Research