PRIM&R
PUBLIC RESPONSIBILITY IN MEDICINE AND RESEARCH

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PRIM&R's response to NIH's Request for Information *Laboratory Animal Welfare: Coordination and Harmonization of Regulations and Policies (*Federal Register Notice 2018-05173: https://www.federalregister.gov/documents/2018/03/14/2018-05173/laboratory-animal-welfare-coordination-and-harmonization-of-regulations-and-policies and NIH Notice number NOT-18-152: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-152.html).

Submitted electronically at: https://grants.nih.gov/grants/rfi/rfi.cfm?ID=71

We are seeking the input of interested stakeholders concerning proposed actions that the agencies have identified to improve coordination and harmonization of regulations and policies. The responses received will provide critical information for final recommendations and implementation.

Below PRIM&R responds to each of the five proposed actions the agencies are considering.

1. Allow investigators to submit protocols for continuing review using a risk-based methodology

Public Responsibility in Medicine and Research (PRIM&R) is a nonprofit organization dedicated to advancing the highest ethical standards in the conduct of research. Since 1974, PRIM&R has served as a professional home and trusted thought leader for the research protections community. Through educational programming, professional development opportunities, and public policy initiatives, PRIM&R seeks to ensure that all stakeholders in the research enterprise appreciate the central importance of ethics to the advancement of science. We serve the animal research community, specifically, by providing professional and educational support to members and staff of Institutional Animal Care and Use Committees (IACUCs) in their critical work of ensuring the ethical care and use of research animals. We appreciate the opportunity to comment on proposals to reduce regulatory burden associated with federally

funded laboratory animal research while protecting the welfare of research animals and maintaining the integrity of science.

While the Request for Information seeks information on specific proposed actions the NIH and other agencies are considering to "improve coordination and harmonization of regulations and policies," PRIM&R's comments will also speak to the broader requirement of Section 2034(d) of the 21st Century Cures Act, which requires the NIH, in collaboration with USDA and FDA, to "complete a review of applicable regulations and policies for the care and use of laboratory animals and make revisions, as appropriate, to reduce administrative burden on investigators while maintaining the integrity and credibility of research findings and protection of research animals."

Indeed, and in the spirit of the mandate in Cures, we hope the federal agencies will be open to considering a wide range of ideas, recommendations, and proposals from the regulated community for revising policies and regulations to reduce administrative burden that does not serve animals or science—whether through this request for information or another mechanism.

Turning now to the specific actions proposed, we support the proposal to allow investigators to submit protocols for continuing review using a risk-based methodology**.** The human subjects regulations at 45 CFR 46 have long used a risk-based framework for both initial and continuing review, allowing institutional review boards to focus their attention and resources on higher risk research. In the context of animal research, risk-determinations should be made based on level of invasiveness and other animal welfare considerations raised by particular research procedures Specifically, PRIM&R endorses a recommendation made in the recent FASEB/COGR/AAMC/NABR report, "Reforming Animal Research Regulations: Workshop Recommendations to Reduce Regulatory Burden" (FASEB Report) calling for the USDA and OLAW to "amend the protocol review requirement to define types of studies involving low-risk, noninvasive, or, minimally invasive procedures. These studies could then be deemed exempt from full consideration or eligible for administrative or single member (expedited) review, without concurrence by the full IACUC."

We also endorse COGR's proposal that such a risk-based methodology would be applicable and is recommended both when an IACUC administrator or member makes an initial risk determination and with respect to continuing protocol review. Again, such a methodology would allow the resources of an IACUC to be directed to where they are most needed, namely, to ensuring the proper care and use of animals in more invasive research. To maintain necessary protections, regulatory policy should emphasize that researchers are responsible for understanding the definition of low-risk, noninvasive, or minimally invasive procedures, and continue to emphasize that researchers must obtain IACUC approval before making significant protocol changes.

2. Allow annual reporting to OLAW and USDA on the same reporting schedule and as a single report through a shared portal

PRIM&R supports this proposal. Allowing institutions to report to both federal agencies on the same schedule and through the same mechanism reduces administrative burdens that do not enhance animal welfare.

3. Harmonize the guidance from NIH and USDA to reduce duplicative considerations of alternatives to painful and distressful procedures

PRIM&R supports this proposal for harmonizing redundant regulatory procedures that do not enhance animal welfare.

We also endorse the FASEB Report's related recommendation that USDA Animal Care Policy #12 be amended to remove the following language: "APHIS continues to recommend a database search as the most effective and efficient method for demonstrating compliance with the requirement to consider alternatives to painful/distressful procedures." We believe that this gloss on the requirement to consider alternatives is unnecessarily prescriptive, overly rigid, and potentially ineffective. The language in the Animal Welfare Regulations says that, in the interest of providing greater flexibility to institutions regarding how their principal investigators fulfill the requirement concerning consideration of alternatives, an IACUC will determine whether a "written narrative prepared by the principal investigator" provides adequate assurance that alternatives were considered. As the FASEB Report points out, the language in USDA Animal Care Policy #12 is inconsistent with AWR.

We urge USDA and OLAW to make their language consistent, and to reinforce that IACUCs have the discretion and authority to determine if the principal investigator has adequately considered alternatives to painful and distressful procedures and detailed those considerations appropriately as part of a protocol submission. Having IACUCs determine that an investigator has adequately considered alternative procedures and provided a narrative description of the methods and sources used to make that determination will enhance flexibility and at the same time strengthen protections over the current process.

4. Provide a minimum 60-day comment period for new OLAW policy guidance

PRIM&R endorses this proposal, as we believe input from the regulated community is essential to making sound policy. We are hopeful that if OLAW adopts this proposal, stakeholder comments will be addressed during the policymaking process and final policy guidance will explain how such feedback was incorporated and/or considered.

Furthermore, it would be helpful to the animal research community if OLAW would provide additional clarity on what it considers policy guidance (for instance, whether its FAQs are considered policy guidance) and on the force of guidance (i.e., with a clear statement that they do not carry regulatory force).

5. Other approaches not previously mentioned

We have a few further recommendations. Some of the suggestions we offer below are derived from PRIM&R's recent *STAT* piece on the topic (statnews.com/2018/04/04/lab-animal-research-policies-reform/).

- First, where possible, revised federal policies should clarify that IACUCs and attending veterinarians have ultimate authority for ensuring the ethical care and use of animals at the institutional level, and for determining whether the anticipated benefits of the particular research study justify the proposed use of laboratory animals.

- Second, we call attention to the ethically arbitrary gaps in the current animal regulatory framework. The treatment of mice and rats—the largest group of laboratory animals by far—is subject to federal oversight and welfare standards only if the research is funded by Public Health Service agencies. From an ethical perspective, the fact that funding source is a trigger for whether a species receives certain welfare considerations is unjustified. We believe this ought to be changed. To be sure, bringing all vertebrate species under one harmonized regulatory framework will require further education of those who oversee research to ensure they are equipped to assess whether all animals are being housed and cared for appropriately. The extension of protections to new species must, then, be accompanied by appropriate education for inspectors and investigators. Funding and mandates for such education should be included in revised regulations and policies.

  A consolidated, consistent set of regulations would also likely garner greater respect and buy in from the scientific community than the current system which has overlapping, bureaucratically intensive regulations that do not necessarily translate to better animal welfare.

- Third, PRIM&R supports the FASEB Report recommendation that with respect to the review of current animal research regulations, USDA, FDA, and NIH consult with experts from federally funded animal research institutions, including investigators who work with animal models, veterinarians, IACUC members, and institutional administrators. The Report also proposes a group to advise the federal government on regulatory burden issues in animal research, proposing for this purpose an "expert subcommittee" of the Research Policy Board mandated by the 21st Cures Act that could then become a permanent advisory body. PRIM&R also supports this

idea, but emphasizes that to be effective, the charge and authority of any new federal advisory body or expert subcommittee, vis-a-vis the regulatory entities it is advising, need to be clearly defined.

Furthermore, we believe any advisory entity tasked with reviewing and refining regulations should represent the full spectrum of individuals involved in the animal research enterprise. In addition to scientists, veterinarians, institutional representatives, and IACUC members associated with research institutions, such bodies should include veterinarians with specialty interests (such as primates), independent animal welfare experts, ethologists, bioethicists, non-scientists, and experts who understand the particular needs of laboratory research animals. The inclusion of such perspectives is crucial to bolstering the public's trust in the animal research enterprise. Indeed, without their inclusion, the advisory process could be seen as excluding stakeholders who do not have a vested interest in the conduct of research with animals, and could thus weaken public support for such research.

Below we provide feedback on whether the following tools and resources are or would be helpful for reducing burden on investigators:

1. Encourage the use of sections of the AAALAC International program description in applicable parts of the OLAW Animal Welfare Assurance, for institutions accredited by AAALAC International

Before we comment on the specific resources listed, we note that each of them is already available to the regulated community. We further point out that each tool is a mechanism for addressing what is often called "self-imposed" regulatory burden—administrative burdens created by institutions' own approaches to implementing regulatory requirements that do not themselves necessarily require such approaches. While suggestions for how institutions can more flexibly or efficiently meet regulatory requirements, and federal endorsement of those approaches, are welcome, it is our understanding of the mandate in section 2034(d) of 21st Century Cures that the agencies are required to take steps to reduce burdens created by redundant, overlapping, and duplicative regulations themselves. None of the proposals in this section of the RFI take such steps.

With respect to the use of sections of the AAALAC International program description (PD) in applicable parts of the OLAW Animal Welfare Assurance, it is worth noting that there is nothing that now prevents institutions from cutting and pasting sections of their AAALAC International PDs into applicable parts of their OLAW Assurance, and indeed, we know many institutions do this. What would be more helpful to regulated institutions, from a burden-reducing perspective, is a mechanism by which the same documents could be used for multiple purposes and regulatory/accrediting agencies. The most sensible option with respect to the AAALAC PD and OLAW Assurance would be to allow institutions to use their

OLAW Assurance as part of their AAALAC PD, such that AAALAC could take advantage of what many of their member facilities are already creating and providing to OLAW.

2. Encourage the use of the FDP Compliance Unit Standard Procedures as a repository of best practices for standard procedures used for research with animals

PRIM&R believes the FDP CUSP is a helpful resource for enhancing efficiency, but notes that this is a volunteer, community-driven resource repository that is only available to FDP members. Whether it is and continues to be helpful to the research oversight community or not depends on the platform being adequately and regularly maintained and operated by dedicated, knowledgeable personnel who are available to assist users in an efficient manner, and it being accessible to all institutions.

3. Encourage the use of the IACUC Administrators Association repository of best practices by IACUCs

While access to a repository of "best practices" that have been vetted as such is a helpful way to streamline procedures and allow IACUCs to focus their energy on animal welfare issues rather than administrative issues, again, the IAA repository is a resource created by the community, so is only as good as what is voluntarily posted there. At this time, there is limited information available on the site, and it is not clear how the community is being encouraged to post there, or whether people are ready to do so. Furthermore, not all resources in the repository are open access. It is therefore not clear the IAA repository is an adequately robust or accessible resource to serve the stated purpose.

4. Encourage the use of new or existing tools to streamline protocol review through use of designated member review (DMR), DMR subsequent to full committee review, and/or Veterinary Verification and Consultation

We agree in principle that use of DMR and VVC, or perhaps new risk-based tools, should be encouraged, not only to streamline review, but also to allow IACUC meetings to be dedicated to more programmatic issues such as policies, infrastructure, training for the IACUC and researchers, and ethical discussions on the procedures occurring at the institution. With respect to VVC, however, we note that some institutions are hesitant to use these strategies due to confusion and concern about being out of compliance. In order for institutions to take full advantage of the burden-reducing benefits promised by a VVC process, additional guidance from OLAW is required. We encourage OLAW to significantly simplify VVC and give greater discretion to the veterinarians employed by the institution to determine what significant changes to research protocols can and cannot be approved by

them. Ultimately, the use of VVC should not only reduce unnecessary burden but also benefit animal welfare.

5. Expanded IACUC training activities that focus on reducing burden on investigators

PRIM&R believes that if NIH and its sister agencies "(1) identify ways to ensure [laboratory animal research] regulations and policies are not inconsistent, overlapping, or unnecessarily duplicative, including with respect to inspection and review requirements by Federal agencies and accrediting associations; (2) take steps to eliminate or reduce identified inconsistencies, overlap, or duplication among such regulations and policies; and (3) take other actions, as appropriate, to improve the coordination of regulations and policies with respect to research with laboratory animals," per the requirements of section 2034(d) of the 21st Century Cures Act, there may be no need for expanded IACUC training activities specifically focused on reducing administrative burden—activities that themselves can be burdensome. This would allow IACUC training to focus instead on strategies for protecting and promoting research animal welfare and the integrity of research findings.