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 UPenn Category B (relieved pain/distress) or C (unrelieved pain/distress) procedures, regardless of species.

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.

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 “alternative”, “simulation”, “model” and “in vitro”.
   b. Consider the potential application of phylogenetically lower animal models, such as fish or invertebrates. Justify why they cannot be used for the proposed studies.
   c. Assess each segment of the “Experimental design” section in ARIES for aspects of the research that may cause pain and/or distress:
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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”, “alternative”, “pain”, “distress”, “humane endpoints.”

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 one might include:
         • cecal ligation and puncture model pain severity
         • cecal ligation and puncture animal pain assessment
         • 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.
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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 and its outcome in the “Narrative/Results of search” portion of the ARIES Literature Search section; this should be done in a narrative format (e.g. paragraph).

References: