Complying with PHS Requirements for Research with Animals

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This review provides a succinct resource and references for investigators to understand the main expectations and requirements when using animals in NIH-funded research and focuses on the US Government Principles as a foundation to ensure animal welfare in keeping with the universally recognized 3Rs of reduction, replacement, and refinement.

Introduction

Investigators conducting biomedical research in the US have a moral and legal responsibility to ensure that their research animal subjects do not suffer unwarranted pain or distress. The US has developed a highly flexible and self-correcting system of animal welfare oversight based on self-monitoring that facilitates the highest quality research in a context of humane animal care and use. The system relies on the foundation of professional judgment and performance standards. Scientists are required to conduct their studies in compliance with a framework of federal, state, local, and institutional rules and regulations. At the federal level, two agencies have primary responsibility for animal welfare oversight. The US Department of Agriculture (USDA), Animal and Plant Health Inspection Service (APHIS), (https://www.aphis.usda.gov/aphis/ourfocus/animalwelfare) regulates the use of most warm-blooded animals in research, excluding mice, rats or birds bred for research. USDA regulation is based on the Animal Welfare Act and Regulations (AWAR; https://www.nal.usda.gov/awic/animal-welfare-act).

The National Institutes of Health (NIH; https://www.nih.gov/) Office of Laboratory Animal Welfare (OLAW; https://olaw.nih.gov/) oversees the welfare of live vertebrate animals in PHS funded activities. All OLAW oversight and guidance is based on the PHS Policy on Humane Care and Use of Laboratory Animals (Policy; NIH 2002). The requirements of the PHS Policy apply to research, research training, and biological testing activities involving the use of live vertebrate animals. This includes animal activities supported by any PHS agency, including the NIH, the Food and Drug Administration (FDA), and the Centers for Disease Control and Prevention (CDC). The PHS policy covers all funding mechanisms, including research and training grants, cooperative agreements, and contracts, conducted at domestic and foreign institutions.

While the institution that receives the funds from a grant or contract is responsible for compliance with the requirements of the PHS Policy, principal investigators (PI) are responsible for leading and directing the project, intellectually and logistically (NIH 2012a). Therefore, PIs must comply with the PHS Policy when using vertebrate animals in PHS-funded activities. Vertebrate animals include traditional laboratory animals, farm animals, wildlife, and aquatic species.

Compliance with the PHS Policy is a broad mandate as the PHS Policy incorporates a number of other standards. Most notably, the US Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training (IRAC 1985). The Principles provide the foundation for all federal regulations regarding animals. The PHS Policy was expressly written in 1985 to implement the Principles. The PI and the institution must exercise care to comply with the Principles in order to maintain an uninterrupted funding stream from PHS funding agencies.

Highlights of the US Government Principles

Principle II addresses the requirement that the research is relevant and has the promise of being beneficial. *"Procedures involving animals should be designed and performed with due consideration of their relevance to human or animal health, the advancement of knowledge, or the good of society."*

Principle III addresses consideration of alternatives to animal use as an integral part of the decision to use animals. It is synonymous with two of the 3R requirements to reduce animal numbers and to replace non-animal models wherever possible. *"The animals selected for a procedure should be of an appropriate species and quality and the minimum number required to obtain valid results. Methods such as mathematical models, computer simulation, and in vitro biological systems should be considered."*

Principle IV is synonymous with the 3R requirement for refinements (e.g., less invasive procedures or use of analgesia). The second sentence in Principle IV has been criticized by some as being overly anthropomorphic. However, it remains as an important presumption for subjective evaluation of pain in animals and one that investigators should consider no matter what type of research with animals they undertake. *"Proper use of animals, including the avoidance or minimization of discomfort, distress, and pain when consistent with sound scientific practices, is imperative." Unless the contrary is established, investigators should consider that procedures that cause pain or distress in human beings may cause pain or distress in other animals."*

With **Principle V**, there is an expanded expectation for refinements to minimize pain and distress using pharmacologic relief and although not even a consideration with today's IACUC oversight, the prohibition of the use of paralytic agents without accompanying anesthesia.*"Procedures with animals that may cause more than momentary or slight pain or distress should be performed with appropriate sedation, analgesia, or anesthesia. Surgical or other painful procedures should not be performed on unanesthetized animals paralyzed by chemical agents."*

Again, **Principle VI** invokes the 3R of refinement through the use of humane endpoints. *"Animals that would otherwise suffer severe or chronic pain or distress that cannot be relieved should be painlessly killed at the end of the procedure or, if appropriate, during the procedure.*"

Principle VII includes the need for veterinarian involvement to ensure appropriate housing and care and the requirement that clinical care be available and provided by a veterinarian. *"The living conditions of animals should be appropriate for their species and contribute to their health and comfort. Normally, the housing, feeding, and care of all animals used for biomedical purposes must be directed by a veterinarian or other scientist trained and experienced in the proper care, handling, and use of the species being maintained or studied. In any case, veterinary care shall be provided as indicated."*

Principle IX empowers the IACUC to be the decider when exceptions to the Principles are needed. *"Where exceptions are required in relation to the provisions of these Principles, the decisions should not rest with the investigators directly concerned but should be made by an appropriate review group such as an IACUC. Such exceptions should not be made solely for the purpose of teaching or demonstration."*

Post-Award Responsibilities

Once funded, the PI has responsibilities for maintaining compliance with the federal animal welfare requirements. These include:

- Obtaining IACUC approval prior to using animals or making significant changes.
- Ensuring research is conducted according to the approved protocol.
- Complying with institutional policies and procedures.
- Addressing significant changes to the use of animals in progress reports to NIH.
- Obtaining prior permission from NIH for the use of animals involving a change in scope, including changes in performance site (Silk et al 2013).

IACUC approval is required prior to award and most IACUCs require investigators to submit information about the care and use of animals on a protocol form. The use of animals approved by the IACUC must be congruent with the description in the grant application. Any modification required by the IACUC that affects the content of the application must be submitted to the NIH along with the IACUC approval date. Under no circumstances may an IACUC be pressured to approve a protocol or be overruled on its decision to withhold approval (NIH 2010). Investigators must also obtain prior approval from NIH for changes in scope that constitute a significant change from the aims, objectives, or purposes of the approved project. The PI must make the initial determination of the significance of the change and should consult with their NIH Grants Management Officer as necessary (OLAW 2013). Conducting research in the absence of a valid IACUC approval or implementing a significant change without IACUC approval are considered serious noncompliance and are to be reported to OLAW and the funding agency supporting the award. In cases where charges have been made for unauthorized animal activities, appropriate adjustments must be made to remove those charges. (NIH 2012b).

Conclusion

NIH is committed to the highest standards of animal care and use in the research it supports and upholds federal regulations that ensure ethical animal use. NIH encourages the use of the most appropriate models. The knowledge gained from this research is used to develop life-saving treatments for diseases and conditions affecting the health of Americans and the world community.

References

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