Workshop 4.3
Search strategies – user requirements

Overview of the Regulatory Requirements for the Consideration of Alternatives

Jodie A. Kulpa-Eddy
United States Department of Agriculture (USDA)-Animal and Plant Health, Inspection Service (APHIS)-Animal Care, Riverdale, USA

Summary
This paper provides a brief history of the development in the United States of the requirement for the principal investigator to consider alternatives to procedures likely to cause pain and/or distress in animals. Countries that require similar considerations are also mentioned.
Inspectors with the U.S. Department of Agriculture (USDA), responsible for enforcing the Animal Welfare Act (AWA), expressed concern regarding researchers' compliance with this regulation, and examples from recent inspection reports are provided.
A list of guidance documents and practical suggestions are provided, followed by a workshop discussion on methods of measuring the impact of the use of alternative measures, and ways to distribute information on alternatives.

Keywords: consideration of alternatives, regulation, compliance

History

The Animal Welfare Act was enacted in the United States in 1966 in response to concerns raised by the public that stolen pets were being sold and used in research facilities. The initial regulations concentrated on record-keeping and identification, to create a method whereby animals could be tracked through the system. Standards of care were written for only six groups of animals, and centred on housing and husbandry. There were no regulations pertaining to the conduct of research using animals.

A groundswell of concern from the public began in the early 1980's regarding animal welfare in research institutions. The University of Pennsylvania Head Injury Clinic served as an example. The clinic had been conducting brain trauma experiments on nonhuman primates (baboons). Information about the experiments was taken from the laboratory and distributed to the public. Some of the procedures being used were questioned, and a National Institutes of Health (NIH) committee determined the procedures were inadequate to prevent the animals from suffering serious pain. Funding for the project was subsequently discontinued, and the publicity from this incident fuelled the public's desire to improve conditions for animals in research and to provide additional oversight.

It was a delicate balancing act, as Senator Robert Dole recognised "experimentation and testing on animals has benefited our society by yielding medical breakthroughs that have aided the development of new knowledge, new drugs and better surgical techniques which have saved countless lives". He understood "the use of animals will need to continue for the time being until alternative methodologies which do not use animals or which reduce the numbers of animals used and reduce the pain they experience can be further developed. At the same time, we need to ensure the public that adequate safeguards are in place to prevent unnecessary abuses to animals and that everything that is reasonably possible is being done to decrease the pain that animals suffer during experimentation and testing." (Dole, 1985).

These amendments to the AWA had the support of animal welfare organisations as well as the American Physiological Society, representing the largest group of users of experimental animals. They were passed by Congress in October 1985. As a result, the regulations promulgated by USDA to enforce the Act were updated. The regulations are intended to ensure that all possible steps have been taken to reduce or eliminate as much pain and distress as possible. This includes assurances that alternatives were considered with respect to all painful procedures

(regardless of whether or not pain relieving drugs are used or withheld) and that the research activities are not unnecessarily duplicating previous experiments.

The U.S. was not the first country to enact these requirements. Norway, Japan and the Netherlands were early pioneers in this area, and there were other international initiatives underway in the mid-1980s. The Council of Europe, European Treaty Series No. 123 on the "European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes" was developed in 1986. It also includes language requiring the consideration of non-animal methods (if reasonably and practicably available), or justification for the use of animals, requiring the minimum number needed and causing the least pain, suffering or lasting harm yet still achieving satisfactory results (Council of Europe, 1986).

Today several countries recognise the need to review the scientific and ethical aspects of animal experimentation. A list of legislation to this effect may be found at http://www.vetmed.ucdavis.edu/Animal_Alternatives/policies&regs.html.

What is an alternative?

The USDA, Animal and Plant Health Inspection Service (APHIS), Animal Care refers to alternative or alternative methods as "those that incorporate some aspect of replacement, reduction or refinement of animal use in pursuit of the minimisation of animal pain and distress consistent with the goals or the research. These include methods that use non-animal systems or less sentient animal species to partially or fully replace animals (for example, the use of an *in vitro* or insect model to replace a mammalian model), methods that reduce the number of animals to the minimum required to obtain scientifically valid data, and methods that refine animal use by lessening or eliminating pain or distress and, thereby, enhancing animal well-being. Potential alternatives that do not allow the attainment of the goals of the research are not, by definition, alternatives." (USDA Policy 12, 2000)

Regulatory concerns

In 1999, USDA conducted a survey by mail of the inspectors of research facilities to "assess their opinions about the effectiveness of USDA's current approach to ensuring the humane care and use of animals at research facilities." (USDA Survey, 2000) One of the concerns identified was the "search for alternatives", with an estimated 600 to 800 facilities having difficulty in this area, making it the most frequently cited noncompliant item. "Avoiding unnecessary duplication" ranked fourth, and involved around 250 facilities.

The specific concerns cited by the inspectors in this survey included:

- inadequate justification provided for the number of animals used in research
- uncertainty by research facility personnel regarding when animals are experiencing pain/distress (examples: seizures, vomiting)
- inadequate documentation of literature searches for alternatives to painful procedures

A review of the 2004 USDA database of noncompliant items at research facilities again shows an inadequate "consideration of alternatives" (9 Code of Federal Regulations, Section 2.31(d)(1)(ii)) as the most frequent citation, but with a smaller number of facilities involved (8% of 1800 research facility inspections, or approximately 150 facilities). The regulation requires principal investigators to "consider alternatives to potentially painful procedures and provide a written narrative". The most common underlying causes for these citations are: (1) an inspector finds animals in pain/distress but there is no consideration of alternatives in the protocol, and/or (2) key words in database search are not related to the painful/distressful procedure.

Some specific examples:

- The search for alternatives to painful procedures (e.g. cutting marginal ear vein) has not been addressed and documented. A search for alternatives to distressful procedures (e.g. weight loss, snuffles and loose stools as a result of immunosuppression) has not been conducted.
- The protocol describes retro-orbital bleeding and toe clipping for hamsters and Jirds. Animals used are categorised as "no discomfort", and no consideration of alternatives was made.
- The written narrative descriptions did not provide enough details to determine what methods and sources were used to determine that alternatives were not available. Protocols indicated only that faculty read current veterinary publications.
- The phrase "in our experience" was used to provide a justification for the potential pain and distress to animals in the study.
- The PI (Principal Investigator) failed to conduct an adequate search for alternatives as the key words used were too vague. "Sheep", "alternative" and "pain" were used at one point, and "sheep", "alternative", "method" at another time in an Agricola search. Neither set does much to identify adequate alternatives to a skull implant procedure in sheep.

Ensuring compliance

The consideration of alternatives, and any justification for not using them, is of critical importance when the animals are likely to experience pain and/or distress as a result of the experiment. The principal investigator (study director) is primarily responsible for providing these assurances and must have training and instruction in how to utilise information services.

The Institutional Animal Care and Use Committee (IACUC, the reviewing committee) provides oversight at the institutional level. They are responsible for ensuring the investigator has made a "good faith" effort to consider and incorporate alternatives. What are some warning signs this may not have been done?

- A statement with no supporting documentation
- A "Google" search
- A review of one database for an area of research that is broader than the journals covered by that database.
- An old narrative (one that has not been updated in three or more years)

The 2000 USDA Employee Survey included a list of successful innovations observed by inspectors in use at various research facilities. Suggestions on how to enhance the development and review of a "consideration of alternatives" narrative include:

- Hire staff or use consultants (internal or external) who are statisticians or biostatisticians
- Include in the facility's training programmes:
  - o Proper methods for recognising, evaluating, alleviating and reporting pain
  - o Animal behaviourist
- Well-designed protocol forms and templates that require three separate answers regarding the need to use animals, the use of a particular species, and the use of a given number of animals
- The search for alternatives should be part of the planning and design stage of the research protocol, rather than considered as a "required afterthought".
- Pair new researchers with experienced librarians to assist with literature searches.

Additional suggestions that principal investigators and IACUCs may want to consider include:

- Guidance documents provided by USDA-APHIS-Animal Care:
  - o Policy #11 "Painful/Distressful Procedures" (http://www.aphis.usda.gov/ac/policy/policy11.pdf)
  - o Policy #12 "Written Narrative for Alternatives to Painful Procedures" (http://www.aphis.usda.gov/ac/policy/policy12.pdf)
  - o "Research Facility Inspection Guide" (http://www.aphis.usda.gov/ac/researchguide.html)
- Attending a workshop given by the USDA-Agricultural Research Service-National Agricultural Library-Animal Welfare Information Center (AWIC) (http://www.nal.usda.gov/awic/awicworkshops/awicworkshops.htm) or similar information service
- Utilising the AWIC alternatives sheet as an addendum to the protocol template (http://www.nal.usda.gov/awic/alternatives/searches/altwksht.pdf)
- Utilising listserves as a way to share information, ask others in the field for guidance, published papers, best practices
- Review the accessibility of free databases to search for alternatives (Donnelly, 2004)
- Review the accessibility of free databases to search for ongoing and previous research projects to avoid the unnecessary duplication of research. The Current Research Information Service (CRIS) is the USDA's documentation and reporting system for ongoing agricultural, food and nutrition, and forestry research. CRIS contains over 30,000 descriptions of current, publicly-supported research projects of the USDA agencies, the State Agricultural Experiment Stations, the State land-grant colleges and universities, State schools of forestry, cooperating schools of veterinary medicine, and USDA grant recipients (http://cris.csrees.usda.gov/). The Computer Retrieval of Information on Scientific Projects (CRISP) is a biomedical database system containing information on research projects and programmes supported by the US Department of Health and Human Services (http:// crisp.cit.nih.gov/).

Conclusions

The requirement to consider alternatives to painful procedures is a performance standard, not an engineering standard. It is understood that there are several means by which one may achieve the intended results. The universality of Russell and Burch's (1959) concept of replacement, reduction and refinement serves us well in this regard: to design research procedures that limit discomfort and pain to animals to that which is unavoidable for the conduct of scientifically valuable research.

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Correspondence to

Jodie A. Kulpa-Eddy, D.V.M.
Staff Veterinarian, United States Department of Agriculture (USDA)-Animal and Plant Health, Inspection Service (APHIS)-Animal Care
4700 River Road, Unit 84, Riverdale, MD 20737-1234, USA
e-mail: jodie.a.kulpa-eddy@aphis.usda.gov