Consideration of Alternatives to the Use of Live Animals
For Research and Teaching

From the ETSU Animal Study Protocol form:

The search for alternatives refers to the three Rs described in the book, The Principles of Humane Experimental Technique (1959) by Russell and Burch. The 3Rs are reduction in the number of animals used, refinement of techniques and procedures to reduce pain or distress, and replacement of animals with non-animal techniques or use of less-sentient species.

Refinement: The use of analgesics and analgesia, the use of remote telemetry to increase the quality and quantity of data gathered, and humane endpoints for the animals are examples of refinements.

Reduction: The use of shared control groups, preliminary screening in non-animal systems, innovative statistical packages or a consultation with a statistician are examples of reduction alternatives.

Replacement: Alternatives such as in vitro, cell culture, tissue culture, models, simulations, etc. are examples of replacement. This is also where you might look for any non-mammalian animal models—fish or invertebrates, for example—that would still give you the data you need.

The AWIC (Animal Welfare Information Center) recommends alternative searches be performed in 2 phases. Phase 1 considers reduction and refinement and the recommendation is NOT to use the word "alternative" unless the particular area of research happens to be an area in which there has been considerable work in developing alternatives (e.g. Toxicology and education). This phase should get after no unnecessary duplication, appropriate animal numbers, the best pain-relieving agents and other methods that may serve to minimize or limit pain and distress.

Phase 2 of the search is focused on Replacement. In this phase the use of the word "alternative" is appropriate and the use of the word "model" is recommended. The result of this second phase of the search is supposed to retrieve information on animal and non-animal models as potential alternatives.

The search strategy consists of the reduction and refinement phase and the replacement phase as mentioned before. The reduction and refinement phase should be similar to the typical literature review done in preparation for a new project or scientific publication. Keywords used will help the researcher determine if there is unintentional duplication, how many animals are necessary using the proposed model, appropriate anesthetics and analgesics, and any other method of minimizing pain and distress. Since much of the refinement and reduction information will be found in the materials and methods sections, it is important for the researcher to review some of the articles that may be of interest.

Many people make the mistake of putting the term alternatives in to the strategy and expect to find all possible alternatives. Because alternatives is a complex concept involving refinement, reduction and replacement, this term is best used only in those areas of study where larger amounts of research have been conducted on alternatives, such as in toxicology or education.

The replacement phase should include keywords for potential alternatives such as "vitro", "culture", or simulation". The word "alternative" may also be included here. The selected animal model, other species, and the word "model" will help retrieve animal and non-animal models as potential alternatives.
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One of the goals of the Animal Welfare Act and the accompanying regulations is the minimization of animal pain and distress via the requirement to consider alternatives and alternative methods. The regulations state that any proposed animal activity, or significant changes to an ongoing animal activity, must include a narrative description of the methods and sources used to consider alternatives to procedures that may cause more than momentary or slight pain or distress to the animals.

The concept of alternatives was conceived as the three R’s by Russell & Burch in 1959. Alternative methods may incorporate one or all of the following: Reduction in number of animals used, Refinement of methods to minimize pain and distress to the animals, and Replacement of an animal model with a nonanimal model or a species lower on the phylogenetic scale. In other words, searching for alternatives should include: 1) methods that reduce the number of animals to the minimum required to obtain scientifically valid data, 2) methods that refine animal use by lessening or eliminating pain or distress and thereby, enhancing animal well-being, 3) methods that use nonanimal systems or less sentient animal species to partially or fully replace vertebrate animals. Although the word ‘alternatives’ is used frequently, it can mean a variety of things. Some animal activists are strong proponents of all animal studies being replaced immediately by non-animal ‘alternatives’, experts on alternatives do not consider this to be a possibility in the near future. Others focus on decreasing animal use (rather than eliminating it) or on mitigating animal pain and distress. Many alternatives are actually improvements over the traditional methods they replaced. A thorough literature search of articles similar to the proposed study may help determine appropriate animal numbers, which may be a reduction alternative.

Consideration of alternatives probably has contributed to the dramatic decline in laboratory animal use during the last 20 years. For example, tissue culture is now widely used in biomedical research. New imaging technology (ultrasound, nuclear magnetic resonance) provides a non-invasive means to examine research animals, thus providing a significant refinement opportunity. Other examples include diagnostic kits that have replaced rabbits in human pregnancy testing. Organisms such as invertebrates, early-stage vertebrate embryos, and microorganisms can be viewed as either replacements or refinements when replacing vertebrates. The CAM Test, or Hen’s Egg Test, is used in lieu of rabbits as a screen for eye irritancy. The Ames Test is using Salmonella bacteria as an alternative to detecting chemicals that cause mutations. State-of-the-art mathematical and computer modeling approaches to biomedical research and testing are likewise replacing and reducing the need for animal testing. Toxicologists use mathematical models known as Quantitative Structure Activity Relationships to predict biological (toxic) activity associated with chemical structure.

There is no universal standard for documenting alternatives searches. At a minimum, the researcher/instructor must provide a narrative including:

1. the names of the databases searched;
2. the date the search was performed;
3. the period covered by the search; and
4. the key words and/or the search strategy used.

Regardless of the alternatives sources(s) used, the written narrative should include adequate information for the University Committee on Animal Care (UCAC) to assess that a reasonable and good faith effort was made to determine the availability of alternatives or alternative methods. If an alternative is found that is useful, but not relevant for the particular project, PIs must justify, in writing, why it cannot be used. The UCAC does not require that a copy of the search is attached to the Animal Study Protocol, but suggests that it be kept on file for future reference.
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When an animal study protocol is modified during its 3-year life span, significant changes are subject to prior review by the UCAC, including the review of the implications of those changes concerning the availability of alternatives.

We all should keep in mind that the consideration of and search for alternatives is not satisfied with a statement concerning duplicate previous research. The researcher must state elsewhere in the animal study protocol that the research in not unnecessarily duplicative. However, the search for alternatives, which is for reduction, refinement and replacement, involves much broader issues and efforts.

To assist in finding more information on the search for alternatives, the College of Medicine Library has collected papers and websites with links at http://com.etsu.edu/medlib/links.asp?CatId=144.

The USDA stresses that the performance of a database search remains the most effective and efficient method for demonstrating compliance with the requirement to consider alternatives to painful/distressful procedures. In some circumstances (as in highly specialized fields of study), conferences, colloquia, subject expert consultants, or other sources may provide relevant and up-to-date information regarding alternatives in lieu of, or in addition to, a database search. When such sources are used in search for alternatives, sufficient documentation, such as the consultant’s name and qualifications and the date and content of the consult, should be provided in the narrative to demonstrate the expert’s knowledge of the availability of alternatives in the specific field of study.

Most researchers run literature searches when designing a study. This helps to determine if the research is original or if there is unnecessary duplication and provides background information on the topic of interest. Such searches can easily be tailored to address alternatives. The search shows that the researcher will stand behind his or her work and that the work is as humane as possible. Sometimes, the adoption of an alternative method is more economical. For example, using an in vitro model vs. housing a colony of animals. It may provide more meaningful data by avoiding confounding factors in the experimental design, such as distress in the animal model. With a little patience and understanding and positive attitude, researchers will see alternatives search as a valuable tool for improving the quality of research.

The search for alternatives may lead to adoption of experimental methods that are less painful, use fewer animals, and make better scientific and economic sense. If alternatives are not found, the search demonstrates that there are no alternatives to the proposed methods.

Internet Sites with Information on Alternatives:

Animal Welfare Information Center (AWIC) at the National Agricultural Library: www.nal.usda.gov/awic AWIC was established in 1986 by the US Congress with the mandate to acquire and disseminate information on alternatives and improved methodologies for the humane care, use, and handling of all animals in research, testing and education. The AWIC site contains a very comprehensive section devoted to "Alternatives and Literature Searches" providing key information on how to search for alternatives, focusing on methods and guidelines, training and education, articles and publications, databases, and organizations.

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quarterly publishes the "Bibliography: Alternatives to the Use of Live Vertebrates in Biomedical Research and Testing". The focus of this bibliography is to assist in identifying methods and procedures helpful in supporting the development, testing application, and validation of alternatives to the use of vertebrates in biomedical research and toxicology testing.

Center for Animal Alternatives at the University of California: http://www.vetmed.ucdavis.edu/Animal_Alternatives/main.htm This site provides investigators who use animals with information on the most current methods for improving all aspects of animal care during their work. It also provides an extensive section on searching for alternatives (including an alternatives search service) as well as search templates; information resources guides, a readings and resources section, electronic versions of their newsletter (UC Alert), and links to other sites of interest.

John Hopkins Center for Alternatives to Animal Testing (Altweb): http://altweb.jhsph.edu is a great site for news, information, discussion, and resources from the field of alternatives to animal testing. A joint effort of Johns Hopkins’ Center for Alternatives to Animal Testing (CAAT): http://caat.jhsph.edu/ and a number of other public and private organizations, it is the most comprehensive resource on animal alternatives for scientists, educators, veterinarians and individuals throughout the world. Altweb includes links to other sources of information on alternatives, and has access to Internet search engines that can be used to search many databases.

The Interagency Coordinating Committee on the Validation of Animal Models (ICCVAM) http://iccvam.niehs.nih.gov/ site provides information on models that have been validated, those under development, and how the process of validation works.

European Centre for the Validation of Alternative Methods (ECVAM) Scientific Information Service: http://ecvam-sis.jrc.it/index.html The ECVAM is an international reference center for the development, scientific and regulatory acceptance of alternative testing methods aimed at replacing, reducing or refining the use of laboratory animals. The Scientific Information Service Consideration of Alternatives Page 4 (SIS) is a database of the European Commission Joint Research Centre. SIS provides factual and evaluated information on advanced non-animal test development and validation for toxicology assessments coming from a wide range of international information sources.

The Norwegian Reference Centre for Laboratory Animal Science & Alternatives (NORINA) at the Norwegian School of Veterinary Science: http://oslovet.veths.no/NORINA/default.html is dedicated to the collection and spread of information on alternatives to the use of laboratory animals in research, education and teaching. It has an efficient search engine and provides extensive information on resources, including a detailed description of the contents, source, price, audience suitability, etc.

Fund for the Replacement of Animals in Medical Experiments (FRAME): www.frame.org.uk FRAME is working towards a future in which the integrated use of computers to model structureactivity relationships and biochemical, physiological and toxicological processes, and in vitro tests using human cells, will be used to assess human risk directly, without recourse to any animal testing of chemicals. FRAME's web site provides an extensive section on how to search for information on alternatives, numerous links to information services on alternatives, other alternatives-related sites and organizations concerned with the use of laboratory animal welfare and alternatives.