The American Physiological Society (APS) thanks the National Academies for the opportunity to provide input on the content and process for updating the Guide for the Care and Use of Laboratory Animals (the Guide). APS is a global, multidisciplinary community of more than 8,500 biomedical scientists and educators. Because the Guide significantly affects how scientists conduct research, APS has a critical perspective on the work of the Standing Committee.

During the April 2024 workshop 'Future Topical Updates to the "Guide for the Care and Use of Laboratory Animals"', speakers raised concerns about the lack of engagement between the Standing Committee and the academic research investigator community. APS comments, reflecting perspectives of that community on the content of the Guide, are attached again here for your consideration. Investigators can offer a unique perspective in that regulatory oversight directly impacts the conduct of their studies. Of equal importance is the burden imposed on investigators when attending to regulatory issues. Their comments are invaluable and deserve highest consideration.

Process improvements to increase investigator engagement

APS would like to offer further recommendations on how the Academies can increase investigator involvement in current and future processes related to the Guide. Given that the content of the Guide directly impacts researchers, it is essential that they are involved in its revision. Stakeholders including investigators, veterinarians, animal care staff, and institution and IACUC administrators each bring a unique perspective and experience with the Guide. However, speakers at the April 2024 workshop highlighted the fact that most of the input received came from the veterinary and animal care community. This may reflect a lack of understanding by investigators of what the Guide is, how it impacts their research, and how they can contribute to its updates and revisions.

Education

To incentivize investigator involvement in future activities related to the Guide, it is important to understand some of the barriers to involvement that investigators face. After the release of the 8th Edition of the Guide in 2011, the new Guide was presented at forums provided by the National Institutes of Health Office of Laboratory Animal Welfare (NIH OLAW) and the American Association of Laboratory Animal Sciences (AALAS). While these entities provide education and outreach to the veterinary and animal care communities, they have limited direct connections with the larger research and investigator community. When a 9th Edition of the Guide is released, the National Academies should include outreach to researchers directly, seeking out platforms and scientific meetings attended by investigators. Meetings like the American Physiology Summit and other scientific conferences attended by bench researchers provide valuable opportunities to present educational material related to the Guide through oral sessions, posters, and other forums. Meeting attendees would have an opportunity to learn about how and why the Guide is important to their work. Engaging researchers through these types of conferences is critical to facilitating the uptake and understanding of the Guide's recommendations within the scientific community. Because there are multiple levels of regulation and oversight, (such as requirements in the Guide, NIH oversight, and institutional rules) investigators often face confusing and conflicting animal care requirements. Education and outreach to investigators can help clarify these requirements by underlining the central role of the Guide. This would in turn encourage participation from the research community in contributing to its future revisions and updates. While organizations such as scientific societies can contribute through

outreach to their members, action is also needed from the National Academies to increase awareness of the importance of the Guide.

Representation

The National Academies should consider requiring a certain number of representatives from the researcher community on each of the committees related to the Guide (Standing Committee, Consensus Committee, etc.). If the Board on Animal Health Sciences, Conservation, and Research (BAHSCR) needs assistance finding additional volunteers to meet such a requirement, they should reach out to scientific societies and organizations (including the American Physiological Society), to provide recommendations. The National Academies should also consider working with societies and organizations to coordinate investigator-based focus groups on this topic.

Transparency

Most stakeholders are unfamiliar with the process that is currently being used to revise the Guide. To foster increased participation from investigators, the National Academies should increase transparency of the revision process wherever possible. Increased documentation on the website, social media, or email communications would greatly help the community understand the process and the progress being made. The more investigators understand and are aware of this process, the more opportunities they will have to participate in it. Additionally, openness about the challenges of revising the guide, such as perspectives that may be missing from discussions, may inspire creative solutions from the community.

Publications

Peer-reviewed and published studies on animal care topics are vital to improving animal care and integral to a science-based update to the Guide. However, researchers frequently face barriers to publishing such studies due to a shortage of funding and a lack of clear avenues to publication. Many relevant studies are conducted internally at research institutions, but without clear pathways and incentives for publication, these projects often remain unpublished and merely provide support to internal policies. The closure of the ILAR Journal removed one of the few outlets for this type of publication. However, even though there are few journals dedicated to animal care topics, there may be opportunities to collaborate with the editors of other scientific journals, like those published by APS and other scientific societies, to solicit papers on topics that would advance content for the Guide or to provide opportunities for invited reviews.

Conclusions

APS encourages the National Academies to consider long-term strategies that will incorporate our recommendations to benefit stakeholders in both the current and future revisions to the Guide. The Guide remains one of the most widely-used and important documents for animal research, and developing partnerships and collaborations with external groups, including scientific societies, can greatly benefit the revision process. It is imperative that the scientific community works together to accomplish this goal.

1. **Facilitated ethical advancement of knowledge**
   The APS holds that it is the responsibility of ILAR to advance of knowledge by facilitating ethical use of animals.

2. **Focus on animal welfare**
   Creating regulatory processes and administrative burden that does not significantly increase animal welfare is counter to the goals of the *Guide*.

3. **The reality of the *Guide* as regulation**
   The scientific community experiences the *Guide* as regulatory document. It should be written in such a way as to minimize over-interpretation by regulatory agencies.

4. **Evidence- and performance-based guidance**
   APS encourages the use of performance-based standards, IACUC-centered problem-solving, recommendation stratification based on quality and quantity of evidence available, and basis in publicly available evidence.

5. **Transparency**
   It is essential to the scientific community that guidance from ILAR come from trustworthy voices, that the decision-making processes for *Guide* revision are made clear, that sources of influence are not hidden, and that guidance is based on publicly available evidence.

Discussion Questions for Listening Session

Question 1: Does the *Guide* pose impediments for innovation and discovery to support robust research in the areas of animal biology, behavior, and pathology?

a. The *Guide* poses an impediment to discovery where prescriptive approaches to animal welfare limit innovative and humane solutions that might best support unique research or programmatic needs. We consider it the responsibility of the authors of the *Guide* to take into consideration how the *Guide* is used by OLAW and other agencies as *de facto* regulation. Further, we consider it to be impeding research even when the *Guide* suggests that such prescriptive approaches could be overruled by considered decision of the local institutional animal care and use committee (IACUC) if the *Guide* does not state that such flexibility is within the purview of the local

IACUC with sufficient clarity and firmness that this is universally understood and implemented.

i. In order to advance critical understanding in medical and biological fields, the *Guide* should direct IACUCs to assist investigators to develop protocols that enable them to address specific research questions, especially when flexibility with regards to *Guide* recommendations is required. Similarly, the *Guide* should support animal care and use programs (ACUPs) in developing innovative and humane animal husbandry solutions that meet local institutional needs. The *Guide* should include examples of how such flexibilities can meet standards for humane research while not conforming to standardized approaches in order to empower IACUCs and ACUPs to address issues at their institution.
ii. The Guide should explicitly reinforce that the local IACUC has the authority needed to develop their own solutions to their own unique institutional situations. This option can be further preserved by avoiding overly prescriptive recommendations in the *Guide*. The types of justifications and data acceptable to support IACUC decision-making should be broad, and examples given in the *Guide*. Examples might include a history of successful outcomes at the institution for a particular solution, or data supporting a solution shared by an institution supporting similar types of studies.
iii. It is NOT reasonable to standardize research methodologies in the *Guide*; innovative research depends on innovative approaches. The expertise for these developments lies with the scientists conducting the work, and cannot be summarized in a static document.

b. The *Guide* poses an impediment to discovery where it promotes institutional and programmatic processes and requirements that do not notably increase animal welfare but do increase administrative burden on IACUC and ACUP staff, and on investigators. Administrative burden at all these levels significantly drains resources and curtails research output. We consider the *Guide* to be impeding discovery even when the *Guide* is intended to be flexible to reduce administrative burden if the language in the *Guide* is not sufficiently clear and strong for it to be universally understood and implemented as intended. The authors of each product produced for the *Guide* should be able to answer to the satisfaction of the research animal care and use community the questions, “In what way does this guidance improve animal welfare?” and, “What is the administrative burden impact of this guidance?”

c. The *Guide* poses an impediment to discovery when IACUC protocol review results in required changes to a study in progress without significant improvements in animal welfare and means that data under the new experimental conditions cannot be compared with data under the old experimental conditions. This makes waste of animals, investigators’ finite time and resources, and sponsors’ resources, thereby impeding discovery. To reduce wasted or redundant studies, the *Guide* should

recommend that IACUC protocol review take into account the necessity of study parameter continuity for studies that span review cycles and, especially, versions of the *Guide*.

Question 2: What are your top priorities for improving the content of the *Guide*?

a. Shifting the *Guide* to consistent use of evidence-based recommendations.

b. Refocusing the *Guide* on animal welfare and eliminating guidance that increases administrative burden for IACUCs and investigators without improving animal welfare.

c. Leading ILAR and the authors of the *Guide* to accept the responsibility that the *Guide* is used as regulation and including in the *Guide* clear and unambiguous statements to help IACUCs embrace their authority to generate flexible solutions.

Question 8: What are the basic requirements that researchers using animals should have to ensure valid and reproducible research results, e.g., maintain statistical power?

a. Experimental design is a constantly evolving field, and current best practices are driven by a multitude of factors, including humane treatment of research animals, statistical considerations, cost, the urgency of the subject studied, technical and logistical limitations, technical innovation, and conceptual innovation. There are many types of research studies using animals, and there are manifold variations on those study types based on the balance of the above factors. It is outside the remit of the *Guide* to either attempt standardization of experimental approaches, or to present itself as giving expert guidance in experimental design; it is best that the *Guide* refer to resources maintained by credible experts, or to refer the reader to current literature where concepts of experimental design are considered.

b. The *Guide* should state that researchers are required to justify their experimental animal numbers to the satisfaction of the local IACUC. Justification may include an analysis of power, reference to similar studies already conducted, and a reasonable request for pilot animals, for instance, but it should be up to the local IACUC to determine if the number is reasonable given the goals and circumstances of the study.

Question 9: Should advice on experimental design (e.g., robustness, power) be included in the *Guide* or similar product?

a. It is not the role of the *Guide* to address appropriate experimental design, including statistical analysis. This is an area of robust analytical and philosophical thought that is outside the expertise and appropriate authority of ILAR. The *Guide* might helpfully mention some resources for experimental design, including statistical considerations, for example the Experimental Design Assistant by NC3Rs.

b. Facilitating humane and necessary animal research is the purpose of the *Guide*, and good animal welfare contributes to rigor and reproducibility. It is not the role of the

Guide to address rigor and reproducibility outside of animal welfare. As for other topics touching on responsible conduct of research that are outside of animal welfare, the *Guide* should mention high-quality resources for improving rigor and reproducibility, for example the ARRIVE Guidelines.

Question 4: Should other Guides, Guidelines, or other resources for the use of agricultural animals, wild birds, mammals, fish, herpetofauna, or other diverse organisms be integrated into the *Guide* and if so, what process might be used?

a. The *Guide* cannot comprehensively address all non-traditional species. To address the animal welfare needs for non-traditional species, the *Guide* should mention that it is expected that for unique species there will be unique solutions developed by ACUPs and IACUCs. Burden is placed on IACUCs to approve these local solutions in accordance with the ethical obligations in the *Guide*. The *Guide* should suggest approaches for developing local solutions, including discussion with outside experts, review of published papers, or other resources developed by ILAR or another body.

b. Researchers who work with wildlife populations (including marine animals) may not be adequately engaged in the formulation and revision process for the *Guide* because it has thus far focused on laboratory animals. These groups of researchers and administrators should be broadly invited into the conversation to discuss the best approach to ensuring humane research approaches, including if their work should fall under the purview of the *Guide*.

c. A large amount of biological variety exists among even closely related species. It is unlikely that a single document, like the *Guide*, could accurately encompass all potential scenarios and species without drastically increasing administrative burden. Rather, the *Guide* should suggest a multi-resource approach to review of such situations.

Question 5: How can the content of the *Guide* (or a similar product) be modified or expanded to benefit animals in a wider range of research environments (i.e., biomedical, natural habitat, exhibits, agricultural settings, clinical practice, etc.)?

a. ILAR should refer to existing resources developed by communities of experts for animals in these other areas rather than create redundant resources. These other resources are already considered to be a gold standard or are required as regulation (for example, those published by the USDA, the Ornithological Society, etc). The *Guide* should point to these other resources rather than including the information within the *Guide*. Creating redundancy would add administrative burden and create regulatory confusion.

Question 6: What are the most common concerns raised by users at your institution (or other stakeholders) about the care and use of animals in research? What options are available to respond to these issues in a cohesive way at the national/global level?

a. Investigators, ACUP administrators and IACUCs complain of administrative burden stemming from language in the Guide which does not improve animal welfare, especially prescriptive language and over-standardization which necessitates many individual justifications and waivers by the IACUC, or regulatory requirements not improving animal welfare.

b. Investigators and ACUP administrators complain of prohibitive costs to programs stemming from changes to the Guide that necessitated replacing equipment, especially when these changes only arguably result in improvements to animal welfare.

c. Investigators complain of seemingly arbitrary changes required in their IACUC protocols at the time of 1 year review, modification submission, or 3 year review, when there have been no changes to the Guide. This disrupts ongoing studies and can lead to wasted animal use. This could be addressed in the Guide by encouraging IACUCs to take into consideration the value of continuity in the context of on-going studies.

d. Similarly, investigators and ACUPs complain of changes to the Guide driving changes to what is allowed in an IACUC protocol, disrupting ongoing studies, and leading to wasted animal use.

e. ILAR should consider the resources required build and maintain a living document. This includes cyber security to keep the document from undue tampering.

f. ILAR should make their revision and review process for the Guide publicly available for the scientific community. This process needs to be defined and publicized. The Standing Committee should consider if there are lessons that can be learned through the preprint publications process (Biorxvs, prococols.io, etc.) that could be applied to a living Guide document.

g. There should be a process outside of the proposed 5-year process by which members of the community can recommend revision or review of portions of the Guide. Just because this mechanism exists, does not mean that it would need to be constantly used. This out-of-cycle process should be reserved for paradigm shifting conversations.

a. The absolute requirement to use pharmaceutical grade products when available at times can interfere with the ability to create induced models and/or investigation of novel approaches to therapeutic interventions. Some mechanism to allow use with adequate justification should be incorporated. Investigators that use concentrations of agents that do not come in pharmaceutical grade are required to justify this departure for every use.

Question 3: Are there knowledge gaps in the *Guide* and, if so, how might these gaps be addressed?

a. We have not developed an answer to this question at this time. We believe that this may be a Phase 2 question.

Question 10: What changes would make the *Guide* (or a similar product):

a. more readily adopted by the scientific community?

    i. An increase in transparency in the updating and revision process would likely make the *Guide* more readily adopted by the scientific community. This would include details about the revision process, clarity on the process by which Standing Committee members are selected, how the process is being funded and by whom. This information should be widely available. Though this is likely to increase animal rights organization's knowledge of the process, it would also create a needed transparency for the scientific community at large.

b. more widely disseminated?

    i. Available as an online document that is easily searchable, well-indexed, and linkable by section, with living links to outside resources.

c. easier and more consistent for users/stakeholders to implement?

    i. The *Guide* would be more consistently implemented by stakeholders if it remained focused on its mission of advancing knowledge by facilitating humane animal research by providing guidance on how to best consider animal welfare in research facilities. Other products than the *Guide* developed by ILAR might become high-quality resources if they had similarly focused missions.

    ii. The *Guide* would be better implemented by stakeholders if the writers of the *Guide* took into consideration how it is used as *de facto* regulation, and avoided prescriptive approaches, clearly and strongly stated where local ACUPS and IACUCs have authority to develop local solutions.

Question 7: How should future research efforts be directed to address the most pressing needs of the animal research community?

a. Considerable institutional knowledge about animal husbandry practices is not widely available to the community, impairing dissemination of best practices or unique solutions, and leading to redundant use of animals and/or increasing the burden on programs to validate practices already validated elsewhere. The ILAR journal could be a resource and repository for this knowledge.

Question 11: Are there distinctions between "the *Guide*" and "the *Guide* as interpreted or implemented by IACUCs"?

a. There are differences between "the *Guide*" and "the *Guide* as interpreted or implemented by IACUCs" because the *Guide* is used as *de facto* regulation by OLAW and other agencies, and because the *Guide* has not been written with this fact in mind. The authors of the *Guide* are in fact writing regulation and should treat it as such. In particular, language must be included to facilitate interpretation of the *Guide* as intended, as an educational and guidance resource by individuals involved in regulation at both the federal and local level, especially with regards to flexibility to develop solutions relying on local expertise, and addressing local program needs.

b. We strongly suggest the implementation of stratified recommendations based on the quality/quantity of the evidence available.
    i. In human clinical practice, evidence-based medicine has become the standard of care. A variety of professional sources help standardize and keep up-to-date clinical decision-making tools. For example, Wolter Kluwer maintains the evidence-based clinical decision-aid UpToDate®, used by many hospitals and medical practices. Similarly, American College of Cardiology takes a standardized approach to recommendation, with different classes of recommendations based on the evidence available at each level. The international Grade Working Group focuses on standardizing what kinds of evidence should be used for each "grade" of recommendation.
    ii. We suggest that the *Guide* use a graded system based on published evidence regarding animal welfare to standardize its recommendation language. In order to maintain a high level of expertise and effectiveness, the *Guide* should focus recommendations strictly on animal welfare. An ILAR working group should be organized to develop a grading system, composed of individuals engaged in discovery using research animals, and those familiar with the administration of ACUPs and IACUCs, together with individuals with expertise in grading systems used in human medicine.
    iii. Recognizing that published evidence regarding animal welfare may be lacking, few high-grade (strongly worded) recommendations may be possible (i.e. "must"). This gap indicates areas in which work needs to be done, and the gaps should not be hidden by inflating the weight of evidence to increase recommendation grades. Consequently, the *Guide* must direct local Animal Care and Use programs to weigh evidence from on-site observations, evidence shared by other institutions, etc, to develop solutions appropriate for local situations. ILAR should consider what avenues they or others could provide for such data to be published in order to improve the quality of evidence on which guidance is based for future *Guide* revisions.

    iv. Any data used to make changes to the *Guide* should be made publicly available.