



International harmonization of guidance on the ethical review of proposals for the use of animals, and on the education and training of animal users in science

Short title:

Harmonization of guidance on ethical review and training

Demers G, International Council for Laboratory Animal Science, 365 Maricourt, St-Hilaire, QC, Canada J3H 4W1

Brown M, Animal Welfare and Training, Charles River Laboratories, 251 Ballardvale Street, Wilmington, MA 01887, USA

Gauthier C, Canadian Council on Animal Care, 1510 - 130 Albert Street, Ottawa, ON, Canada K1P 5G4

Rozmiarek H, Fox-Chase Cancer Center and University of Pennsylvania, 6491 Drexel Road, Philadelphia, PA 19151, USA

Griffin G, Canadian Council on Animal Care, 1510 - 130 Albert Street, Ottawa, ON, Canada K1P 5G4

Bédard M, Canadian Council on Animal Care, 1510 - 130 Albert Street, Ottawa, ON, Canada K1P 5G4

Corresponding author:

Gilles Demers
365 Maricourt
St-Hilaire, QC
Canada J3H 4W1

Tel: 450- 467-4221

Fax: 450- 467-6308

E-mail: gdemers@ccac.ca

Abstract

A wide variety of frameworks for the oversight of animal-based science exist throughout the world, and include various combinations of local, regional, national and international guidance, regulations and/or legislation. This variety of mechanisms creates challenges given the global nature of science. International collaborations and publications, and the comparison and reproducibility of animal-based studies, are complicated by varying standards. International trade can also be affected, with the geographically separate sites of global companies having to operate within different oversight frameworks. The impact of these challenges can be strongly felt within developing countries as they work to establish international collaborations and their own oversight systems. There are also concerns related to animal-based studies being moved to countries with weaker requirements for animal-based science. The International Council for Laboratory Animal Science (ICLAS) strives to facilitate international scientific work and collaborations while fostering the ethical use and appropriate care of animals in science, in particular through its Working Group on Harmonization. It establishes *ad hoc* committees to identify guiding principles and recommend acceptance of guidance documents in specific areas of animal care and use in science. The present report outlines the guiding principles and accompanying references proposed by two of these committees, one having examined the ethical review of proposals for animal use in science, and the other the education and training of animal users in science. These principles and the accompanying references have been accepted by the ICLAS Working Group on Harmonization and the ICLAS Governing Board.

Keywords

International guidance; ethical review; education; training; refinement

In 1985, the Committee of International Organizations of Medical Sciences (CIOMS) which works closely with the World Health Organization stated that “The varying approaches in different countries to the use of animals for biomedical purposes, and the lack of relevant legislation or of formal self-regulatory mechanisms in some, point to the need for international guiding principles elaborated as a result of international and interdisciplinary consultations”.¹

Since 1959, the International Council for Laboratory Animal Science (ICLAS,²) has brought members of the international laboratory animal science community together with the goal of advancing human and animal health by promoting the ethical use and appropriate care of laboratory animals in science. More particularly, in 2004, ICLAS established a Working Group on Harmonization of Guidelines on the Use of Animals in Science, composed of representatives from major organizations producing and/or using relevant guidance documents.³ The remit of the Working Group is to identify and

recommend international acceptance of guidance documents with the goal of facilitating international scientific collaboration.

ICLAS supports the harmonization of animal care and use guidance as a reflection of the globalization of research. However, harmonization must be distinguished from standardization; each nation should be able to maintain an oversight mechanism for animals used in science that reflects its cultures, traditions, religions, laws and regulations. The Working Group bases its deliberations on internationally recognized principles including the CIOMS *International Guiding Principles for Biomedical Research Involving Animals*,¹ which are also now under revision by ICLAS, working with CIOMS. ICLAS is also involved in the work of the World Organisation for Animal Health (OIE) to create guidance for the *Use of Animals in Research and Education* as a chapter of the document produced by the *OIE Terrestrial Animal Health Standards Commission*.

The intention of the ICLAS Working Group on Harmonization is not to publish detailed guidance, nor to identify optimal practices in specific fields, as national and international groups are already doing. The purpose of the group is to summarize existing guidance and general principles in broad areas of animal care and use, and bring these to the attention of all concerned. This is meant to assist countries that have not yet fully established animal care and use oversight systems by providing them with common, summary points of international guidance as a basis for the development of their own systems. It is also meant to facilitate the work of regulators overseeing animal-based projects that involve scientists from different countries by identifying the common points that they can work from.

The Working Group established its two first *ad hoc* committees to work on international guidance for endpoints and euthanasia in 2004, as reported in *Science* in 2006.⁴ In November 2005, the Working Group met in St. Louis, MO, USA and created two new *ad hoc* committees: one to examine international guidance for the ethical review of proposals to use animals in science; and the other to examine international guidance for animal user education and training. The *ad hoc* committees considered information from around the world, including the Americas, Asia, Australia, Europe and New Zealand. The Working Group and *ad hoc* committees pursued their work electronically and at a meeting in June 2007 in Cernobbio, Italy. Their findings were accepted by the ICLAS Governing Board at its meeting in May 2008 in Tartu, Estonia. The documents as approved by the Governing Board are available on the ICLAS website.^{5, 6}

Ethical review of proposals to use animals in science

In examining the ethical review of proposals to use animals in science, the ICLAS Working Group *ad hoc* committee on the matter recognized that meeting societal expectations for improvements in the health of humans, animals and the environment currently requires scientific studies involving the use of animals. However, the public also has expectations that this use of animals will be regulated. Therefore, scientists who want to carry out animal-based research need to fulfill a number of obligations. This may include adherence to institutional, local, regional, national or international requirements regarding animal use. These requirements relate to standards of animal care and ethical animal use established by institutions, agencies, organizations and government departments that fund, undertake or oversee animal-based science. Many international and national scientific journals also have in place requirements for meeting specific standards of animal care and use.

Whether legislated or voluntary, most systems for overseeing the ethical use of animals in science incorporate the Three Rs⁷ (Replacement, Reduction and Refinement) principles of humane experimental technique. A variety of mechanisms are used to ensure that a cost-benefit analysis of any animal-based study is carried out and that the implementation of the Three Rs and other ethical principles have been considered. Some countries use local or institutional committees as ethical review committees, referred to by a variety of titles: institutional animal care and use committees (USA), animal ethics committees (New Zealand and Australia), animal care committees (Canada), institutional animal ethics committees (India), animal research ethical committees (Brazil), internal committees (Israel) and local review committees (Thailand). Some countries use national ethical review processes, some use regional processes, and some work through individuals (officers, officials, inspectors) designated with the responsibility for ethical oversight. In many countries, the ethical review process involves a combination of different approaches.

It is worth noting that there is no single, best approach meant to work in all parts of the world. The mechanism that has emerged in each jurisdiction is generally reflective of the local traditions and culture of the country, and is best adapted to the area in question. Nonetheless, “The patchwork of mechanisms can be especially daunting for developing countries, in elaborating their own mechanisms and in international collaboration”.⁴ It is therefore important that ICLAS continue to actively identify solid, practical guidance that can easily be used by the international community to promote good animal welfare while conducting sound animal-based science.

International References

The ICLAS Working Group on Harmonization recognizes that there are many sources of guidance and information on ethical review of animal experiments.⁸⁻¹⁹ After review of many of these documents and based on the work of the *ad hoc* committee on ethical review of proposals to use animals in science, the ICLAS Working Group recommends three documents as suitable for use as international references, namely the:

- US Office of Laboratory Animal Welfare (OLAW)/ Applied Research Ethics National Association (ARENA) *Institutional Animal Care and Use Committee Guidebook*, 2002, including in particular Section C – Review of Proposals (pp. 83-156) of this document;⁸
- Canadian Council on Animal Care (CCAC) *guidelines on: animal use protocol review*, 1997;⁹
- Principles and Practice in Ethical Review of Animal Experiments across Europe: A report of the Federation of European Laboratory Animal Science Associations (FELASA) Working Group on Ethical Evaluation of Animal Experiments, 2007.¹⁰

These references provide general guidance on ethical review of proposed animal use in science that is suitable for local or institutional committees, but whose principles can also be extended to regional and national processes. They are all based on the general principles included in the next section of this document. The Canadian and US documents are best suited to systems where institutional committees are at the centre of the regulatory framework, and responsibility is largely delegated to the local level. The FELASA report details thirty overarching principles for an ethical review process. The US document, in particular Section C, describes legal requirements in the US and, like the Canadian and European documents, also describes fundamental elements that should be included in the ethical review of proposed animal use.

General Principles

The ICLAS Working Group agreed on general principles for ethical review of animal-based studies that are part of most of the ethical review processes studied. These principles are intended to provide guidance to countries that do not yet have ethical review processes for proposed animal use in science, as well as to those countries, regions, organizations and institutions that may wish to refine their existing processes.

- Whenever possible, methods employed to achieve scientific objectives should avoid the use of animals.
- Where animal use is unavoidable, the proposed project should have been demonstrated to have merit, in terms of its potential to advance scientific knowledge and/or benefit human or animal health (scientific merit), to

protect/benefit humans, animals and/or the environment with respect to new products/devices or to toxic substances (regulatory testing) or to teach animal-based principles and procedures (pedagogical merit).

- The expected benefits to humans, animals or the environment of the proposed project involving live animals should be weighed against the likely harms done to the animals, and opportunities should be sought to maximize benefits and minimize harms.
- The species/strain and numbers of animals to be used should be scientifically justified to use the most appropriate animal model and the optimal number of animals, neither too many nor too few. The experimental design should be optimized according to the type of study undertaken.
- Studies should be designed to refine procedures undertaken on animals to the greatest extent possible, and the care, housing, transport and restraint of animals should also be optimized.
- Pain or distress likely to be experienced by the animals must be prevented, or minimized to the greatest extent possible, with veterinary advice for the use of appropriate anesthesia, analgesia and/or other measures as applicable to the type of animal and study.
- Those who use or care for animals must be skilled and competent to do so, both for their own safety and for the health and welfare of the animals (see the following section on Education and training of animal users in science).
- The earliest possible endpoint for the animals should be used consistent with the scientific objectives of the study.⁴
- A method of euthanasia that is appropriate for the species, life stage and type of work should be described and chosen.⁴
- There should be a mechanism to ensure initial and ongoing review of the work and to use the results of the work to inform future scientific, welfare and ethical reviews.

Education and training of animal users in science

The *ad hoc* committee on the education and training of animal users in science recognized that personnel involved with the use of animals in research, testing and teaching must be adequately educated, trained and/or qualified in the principles of laboratory animal science to assure high quality science and to minimize negative impacts on animal welfare. The objective of the *ad hoc* committee was to provide guidelines for harmonization of such education and training and thus enhance science and animal welfare internationally.

For the purpose of this document, education is defined as presentation of information (usually didactically) and training is defined as acquisition of practical knowledge and skills. The focus of the *ad hoc* committee was to look at education and training which should be provided to the animal user, defined as someone using animals for scientific purposes, rather than someone with animal care as their primary duty. However, it is recognized that these delineations can be blurred if animal technicians or veterinarians carry out some of the animal-based procedures involved in a research project. Such education and training may not be part of a formal educational degree. If the quality of training and documentation of experience is proven to be sufficient, it may well facilitate the collaboration and the work of scientists moving from one institution to another, while also enhancing science and animal welfare.

Education and training are needed to provide the theoretical information and the hands-on experience to enable animal users to acquire necessary knowledge and develop other attitudes and skills required to ensure the performance of high quality science with minimal animal suffering, and to establish a culture of care and provide assurance to the public that animal research is undertaken responsibly. Prerequisites for training activities may vary, based upon national requirements, institutional research programs and previous experience of trainees. Likewise, delivery of education and training depends upon resources and training objectives. Flexibility and diversity of delivery systems/formats is encouraged. In addition to traditional classroom and workshop formats, web-based courses, small group discussions, directed readings, mentored laboratory experience, etc. should be considered.²⁰⁻²⁵ The duration and/or intensity of the training program should be related to the severity and complexity of the procedures to be carried out on the animals. Regardless of the duration of the educational and training experience or of the format, it is important to have some type of comprehension and skill assessment to ensure that the objectives of the education/training have been met. Documentation should be provided of how assessments were made.

International References

The ICLAS Working Group on Harmonization recognizes that there are several sources of guidance and information on education and training.²⁰⁻²⁵ After review of these documents and based on the work of the *ad hoc* committee on the education and training of animal users in science, the ICLAS Working Group recommends three guidelines as international reference documents, namely the:

- CCAC *guidelines on: institutional animal user training* with accompanying *Recommended Syllabus for an Institutional Animal User Training Program*, 1999;²⁰
- FELASA recommendations for the education and training of persons involved in animal experiments, Reports of FELASA Working Groups;²¹
- ILAR *Education and Training in the Care and Use of Laboratory Animals, A Guide for Developing Institutional Programs*.²²

Although there are some differences between these three documents, institutions and their ethical review committees can use them alongside the general principles (below) to establish their own training programs and to assess the training of animal users who have completed training programs at other institutions. In general, a core curriculum should be adopted which is based upon the key elements needed to establish a culture of responsible animal use. This curriculum should include core modules that cover the responsibilities of the scientists, their relationship to the ethical review committee, the requirement for protocol compliance and the benefits of a team approach. The core curriculum should contain modules which are similar across jurisdictions, regardless of national location, program size etc., and that can be supplemented with additional education and training based upon species, procedure and institution-specific needs.

General Principles

The ICLAS Working Group agreed on the following general principles for animal user education and training:

- All personnel involved with the use of animals in research, testing and teaching should be adequately educated, trained and qualified in the principles of laboratory animal science and the ethical considerations of animal use, and should have demonstrable knowledge and expertise in the specific animal procedures proposed on the species to be used.
- Training programs should be tailored to the specific needs of the animal user and institution, however some components should be compulsory:
 - Overview of pertinent laws, regulations and guidelines and institutional policies including documentation and record keeping;

- Roles and responsibilities of ethical review committee, animal user, veterinarian, animal care staff and others and the importance of adhering to appropriately approved protocols and procedures;
 - Ethical issues involving the use of animals in research, testing and teaching;
 - Principles of the Three Rs (replacement, reduction and refinement);
 - Experimental design, including non-experimental variables;
 - Introduction to the principles of animal care including housing, care routines, environment of commonly used species, and non-experimental variables;
 - Recognition of pain and distress, the use of anesthetics, analgesics, tranquilizers and other palliative measures; the importance of setting and implementing both scientific and humane endpoints as well as understanding the potential effects of both pain and distress and their treatments on science;
 - Euthanasia, including theory of humane death and common methods and adherence to acceptable standards;
 - Principles of aseptic technique and other basic commonly used procedures; and
 - Principles of occupational health and safety when working with animals.
- Complete education and training should be offered to the young/new scientist; the approach will likely be different from that taken with more experienced scientists.
 - Ongoing educational programs, termed continuing education or refresher courses, should be offered to reinforce training and provide updates to reflect changes in technology, legislation, etc. Frequency of training should ensure that all animal users receive adequate training prior to commencement of animal work.
 - Assessment programs should be implemented and documented to evaluate the effectiveness of institutional training programs and level of competency of animal users participating in institutional training programs. This should include a determination of the competency of animal users who have been involved in training programs at other institutions. Additional training in institutional and national policies and protocols may be necessary.
 - Training and assessments of competency of each individual should be documented.
 - Institutions are responsible for providing appropriate resource material to support the training program; however, the ethical review committee is responsible for providing oversight.

Concluding Remarks

The harmonization of guidance on the ethical review of proposals for the use of animals in science, and on the education and training of animal users, represent the third and fourth statements issued by the ICLAS Working Group on Harmonization of Guidelines on the Use of Animals in Science. ICLAS will continue to work with its many partners around the world to identify solid practical guidance that can easily be used by the international community to promote good animal welfare while conducting sound animal-based science.

References

1. Bankowski Z, Howard-Jones N. International Guiding Principles for Biomedical Research Involving Animals, *Committee of International Organizations of Medical Science (CIOMS)*, 1985. See http://www.cioms.ch/frame_1985_texts_of_guidelines.htm
2. Erichsen S, Hupla CE. History of the International Council for Laboratory Animal Science, 2004. See <http://www.iclas.org/Document/History%20of%20ICLAS.pdf>
3. Federation of European Laboratory Animal Science Associations (FELASA) First ICLAS meeting for the harmonization of guidelines on the use of animals in science, in *Proceedings of the Ninth FELASA Symposium*, Section 2, International Harmonisation of Care and Use Issues, Nantes, France 13&14 June 2004 (FELASA, London, 2005) (www.lal.org.uk/pdffiles/FELASA/Section2.pdf) p.40
4. Demers G, Griffin G, De Vroey G, Haywood JR, Zurlo J, Bédard M. Harmonization of animal care and use guidance. *Science* 2006;**312**:700-701
5. International Council for Laboratory Animal Science Working Group on Harmonization of Guidelines on the Use of Animals in Science, Ethical review of proposals to use animals in science, see <http://www.iclas.org/harmonization.htm>
6. International Council for Laboratory Animal Science Working Group on Harmonization of Guidelines on the Use of Animals in Science, Education and training of animal users in science, see <http://www.iclas.org/harmonization.htm>
7. Russell WMS, Burch RL, eds *The Principles of Humane Experimental Technique*. London: Methuen, 1959. Reprinted by UFAW (Universities Federation for Animal Welfare) South Mimms, Potters Bar, 1992.
8. Office of Laboratory Animal Welfare (OLAW)/Applied Research Ethics National Association (ARENA) *Institutional Animal Care and Use Committee Guidebook*. 2nd edn. Bethesda, MD, 2002. See <ftp://ftp.grants.nih.gov/IACUC/GuideBook.pdf>
9. Canadian Council on Animal Care (CCAC) *guidelines on: animal use protocol review*. 1997. See

- http://www.ccac.ca/en/CCAC_Programs/Guidelines_Policies/GDLINES/PROTOCOL/PROTGDE.HTM
10. FELASA Working Group on Ethical Evaluation of Animal Experiments, Principles and Practice in Ethical Review of Animal Experiments across Europe: A report of the Federation of European Laboratory Animal Science Associations (FELASA) Working Group on Ethical Evaluation of Animal Experiments. *Laboratory Animals* 2007;**41**:143-160
 11. Australian Government National Health and Medical Research Council *Australian code of practice for the care and use of animals in scientific procedures*, 2004. See <http://www.nhmrc.gov.au/publications/synopses/ea16syn.htm>
 12. Canadian Council on Animal Care CCAC *policy statement on: terms of reference for animal care committees*, 2006. See http://www.ccac.ca/en/CCAC_Programs/Guidelines_Policies/POLICIES/TERMS00E.HTM
 13. Institute for Laboratory Animal Research, Commission on Life Sciences, National Research Council *Guide for the Care and Use of Laboratory Animals*. Washington DC: National Academy Press, 1996.
 14. Jennings M, Miller J Harmonising IACUC practices, pp. 1705-11, in *Progress in reduction, refinement and replacement of animal experimentation* (Balls M, van Zeller AM, Halder ME, eds). Elsevier Science BV: The Netherlands, 2000
 15. New Zealand National Animal Ethics Advisory Committee Good practice guide for the use of animals in research, testing and teaching, 2002. MAF: Wellington. See <http://www.biosecurity.govt.nz/animal-welfare/naeac/papers/guide-for-animals-use.htm>
 16. Science Council of Japan, Guidelines for Proper Conduct of Animal Experiments, 2006. See <http://www.scj.go.jp/ja/info/kohyo/pdf/kohyo-20-k16-2e.pdf>
 17. UK Animal Procedures Committee Review of cost-benefit assessment in the use of animals in research, 2003. See <http://www.apc.gov.uk/reference/costbenefit.pdf>
 18. US Public Health Service *Policy on Humane Care and Use of Laboratory Animals*, 2002. See <http://grants.nih.gov/grants/olaw/references/PHSPolicyLabAnimals.pdf>
 19. US Government *Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research and Training*, 1985. See <http://fmp-8.cit.nih.gov/OACU/GuidePI/references/2Govprinciple.pdf>
 20. Canadian Council on Animal Care (CCAC) *guidelines on: institutional animal user training, with accompanying recommended syllabus for an institutional animal user training program*, 1999. See http://www.ccac.ca/en/CCAC_Programs/Guidelines_Policies/GDLINES/NIAUT/NIAUTCOV.HTM

21. FELASA recommendations on the education and training of persons working with laboratory animals: Categories A and C Reports of the Federation of European Laboratory Animal Science Associations (FELASA) Working Group on Education accepted by the FELASA Board of Management. *Laboratory Animals* 1995;**29**:121-31
22. ILAR *Education and Training in the Care and Use of Laboratory Animals, A Guide for Developing Institutional Programs*. Washington, DC: National Academy Press, 1991.
23. Training personnel, an Animal Ethics Infolink, New South Wales (Australia) Department of Primary Industries and Animal Research Review Panel Initiative, see <http://www.animaethics.org.au/policies-and-guidelines/training-personnel>
24. Training and Adult Learning Strategies for the Care and Use of Laboratory Animals. *ILAR Journal* 2007;**48**(2)
25. FELASA recommendations for the accreditation of laboratory animal science education and training. *Laboratory Animals* 2002;**36**:373–377. See <http://www.lal.org.uk/pdf/files/f-accreditation.pdf>