



Consideration of Alternatives to Painful Procedures

The information presented in this guideline was collected from several sources, principally two brochures entitled, “Alternatives and the Animal Welfare Act,” (Animal Welfare Information Center, National Agricultural Library, US Department of Agriculture) and “Searching for Alternatives to Painful Procedures Used on Research Animals” (NIH Library). These brochures are also attached and posted on the IACUC webpage.

The “3 R’s” (1) endorsed and embraced by animal research ethicists and animal welfare regulatory bodies require that scientists carefully consider any possible refinement to procedures that may be associated with pain and/or distress. Both the Animal Welfare Act (2) and PHS Policy (3) require that pain and distress be limited to those procedures absolutely necessary to meet scientific aims. IRAC Principle (4) IV provides the “rule-of-thumb” for classifying procedures as potentially painful or distressful: “unless the contrary is established, investigators should consider that procedures that cause pain or distress in human beings may cause pain or distress in other animals.” The USDA Regulations (5) state that a painful procedure “...as applied to any animal means any procedure that would reasonably be expected to cause more than slight or momentary pain or distress in a human being to which that procedure was applied, that is pain in excess of that caused by injections or other minor procedures.”

These federal regulations therefore stipulate that scientists provide a description of their consideration of potential alternatives for IACUC review. At UofL, this is provided in the “Proposal to Use Laboratory Animals in Research and Teaching” (“Proposal”) form, which must contain a narrative which can assure the committee that the PI has carefully and methodically sought and considered any and all possible means of refinement that could reduce potential pain and distress. This description must

include the methods and sources used to determine that suitable alternatives are unavailable.

Some methods of considering alternatives include consulting with subject matter experts and attendance at scientific meetings, conferences, *etc.* (6). If using the former, the written narrative should contain: a) the name and qualifications of the expert, b) the date of the consultation, and c) a description of the substance of the consultation. If the latter, the narrative should contain: a) names and dates of pertinent conferences and b) a description of the substance of meetings relative to alternatives. However, in its Policy 12, the USDA suggests 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.”

The Animal Welfare Information Center (AWIC) affirms that PI’s should:

1. Complete and review the search before completing the protocol;
2. Assess and evaluate the alternative possibilities and be prepared to support their use or non-use in writing;
3. Check to make sure the terminology, strategy, databases searched and dates of search are provided; and
4. Keep a copy of the strategy, databases searched, and years of search for future use.

Performing Literature Database Searches

There are two times searches are often performed in response to IACUC questions: 1) assurance of unnecessary duplication and 2) alternatives to painful procedures. Keywords and even databases may be different for these. The two brochures attached provide helpful information in formulating a search strategy based on the 3R’s.

John Chenault, Reference Librarian for the Kornhauser Health Sciences Library, has kindly agreed to assist investigators in conducting literature database searches for both alternatives to potentially painful or distressful procedures and assurance of unnecessary duplication:

j0chen05@louisville.edu
502-852-3901

Included in these guides are numerous example keywords. You are reminded to consider synonyms, alternate spellings and variations of words (such as tense). You are also advised to use truncation symbols appropriate for each database used. For example, when using MEDLINE/Science Direct, an exclamation point (!) can be used with behav! To identify behave, behavior, behavioral, behavioural, *etc.* Other common truncation symbols are dollar sign (\$) or colon (:), for Ovid and the asterisk (*) for PubMed and Web of Science.

Do not simply rely on MEDLINE or PubMed. There are numerous databases that can be helpful when reviewing the literature for alternatives. Several dozen are listed in the attached brochures, many with their respective URL.

The following are “red flags” used by regulatory agencies to determine that searches were insufficient:

1. Only one (1) database was searched.
2. Search does not include terms for the painful procedure itself (*e.g.*, craniotomy, uveitis).
3. Search terms included only for painful, but not otherwise distressful, aspects.
4. The term “alternative” was used alone with no other alternative terms (*e.g.*, analges*, anesthe* or anaesthe*, advers*, monitor*, pain*, distress*, stress*, welfare).
5. Keywords were not relevant to the protocol.
6. Keywords and concepts were linked incorrectly.
7. An inadequate time period was searched (< 5 years).



As written in the instructions for UofL IACUC “Proposal” form, “...to satisfy federal requirements, ‘the minimal written narrative should include the *databases searched* or other sources consulted, the *date of the search*, the *years covered* by the search, and the *key words* and/or search strategy used when considering alternatives or descriptions of other methods and sources used to determine that no alternatives were available to the painful or distressful procedure. The narrative should be such that the IACUC can readily assess whether the search topics were appropriate and whether the search was sufficiently thorough.’ The **replacement** of animals with a non-animal model, the **reduction** of animal numbers, and/or the **refinement** of study protocol to reduce pain or stress must be addressed. Additionally, for those study protocols that may include elements of pain or distress for which pain relieving agents will not be provided (Class III proposals), Project Directors *must include written scientific justification for withholding such agents.*”

References and Additional Information:

1. Russell, WMS, and RL Burch. 1959. *The Principles of Humane Experimental Technique*. Universities Federation of Animal Welfare.
2. *Animal Welfare Act*, Public Law 89-544, as amended by P.L. 91-579, P.L. 94-279, P.L. 99-198, P.L. 101-624.
3. National Institutes of Health. 2002. Public Health Service Policy on Humane Care and Use of Laboratory Animals. NIH Office of Laboratory Animal Welfare, Bethesda.
4. Interagency Research Animal Committee (IRAC). 1984. *U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training*.
5. Animal Welfare Regulations, United States Department of Agriculture (USDA), Code of Federal Regulations, Title 9, 2.31.
6. Willems, RA. 2007. How to Monitor and Determine Pain and Distress: Policy and Practicality – Is It Adequate? MSMR Conference, Phoenix, AZ, February 14-15, 2007.
- National Agricultural Library and Animal Welfare Information Center, “Worksheet and Instructions for Alternatives Literature Searching”:
<http://www.nal.usda.gov/awic/alternatives/searches/altwksht.pdf>
Including “Sample Literature Searches for Alternatives”:
<http://www.nal.usda.gov/awic/alternatives/searches/sample.htm>
- Allen, T, and D Jensen. 2006. Searching Bibliographic Databases for Alternatives. *Animal Welfare Information Center Bulletin*, Vol. 12 No. 3-4, Summer 2006.