
Statement for the Use of Animals in Ophthalmic and Vision Research

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Introduction

Research in vision and ophthalmology improves quality of life. This improvement stems from progress in ameliorating human and animal injury/disease and disability through advances in human and veterinary medicine, and by improving our understanding of human and animal life. Because so much of vision research is aimed at understanding the structure and function of complex and intricately connected biological systems, work with living animals is vital to continued progress in many areas of clinical and basic research on vision. The proper use of animals in research is, therefore, an honorable and essential contribution to the improvement of both human and animal lives.

Our concern for the humane treatment of animals obliges us to always establish that the potential benefits to human and animal health outweigh the cost in animal lives. It is therefore essential for scientific societies such as The Association for Research in Vision and Ophthalmology to formulate guidelines for the humane use of laboratory animals in research.

The remainder of this document provides guidelines for the humane treatment and ethical use of animals for vision research. These are based on guidelines that are generally considered acceptable and reasonable by the biomedical research community and are intended for the investigator who is responsible for the humane, ethical care and use of animals in vision research. The discussion deals mainly with endothermic (warm-blooded) vertebrates, but the principles can be applied generally. Ethical issues involving the use of any species should be considered in relation to the complexity of its central nervous system and its apparent awareness of its environment.

Guidelines for the design of experiments

ARVO strongly advocates for the responsible use of animals in biological and biomedical research and follows two fundamental principles: (1) Although animal models are vital and irreplaceable for scientific progress, combating devastating ocular diseases, and improving human and animal health, the investigator's first concern must be to avoid the use of animals when possible, and (2) The principles of the 3R's: replacement, reduction and refinement, should be used as a framework for conducting high quality science.

When designing experiments, first and foremost, the investigator and other qualified personnel should determine that the use of animals is a necessity for scientific progress, with consideration given to the use of mathematical models, computer simulation and/or in vitro biological systems. All experiments and procedures involving animals must be designed and performed with specific consideration of their relevance to human or animal health, the advancement of knowledge and the benefit to society.

When embarking on studies that cannot be completed without animals, the investigator must justify the use of animals, identify the appropriate species and use the minimum number needed to provide reliable and valid results. Thoughtful experimental design may include performing pilot studies to estimate the minimum number of animals required to obtain answers without compromising scientific quality. Knowledge from pilot studies to evaluate safety and/or efficacy of experimental procedures, interventions and/or treatments can help identify unanticipated problems in an experiment before larger numbers of animals are used. Pilot studies may provide critical insight into study outcomes or effect sizes to allow for appropriate power calculations for future studies, as well as enabling the refinement of experimental protocols to minimize subsequent animal use and/or discomfort. Additionally, in accordance with the National Institutes of Health's commitment to improving the health outcomes of men and women, all research experiments must consider sex as a biological variable. Strong justification from the scientific literature, preliminary data, scarce research resources such as nonhuman primates, or other relevant considerations must be provided for experiments that study only one sex. Finally, experiments should be designed to avoid depletion of endangered species.

Critical to experimental design and implementation is disciplined adherence to proper use and care of animals including the avoidance or minimization of distress, discomfort and pain. This includes following strict attention to anthropomorphic judgements made by qualified, experienced and prudent human observers. Unless otherwise demonstrated, investigators should consider that procedures which may cause pain or distress to human beings may also cause pain in animals. Although most research on animals causes little or no distress or discomfort, certain important scientific questions may demand experimental studies that inevitably give rise to some discomfort or short-term distress. Decisions related to the design and implementations of these experiments should be made in consultation with appropriate review groups such as the institutional animal care and use committee (IACUC) as well as the institution's appointed veterinarian/s.

In all experiments, discomfort or distress must be minimized by careful protocol design outlining pre- and post-procedural use of analgesics, anesthesia, sedation and when necessary euthanasia. There is no difference between distress and discomfort that result from

either the design of a study or its unintended side effects. The investigator must therefore identify and eliminate all avoidable sources of discomfort or distress, taking advantage of veterinary expertise. The subsequent recovery of animals from procedures must also be monitored to ensure their welfare.

Guidelines for the conduct of experiments

The quality of the information obtained through research depends in no small measure on the health and general condition of the animals used. Proper animal husbandry is fundamental to the success of any research effort that uses animals.

Research animals must be obtained and cared for in accordance with the commendations of the Guide for the Care and Use of Laboratory Animals (http://www.nap.edu/catalog.php?record_id=12910), Institute of Laboratory Animal Resources, the Public Health Service Policy on Humane Care and Use of Laboratory Animals (<http://grants.nih.gov/grants/olaw/references/phspol.htm>), and the Guide to the Care and Use of Experimental Animals by the Canadian Council of Animal Care (<http://www.ccac.ca/en/standards/guidelines/>) (if conducting research in Canada). In the United States, the Office of Laboratory Animal Welfare (OLAW) (<http://grants.nih.gov/grants/olaw/olaw.htm>) provides guidance and interpretation of the Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals and monitors compliance with the Policy.

Investigators in the United States must comply with relevant local, state and federal laws, including the U.S. Animal Welfare Act (https://www.aphis.usda.gov/aphis/ourfocus/animalwelfare/sa_awa/ct_awa_program_information), as amended and its accompanying regulations. An Institutional Animal Care and Use Committee (<https://grants.nih.gov/grants/olaw/GuideBook.pdf>), must review and approve the use of animals in vision research in the United States and Canada.

Surgery should be carried out or directly supervised by persons with appropriate levels of experience and training, and surgery performed on animals that will survive (for example, on animals intended for long-term studies) should be undertaken with careful attention to aseptic technique and prevention of infection. Major surgical procedures should be completed under anesthesia that will render the animal insensitive to pain. Muscle relaxants and paralytics have no anesthetic action and must not be used as a substitute for anesthesia. Postoperative care must include efforts to minimize discomfort and the risk of infection.

Some studies require surgical preparation of animals that are not intended to survive. In such cases the animals ordinarily should be maintained unconscious throughout the experiment. At the end of the experiment animals must be euthanized without recovering consciousness. In this and all other cases of euthanasia, the investigator should follow the AVMA Guidelines for the Euthanasia of Animals. (<https://www.avma.org/KB/Policies/Documents/euthanasia.pdf>).

Where experiments require physical restraint and/or the withholding of food or water, the effects of which are not themselves the objects of study, care must be taken to minimize discomfort or distress and to ensure that good general health is maintained. Only when there is no alternative procedure should animals be subjected to immobilization or restraint to which they cannot be adapted readily. Whenever it is possible, the experimental schedule should be designed to include reasonable periods of rest and readjustment. In the rare cases where distress and discomfort are unavoidable attributes of a well-designed study, the investigator must, within the limits of the design, take all possible steps to minimize these effects and to minimize the duration of the procedure and the number of animals used.

ARVO will amend The Association for Research in Vision and Ophthalmology (ARVO) Statement for the Use of Animals in Ophthalmic and Vision Research pending changes to US and EU guidelines ([FELASA \(http://www.felasa.eu/\)](http://www.felasa.eu/) and [EU legislation \(http://ec.europa.eu/environment/chemicals/lab_animals/home_en.htm\)](http://ec.europa.eu/environment/chemicals/lab_animals/home_en.htm)).

Factors that relate specifically to the conduct of vision and ophthalmology experiments

Besides the considerations generally applicable to all animal experiments, production of visual disability is a special animal welfare consideration that may apply to some vision research protocols. Visual disability of experimental animals may be either an intrinsic or an unplanned consequence of experimental design. In its definition of major survival surgery, the Guide to the Care and Use of Laboratory Animals includes any surgical intervention that “produces substantial impairment of physical or physiologic functions” in an animal that is expected to recover. Hence, any experimental procedure that results in, or has the potential to result in, a level of visual disability sufficient to disrupt an animal's normal daily activity should be considered a major survival procedure. Such procedures require appropriate justifications and suitable animal care accommodations.

Protocols involving bilateral survival ocular procedures require special consideration and justification, with particular attention to the likelihood of adverse events and rate of onset, nature and duration of any visual consequences. Such procedures include, but are not necessarily limited to, bilateral ocular surgeries, injections or implantations, whether performed simultaneously or sequentially, and any other experiments with the potential to affect vision bilaterally. In the interests of transparency, rates of adverse events following ocular procedures should be clearly documented and included by investigators in reports arising from their studies. Investigators should consider species differences in ocular anatomy and physiology, importance of visually-guided behaviors, likelihood of adverse events following specific ocular procedures, and response to experimental manipulations and drugs when designing experiments. The Guide to the Care and Use of Laboratory Animals strongly recommends that animals not be subjected to multiple major survival surgical procedures unless they are related components of a particular research project. Accordingly, a visually disabling procedure should not be performed bilaterally unless the two procedures are related and unavoidable components of a specific project. As noted in the Guide to the Care and

Use of Laboratory Animals, cost savings alone is not an adequate justification for performing multiple survival surgical procedures, and investigators should carefully consider whether or not inclusion of the contralateral eye represents an appropriate control under their specific experimental design.

In all instances, appropriate pre-emptive analgesia strategies of recognized efficacy in the management of ocular pain in animals should be incorporated in study designs to minimize discomfort. When necessary, species-appropriate environmental adaptations should be made in order to minimize impact of visual compromise.

Vision investigators are encouraged to distribute unrelated tissues to investigators in other research areas and, where practical, to obtain suitable ocular tissues from investigators working on other organs. This recommendation applies to all species.

Inherited disorders of the visual system are significant health problems for both humans and animals. Significant differences exist in the impact of visual compromise on normal physiological functions between diverse species, strains and disorders. The deliberate breeding of and generation of animals with genetic disorders leading to blindness requires scientific justification, and consideration of appropriate modification of standard husbandry procedures as needed to minimize the impact of visual compromise on normal behaviors and physiological functions. Investigators who breed genetically impaired animals are encouraged to share such animals and tissues with qualified investigators having complementary expertise, including those outside their own institution, and to develop a plan for resource sharing.

Investigators outside the United States

Although the laws that regulate the care and use of animals in the United States are not directly applicable to citizens of foreign countries, ARVO endorses the policies in the Guide for the Care and Use of Laboratory Animals (<https://www.nap.edu/catalog/12910/guide-for-the-care-and-use-of-laboratory-animals-eighth>), the Public Health Service Policy on the Humane Care and Use of Laboratory Animals (<http://grants.nih.gov/grants/olaw/references/phspol.htm>), (revised 2015), and the U.S. Animal Welfare Act (https://www.aphis.usda.gov/aphis/ourfocus/animalwelfare/sa_awa/ct_awa_program_information), as amended. If ARVO is to support a vision scientist under scrutiny by animal activists, the vision science experiment involving animals must conform to the guidelines established in these documents, even though they are not necessarily enforceable by law in the country in which the experiment is performed.

In addition to these guidelines, references in the following resources are recommended:

Animal use guidelines

- Guide for the Care and Use of Laboratory Animals (NRC2011): Main resource used by Association for Assessment and Accreditation of Laboratory Animal Care's (AAALAC's) Council on Accreditation; also a primary reference on animal care and use (required if research is conducted with PHS funds). The Guide (<http://www.aaalac.org/resources/theguide.cfm>).
- Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals (<http://grants.nih.gov/grants/olaw/references/phspol.htm>).
- NIH Grants Policy Statement (2015) (<http://grants.nih.gov/grants/policy/nihgps/HTML5/introduction.htm>).
- Institutional Animal Care and Use Committee Guidebook (<https://grants.nih.gov/grants/olaw/GuideBook.pdf>).
- 2008 Guidance for Researchers and Institutions: Good animal care and good science go hand-in-hand (http://grants.nih.gov/grants/policy/air/researchers_institutions.htm).
- A tutorial for new animal care and use committee members, institutional administrators, investigators, animal care personnel and veterinarians. OLAW PHS Humane Care and Use of Laboratory Animals Tutorial (<http://grants1.nih.gov/grants/olaw/tutorial/index.htm>).
- IACUC Bookmarks (<http://netvet.wustl.edu/iacuc.htm>).
- NIH Medical Research with Animals Website: The site contains information for researchers and institutions, as well as the general public, including a fact sheet on the benefits of biomedical research, and a Frequently Asked Questions section. NIH Medical Research with Animals website (<https://grants.nih.gov/grants/policy/air/>).
- NIH iEdison (<http://iedison.gov/>): Helps government grantees and contractors comply with laws and regulations
- US Department of Agriculture (USDA), Animal Welfare Act and Regulations (<http://awic.nal.usda.gov/government-and-professional-resources/federal-laws/animal-welfare-act>): a document with regulations to improve animal care and use in research, testing, teaching and exhibition. See also, USDA Animal Welfare Information Center FASS Guide for the Care and Use of Agricultural Animals in Agricultural Research and Teaching (http://www.fass.org/docs/agguide3rd/Ag_Guide_3rd_ed.pdf).
- Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research, National Academies Press (http://www.nap.edu/catalog.php?record_id=10732#toc).
- Canadian Council on Animal Care list of guidelines: Guide to the Care and Use of Experimental Animals (<http://www.ccac.ca/en/standards/guidelines/>).
- Expectations of the major research council and charitable funding bodies: Medical Research Council guide for the use of animals. Responsibility in the use of animals in bioscience research. (<https://www.nc3rs.org.uk/sites/default/files/Responsibility%20in%20the%20use%20of%20animals%20in%20bioscience%20research%20-%20expectations%20of%20the%20major%20research%20councils%20and%20charitable%20funding%20bodies%2008.07.15.pdf>).

Alternatives to animal research

- Bibliography on alternatives to animal testing: ALTBIB (<https://toxnet.nlm.nih.gov/altbib.html>).
- Global clearing house for information on alternatives to animal testing: AltWeb (<http://altweb.jhsph.edu/>).

- Center for Alternatives to Animal Testing (Johns Hopkins University): [CAAT \(http://caat.jhsph.edu/\)](http://caat.jhsph.edu/).
- Center for Animal Alternatives (UC Davis) [CAA \(http://guides.lib.ucdavis.edu/animalalternatives/\)](http://guides.lib.ucdavis.edu/animalalternatives/).
- Animal use alternatives terminology (National Agricultural Library): [USDA Thesaurus \(https://pubs.nal.usda.gov/animal-use-alternatives-thesaurus-terminology-alphabetical-listing\)](https://pubs.nal.usda.gov/animal-use-alternatives-thesaurus-terminology-alphabetical-listing).
- Interagency Coordinating Committee on the Validation of Alternative Methods [ICCVAM \(http://ntp.niehs.nih.gov/pubhealth/evalatm/iccvam/index.html\)](http://ntp.niehs.nih.gov/pubhealth/evalatm/iccvam/index.html).
- Alternative Methods Accepted by US Agencies [Alternative Methods \(http://ntp.niehs.nih.gov/pubhealth/evalatm/iccvam/acceptance-of-alternative-methods/index.html\)](http://ntp.niehs.nih.gov/pubhealth/evalatm/iccvam/acceptance-of-alternative-methods/index.html).

Animal use resources

The purpose of these resources is to provide information about model species (traditional and non-traditional) that are used for biomedical research:

- [NIH Model Organisms for Biomedical Research \(http://www.nih.gov/science/models/\)](http://www.nih.gov/science/models/).
- [NIH Using Model Organisms to Study Health and Disease \(https://www.nigms.nih.gov/Education/Pages/modelorg_factsheet.aspx\)](https://www.nigms.nih.gov/Education/Pages/modelorg_factsheet.aspx).
- Information on Non-traditional model species
- [Model Organisms: Beyond the Inner Circle \(http://www.nature.com/nmeth/journal/v10/n6/full/nmeth.2484.html\)](http://www.nature.com/nmeth/journal/v10/n6/full/nmeth.2484.html).

Organizations that promote proper and ethical use of laboratory animals

- [Office of Laboratory Animal Welfare \(OLAW\) \(https://grants.nih.gov/grants/olaw/olaw.htm\)](https://grants.nih.gov/grants/olaw/olaw.htm).
- [American Association for Laboratory Animal Science \(AALAS\) \(http://www.aalas.org/\)](http://www.aalas.org/).
- [American College of Laboratory Animal Medicine \(ACLAM\) \(https://www.aclam.org/\)](https://www.aclam.org/).
- [Association for Assessment and Accreditation of Laboratory Animal Care \(AAALAC\) International \(http://www.aaalac.org/\)](http://www.aaalac.org/). This site contains a listing of international regulations and resources by country.
- [Asian Federation of Laboratory Animal Science Associations \(AFLAS\) \(http://www.aflas-office.org/\)](http://www.aflas-office.org/).
- [Canadian Association for Laboratory Animal Science \(CALAS/ASCAL\) \(http://calas-acsal.org/\)](http://calas-acsal.org/).
- [Federation of European Laboratory Animal Associations \(FELASA\) \(http://www.felasa.eu/\)](http://www.felasa.eu/).
- [International Council for Laboratory Animal Science \(ICLAS\) \(http://iclas.org/\)](http://iclas.org/).
- [National Centre for the Replacement, Refinement and Reduction of Animals in Research \(NC3Rs\) \(http://www.nc3rs.org.uk/\)](http://www.nc3rs.org.uk/).
- [National Association for Biomedical Research \(NABR\) \(http://www.nabr.org/\)](http://www.nabr.org/).
- [Foundation for Biomedical Research \(FBR\) \(https://fbresearch.org/\)](https://fbresearch.org/).

