The University of Pennsylvania Institutional Animal Care and Use Committee (IACUC) has developed the following guideline to help research investigators complete the ‘Literature Search for Alternatives’ section of the ARIES protocol, which is required by Animal Care Policy #12 (USDA) and Penn’s Animal Welfare Assurance, for all Penn Category B (relieved pain/distress) or C (unrelieved pain/distress) procedures, regardless of species. If the protocol contains more than one unrelated procedures that involves relieved or unrelieved pain/distress, a separate literature search may be needed for each procedure. If there is a major modification to a protocol in which a relieved or unrelieved pain/distress procedure is significantly changed or added, a new literature search will be needed to be performed. Literature searches should be updated at least every three years.

In most cases the literature search should include more than one database. Conferences, consultants and other sources may also be used, usually in addition to a database search. Consultants include statisticians and subject matter experts. For non-database sources, please supply the consultant’s name, qualifications, and the date and content of the consult in the ARIES description.

The purpose of the literature search is to look for ways to incorporate the “3 Rs” into an animal use protocol:

- **Replacement**: the study uses a non-animal model or a species deemed to be lower on the phylogenetic scale, e.g., *in vitro* culture instead of an animal, or a mouse model instead of a dog.
- **Refinement**: the study has minimized animal pain and distress. This includes using the least painful technique, using appropriate anesthesia and analgesia, and incorporating humane endpoints for treatment or for early intervention, potentially with removal of an animal from the study prior to the experimental endpoint.
- **Reduction**: the study uses the minimum number of animals necessary to accomplish experimental objectives. Statistical tests (e.g., power analysis) should be used to confirm that the minimum number of animals is requested for the protocol. Please note that using an animal for multiple experiments to reduce the overall number may not always be the best practice for reduction and should be justified by the scientific objectives, as this may create additional pain and distress for the animal.

Consider contacting a University of Pennsylvania librarian to assist in the search. Other useful tools include the Animal Welfare Information Center at the National Agricultural Library (AWIC), the UC-Davis Center for Animal Alternatives, Altweb at Johns Hopkins, and the references specifically cited elsewhere in this document.

Step-by-step process to perform an acceptable literature search for alternatives:

1. Develop a comprehensive list of keywords.
   a. Consider non-animal models that may be available, such as computer simulations or *in vitro* cultures. Potential search terms include “simulation”, “model”, and “*in vitro*”. Use of the term “alternative” should be limited in the search as this may only return studies
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designed specifically to look for alternative procedures and models and exclude those in which these alternatives were used or developed as part of a larger study.

b. Consider the potential application of phylogenetically lower animal models, such as fish or invertebrates.

c. Assess each segment of the “Experimental design” section in ARIES for aspects of the research that may cause pain and/or distress:

i. Add keyword search terms pertaining to the specific research objectives, any procedures listed as Category B or C, particular techniques, drugs, anesthesia and analgesia, species and strain of animal, and ‘endpoints’.

ii. Use synonyms, acronyms, and alternative spelling to increase the number of search results. The MeSH function in Pubmed will help find the medical subject heading and any subheadings, allow restriction or explosion of the heading, and help build searches.3

iii. Use of the terms “severity” or “assessment” in the search string may help find refinements or humane endpoints.4

iv. The IACUC expects the following specific terms be included in a search of each painful or distressful (category B or C) procedure: “refine” or “refinement”, “analgesia”, “pain”, “distress”, “humane endpoints”, and the species being used.

2. Combine keywords into brief search strings.

a. Keep strings brief to maximize search results or ‘hits’.

i. For example: when considering search strings for refinements (nonpainful or less painful alternatives to painful/distressful procedures) to a mouse cecal ligation and puncture procedure, a model of peritonitis, one might include:
   - mouse cecal ligation and puncture model pain severity
   - mouse cecal ligation and puncture animal pain assessment
   - mouse cecal ligation and puncture analgesia

ii. Further examples of search strings looking for replacement and reduction (alternatives to the species used) could include:
   - peritonitis simulation
   - septic peritonitis in vitro
   - peritonitis sample size
   - ("Peritonitis"[MeSH]) AND ("Animal Use Alternatives"[MeSH])
   - peritonitis AND ("birds" OR "reptiles" OR "amphibians" OR "fish"

b. If searches resultant in excessive ‘hits’, consider adding or combining terms to help narrow the search.

c. Develop separate search strings for each potentially painful/distressful procedure. For your convenience, ARIES will list the title of each procedure designated as a “B” or “C” Penn pain/distress category.
3. Select databases based on your research area. Commonly used databases include PubMed, EMBASE, BIOSIS, CAB, and ERIC.

4. Search the strings in the databases. Be sure to record the database, search string, date searched, and dates the search covered. ARIES will request that you input this information. Most databases allow you to save searches. For example, “My NCBI” in PubMed and “My Workspace” in BIOSIS allow saving and customization of searches.

5. In addition, ARIES will request that you indicate whether each search was for non-painful alternatives to painful/distressful procedures, or for alternatives to the species used, or both. Be sure to respond “Yes” to the appropriate search when ARIES requests this under “Search type” in the Literature Search section. “Yes” means that you have performed this search.

6. Review any relevant papers that you find; ‘Materials and methods’ sections of papers are especially important to review for alternatives.

7. Determine whether you can incorporate any of your search findings into your research plan and related IACUC protocol application.

8. Briefly describe your search in the “Narrative/Results of search” portion of the ARIES Literature Search section; this should be done in a narrative format (e.g. paragraph). Search strings indicating how the keywords listed in the table were combined should be included in this section. You may also describe any relevant results of your search, excluding whether or not alternatives exist or justifications as to why they are not used, as that should be described in the subsequent ‘Alternatives to painful or distressful procedures’ section.

References:

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