What Investigators Need to Know About the Use of Animals

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Abstract

Investigators conducting research with animal subjects have an ethical and legal responsibility to ensure they are treated humanely. The system of animal research oversight in the United States consists of a framework of federal, state, local, and institutional requirements. Institutions supported by the Public Health Service (PHS) are required to follow the guidelines mandated by the PHS Policy on Humane Care and Use of Laboratory Animals and establish institutional animal care and use committees (IACUC) to oversee animal research activities. This system of self-monitoring at the local level is central to assuring an effective and compliant animal care and use program. Integral to this system is the responsibility of the investigator for the stewardship of their research animal subjects. No activities may be conducted without IACUC approval. Investigators are accountable for all aspects of their animal research activities from preparing their funding applications and complying with the terms and conditions of awards to protecting the investment in research with animals. This review acts as a succinct resource and provides references for investigators supported by the PHS to understand the main expectations and requirements when using animals in research.

Key Words: animal welfare; assurance; humane; IACUC; investigator; PHS policy

> *Proper use of animals, including the avoidance or minimization of discomfort, distress, and pain when consistent with sound scientific practices, is imperative.*
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> – US Government Principle IV
> ([IRAC] Interagency Research Animal Committee 1985)

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United States Biomedical Research Oversight

Investigators conducting biomedical research in the United States have a moral and legal responsibility to ensure that their research animal subjects do not suffer unwarranted pain or distress. Biomedical research is complex and ever advancing. The United States 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. Individuals involved in animal care and use draw upon their education and experience to determine the best course of action to follow in a specific situation. Engineering standards that define each step to be taken to achieve a desired result are at the other end of the continuum and are less heavily relied upon.

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 Animal Care program of the Animal and Plant Health Inspection Service of the US Department of Agriculture (USDA) (www.aphis.usda.gov/animal_welfare/index.shtml) regulates the use of most warm-blooded animals in research, excluding mice, rats, or birds bred for research. Another organization at the USDA, the Animal Welfare Information Center of the National Agriculture Library (http://awic.nal.usda.gov/), provides information for the improved care of animals used in research, testing, training, and exhibition. USDA regulation is based on the Animal Welfare Act and Regulations (7 U.S.C. 54 and 9 C.F.R. 1A http://awic.nal.usda.gov/government-and-professional-resources/federal-laws/animal-welfare-act).

Our office, the Office of Laboratory Animal Welfare (OLAW; http://grants.nih.gov/grants/olaw/olaw.htm) at the National Institutes of Health (NIH; www.nih.gov/), oversees the welfare of live vertebrate animals in Public Health Service (PHS)–funded activities. All OLAW oversight and guidance is based on the PHS Policy on Humane Care and Use of Laboratory Animals (hereafter, Policy) (NIH 2002).

PHS Policy

The requirements of the PHS Policy apply to research, research training, and biological testing activities that involve

the use of live vertebrate animals. This includes both extramural and intramural animal activities supported by any PHS agency, including the NIH, the Food and Drug Administration, and the Centers for Disease Control and Prevention. The PHS Policy covers all funding mechanisms, including research and training grants, cooperative agreements, and contracts, at domestic and foreign institutions.

Although the institution that receives the funds from a grant or contract is responsible for compliance with the requirements of the PHS Policy, principal investigators are responsible for leading and directing the project, both intellectually and logistically (NIH 2012a). Therefore, principal investigators must comply with PHS Policy when using live 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 becuase PHS Policy incorporates the US Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training (IRAC 1985), the *Guide for the Care and Use of Laboratory Animals*, 8th edition ([NRC] National Research Council 2011), the applicable Animal Welfare Act and Regulations mentioned earlier, and the American Veterinary Medical Association (AVMA) Guidelines for the Euthanasia of Animals: 2013 Edition (AVMA 2013). The principal investigator and the institution must exercise care to comply with the principles, policies, and operational guidance provided in all of these documents to maintain an uninterrupted funding stream from PHS funding agencies.

Before the PHS may award a grant or contract that involves the use of animals, the recipient institution and all performance sites using animals must have an OLAW-approved Animal Welfare Assurance (hereafter, Assurance) on file with OLAW. The Assurance is the cornerstone of a contractual and trust relationship between the institution and the PHS. Included in the Assurance are the following:

(1) A commitment that the institution will comply with the PHS Policy, the *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act and Regulations.
(2) A description of the institution's program for animal care and use.
(3) A designation of the institutional official responsible for compliance with the PHS Policy. The institutional official is "[t]he individual who, as a representative of senior administration, bears ultimate responsibility for the Program and is responsible for resource planning and ensuring alignment of Program goals with the institution's mission" (NRC 2011, 13).

There are three types of Assurances: domestic, interinstitutional, and foreign. Each institution conducting PHS-funded research using animals must have one of these types of Assurances.

Domestic Assurances are negotiated with US institutions that control their own animal facilities, conduct animal research on-site, and have an animal care and use program with an institutional official, an institutional animal care and use committee (IACUC), and a veterinarian with program authority.

An interinstitutional Assurance is required if the recipient organization has no animal facility and will do the work at an Assured performance site. The interinstitutional Assurance binds the awardee institution with the Assured performance site to ensure the humane care and use of animals.

A foreign Assurance is required if the direct award is made to an institution outside the United States or if the domestic awardee has a foreign performance site. In the situation where there is collaboration between a domestic awardee and a foreign institution, the domestic institution must provide IACUC approval. The foreign institution agrees to follow the International Guiding Principles for Biomedical Research Involving Animals ([CIOMS] Council for International Organizations of Medical Sciences/[ICLAS] International Council for Laboratory Animal Science 2012) developed by CIOMS (www.cioms.ch/) and ICLAS (http://iclas.org/) and to comply with all laws, regulations, and policies regarding the humane care and use of laboratory animals in their country of origin.

The PHS Policy is based on a system of monitored self-identification and correction of deficiencies within the animal care and use program. Upon approval of an Assurance by OLAW, the institution is expected to abide by the commitment made and independently regulate itself through the IACUC, institutional policies, and the guidance documents cited above. OLAW monitors institutions by evaluating self-reported noncompliance and annual reports and, potentially, by conducting a site visit. If noncompliance is identified, the institution is given a reasonable opportunity to take corrective action, and if no action is taken, OLAW has the authority to restrict or withdraw the Assurance, which then precludes the receipt of PHS support for the conduct of animal activities.

Institutional Animal Care and Use Committees

Oversight by OLAW on behalf of the NIH and the PHS is based on self-monitoring and self-regulation by the overseen entities. The idea of self-monitoring came from the 90th Congress of the United States, which passed the Health Research Extension Act of 1985 (42 U.S.C. 289d, Public Law 99-158; http://grants.nih.gov/grants/olaw/references/hrea1985.htm). This is the statute that gives OLAW the authority to administer the PHS Policy. The Conference Report that accompanied the Health Research Extension Act stated: "The requirement to establish animal care committees is intended to provide the most constructive assurance that NIH guidelines for the care and treatment of animals are met. It is far preferable to place primary responsibility for assuring compliance

with NIH guidelines on committees within institutions, rather than relying on intrusive Federal inspections as in presently the case" (Conference Report 99-157 1985, 85). The "committee" referenced is the IACUC.

IACUC Responsibilities

IACUCs oversee animal research at the local level within the institution where the research is being conducted and are central to the concept of self-monitoring. IACUCs must meet the following responsibilities, as defined in the PHS Policy (NIH 2002, section IV.B):

(1) Review animal research protocols.
(2) Review significant changes to protocols.
(3) Evaluate institutional compliance with PHS Policy, the Animal Welfare Act and Regulations, the *Guide for the Care and Use of Laboratory Animals,* and institutional policies.
(4) Monitor institutional animal care and use programs and inspect animal facilities.
(5) Review concerns about animal care and use.
(6) Report noncompliance and suspensions to NIH OLAW.

The NIH and other PHS agencies will not fund research that uses animals if the IACUC has not approved the proposed study. Throughout the research process, the IACUC monitors the care and use of animals at the institution, and it has the authority to suspend any activities involving animals if the research is not in compliance with federal requirements. PHS-supported institutions are required to promptly notify OLAW with a full explanation of the circumstances and actions taken with respect to any serious or continuing noncompliance with PHS Policy, any serious deviation from the provisions of the *Guide for the Care and Use of Laboratory Animals*, or suspension of an animal activity by the IACUC (NIH 2002, section IV.F.3). OLAW will evaluate the effectiveness of the proposed corrective measures to prevent a recurrence of the noncompliance.

Investigator Responsibilities in Preparing Applications or Proposals

PHS-supported scientists are held accountable by the NIH for the protection of the research animals in their care from the earliest stages of planning until the project's completion. Before beginning the research, investigators must provide a written justification for animal use in their grant application or contract proposal. This section of the application or proposal is called the Vertebrate Animal Section (VAS), and it must contain the following information:

(1) A detailed description of the proposed use of the animals, including species, strains, ages, sex, and the number of animals to be used.
(2) Justification of the use of animals, choice of species, and numbers to be used.
(3) Information on the veterinary care of the animals.
(4) A description of the procedures for ensuring humane treatment (i.e., minimization of discomfort distress, pain, and injury).
(5) The method of euthanasia, the reason for its selection, and consistency with the AVMA Guidelines for the Euthanasia of Animals (NIH 2006).

Investigators must provide a VAS if their work involves the use of live vertebrate animals, including the generation of custom antibodies or the obtaining of tissues or other materials from live vertebrate animals. Antibodies are considered customized if produced using antigens provided by or at the request of the investigator (i.e., not purchased off the shelf). An organization that produces custom antibodies for an awardee must have or obtain an Assurance or be included as a component of the awardee's Assurance (OLAW 2013b). If there is more than one performance site for the animal studies, the investigator must address all five points for each performance site in the grant application or contract proposal.

NIH Scientific Review Groups (SRGs) evaluate the involvement of animals as part of the scientific assessment to ensure that only the highest quality research projects are considered for funding. SRGs verify that any proposed research with animals is scientifically appropriate; this includes verifying the validity of the animal model and effective animal protections. Because reviewers are asked to consider the VAS as an additional review criterion in the determination of scientific and technical merit, the impact/priority score may be affected when scientific questions related to the proposed animal use arise. The final scoring of the application is therefore impacted by the reviewers' assessment of the thoroughness and appropriateness of the VAS (NIH 2010). NIH provides a worksheet (http://grants.nih.gov/grants/olaw/VAChecklist.pdf) to assist applicants in preparing the VAS and as guidance to reviewers in evaluating the VAS.

Peer reviewers rate the application as acceptable or unacceptable with respect to the proposed animal use and include specific comments assessing the information provided. A vertebrate animal concern may be raised requiring resolution before an award is granted. Examples of vertebrate animal concerns include the following: (1) inappropriate animal model or unjustified number of animals; (2) unnecessary pain or distress; (3) lack of veterinary care; (4) inappropriate anesthetic or inappropriate use of tranquilizing drugs or restraining devices; and (5) method of euthanasia that is inconsistent with the recommendations of the AVMA Guidelines for the Euthanasia of Animals without adequate justification.

If the SRG has insufficient information from the application to make a determination regarding the VAS, it is also a vertebrate animal concern. Appropriately addressing a concern helps to ensure that required information on animal care and use is in place before an award is granted. Investigators

may consider consulting their institution's veterinarian for assistance in the development of an application or proposal involving animals before submission. The SRG review does not supersede or serve as a replacement for IACUC review or IACUC approval of an animal study protocol (NIH 2010).

Other Responsibilities

The principal investigator has additional responsibilities for maintaining compliance with the federal animal welfare requirements. These include the following:

(1) Obtaining IACUC approval before using animals and before implementing significant changes.
(2) Ensuring research is conducted according to the approved protocol.
(3) Complying with institutional policies and procedures.
(4) Addressing significant changes to the use of animals in progress reports to the NIH.
(5) Obtaining prior permission from the NIH for the use of animals involving a change in scope, including changes in performance site (NIH 2006).

Obtaining IACUC Approval

IACUC approval is required before an award is granted. Most IACUCs require investigators to submit information about the care and use of animals on a protocol form. The *Guide for the Care and Use of Laboratory Animals*requires the following elements be addressed in the protocol for review by the IACUC:

(1) A rationale and purpose of the proposed use of animals.
(2) A clear and concise sequential description of the procedures involving the use of animals.
(3) Availability or appropriateness of the use of less invasive procedures, other species, isolated organ preparation, cell or tissue culture, or computer simulation.
(4) Justification of the species and number of animals proposed.
(5) Prevention of unnecessary duplication of experiments.
(6) Nonstandard housing and husbandry requirements.
(7) Impact of the proposed procedures on the animals' well-being.
(8) Appropriate sedation, analgesia, and anesthesia.
(9) Conduct of surgical procedures.
(10) Postprocedural care and observation.
(11) Description and rationale for anticipated or selected endpoints.
(12) Criteria and process for timely intervention or euthanasia if painful or stressful outcomes are anticipated.
(13) Method of euthanasia or disposition of animals.
(14) Adequacy of training and experience of personnel and roles and responsibilities of the personnel involved.
(15) Use of hazardous materials and provision of a safe working environment (NRC 2011).

The use of animals approved by the IACUC must be congruent with the description in the grant application or contract proposal. Any modification required by the IACUC that affects the content of the application or proposal must be submitted to the NIH funding officer 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).

Receiving an Award

To receive an award, the awardee organization and every performance site where animal work will be performed must have an Assurance approved by OLAW as described previously. OLAW will contact an organization when an Assurance is required and provide guidance on the preparation and submission of the document. Investigators receiving awards through the Small Business Innovation Research and Small Business Technology Transfer Programs from NIH should be aware of the requirements for interinstitutional Assurances so that the Assurances are in place and awards are not delayed (OLAW 2012).

Post-Award Responsibilities

PHS Policy requires IACUC approval at least every 3 years and annually for activities covered by USDA Animal Welfare Act and Regulations. Significant changes in animal care and use are to be approved by the IACUC before implementation (OLAW 2013d). Because local policies may vary, investigators should consult with their IACUC to determine what constitutes a significant change.

Awardees must also obtain prior approval from the NIH for changes in scope that constitute a significant change from the aims, objectives, or purposes of the approved project. The principal investigator must make the initial determination of the significance of the change and should consult with his/her NIH Grants Management Officer as necessary (OLAW 2013c).

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).

Because local institutional policies involving research with animals may be more restrictive, investigators must be aware of and comply with such requirements.

Protecting the Investment

The NIH requires institutions to have disaster plans that address both the well-being of animals and personnel during unexpected events that compromise ongoing animal care (OLAW 2013e). Plans should consider failure of critical systems, including the heating, ventilation, and air conditioning systems and alarm systems, as well as failures in primary and emergency power sources; mechanisms for maintaining appropriate temperatures, ventilation, food, and water sources; and the logistics for relocating or euthanizing animals when power cannot be restored or repairs effected promptly. Contingencies for preserving valuable animals through cryopreservation or other methodologies are prudent practices. OLAW provides a Disaster Planning and Response Resources webpage to assist institutions in planning and responding to natural and other disasters affecting animal facilities (OLAW 2013a).

Unexpected events can be devastating to an institution's animal program and research and may require a long recovery time. Crises may come in many forms; disease outbreaks in animal colonies, critical equipment failures, natural disasters, laboratory break-ins, and threats and intimidation aimed at researchers or institutions are but a few. Each of these events is unique, but the basic components of being prepared are the same. A strong institutional commitment to preparedness helps to mitigate the effects of any crises. It also provides an opportunity to build positive relationships between the institution, the emergency response team, and the local community ([OER] Office of Extramural Research 2011).

The NIH shares the concerns of institutions and investigators about the threats and intimidation they may face from activist organizations. The NIH has provided guidance on institutional preparedness (OER 2012). It encourages investigators to be aware of their institution's crisis management plan and participate in its refinement. Such cooperation and involvement by investigators contributes to a positive atmosphere and encourages safe, productive, and effective animal research and welfare.

Conclusion

The NIH has a longstanding slogan about research with animals: Good animal care and good science go hand in hand (NIH 2013). The collaborative efforts of the principal investigator, the IACUC, the institutional official, and others involved in the conduct of a compliant and humane animal care and use program lead to better scientific outcomes. Such efforts benefit the development of knowledge necessary for the improvement of the health and well-being of both humans and animals.

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