

Institutional Animal Care and Use Committee (IACUC) Directive 9.0: Guidelines on Literature Search for Alternatives

1.0 Directive Purpose

The purpose of this directive is to help Principal Investigators (PIs) complete the “Literature Search for Alternatives” component of an animal use protocol for all [Category D](#) or [Category E](#) procedures for United States Department of Agriculture (USDA)-regulated species and/or Department of Defense (DoD) / Office of Naval Research (ONR) funded protocols.

2.0 To Whom the Directive Applies

This directive applies to all individuals using live vertebrate animals under an IACUC-approved animal use protocol at Brown University.

3.0 Directive Statement

The purpose of the Literature Search for Alternatives is to ensure the PI has considered the “3 Rs” ([Replacement](#), [Refinement](#), and [Reduction](#)) and incorporated associated measures into the animal use protocol. The Literature Search for Alternatives must be conducted using a minimum of two different databases. To supplement the required two database searches, conference proceedings, consultants (*i.e.*, subject matter experts, statisticians), and/or search engines (*i.e.*, Google Scholar) may also be used.

PIs are encouraged to contact a Brown University librarian to assist with the literature search. An [Alternative Search Guide](#) was developed by the University Library and the IACUC to aid researchers. Other useful tools include the [Animal Welfare Information Center](#) (AWIC), the [UC-Davis Center for Animal Alternatives](#), [Altweb at Johns Hopkins University](#), and [Altbib](#).

3.1 Acceptable Literature Search for Alternatives

To conduct an acceptable Literature Search for Alternatives, the PI should employ the following procedures to develop a comprehensive list of keywords:

- 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.”
- Consider the potential application of phylogenetically lower animal models, such as fish or invertebrates. Justify in the IACUC protocol why these animal models cannot be used for the proposed studies



- Add keyword search terms pertaining to the specific research objectives, any procedures listed as Category D or E, particular techniques, drugs, anesthesia and analgesia, species and strain of animal, and endpoints.
- Use synonyms, acronyms, and alternative spellings 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 expansion of the heading, and help build searches.
- Use the terms “severity” or “assessment” in the search string to help find Refinements or humane endpoints. A search of each painful or distressful (Category D or E) procedure must include at least one of the following search terms: “Refine” or “Refinement,” “analgesia,” “alternative,” “pain,” “distress,” or “humane endpoints.”

3.2 Combining Keywords into Brief Search Strings

PIs should combine keywords into brief search strings to maximize search results or hits.” For example, when considering search strings for Refinements to a mouse cecal ligation and puncture procedure, one might include the following search strings:

- cecal ligation and puncture model pain severity;
- cecal ligation and puncture animal pain assessment; and
- cecal ligation and puncture analgesia.

Search strings looking for Replacement and Reduction could include, for example, the following:

- peritonitis simulation;
- septic peritonitis in vitro;
- peritonitis sample size;
- (“Peritonitis”[MeSH]) AND (“Animal Use Alternatives”[MeSH]); and
- peritonitis AND (“birds” OR “reptiles” OR “amphibians” OR “fish”).

If searches result in excessive hits, consider adding or combining terms to help narrow the search. Develop separate search strings for each potentially painful or distressful procedure.

3.3 Searching Databases and Recording Results

To search databases and properly record such searches, the PI must do the following:

- Select databases based on the specific research area. Commonly used databases include PubMed, Biological Abstracts, PsychInfo, Agricola, Web of Science, TOXNET, Scopus, and BIOSIS. Some laboratory animal and welfare focused journals and magazines can also be useful resources, including Altex, Lab Animal, JAALAS, JAAWS. Search engines may also be used as resources (*e.g.*, Google Scholar), but a minimum of two different databases is required.



- Search the strings in the databases and record in the IACUC protocol the database, search string, date searched, and dates the search covered. Most databases allow one to save searches by creating an account, for example, “My NCBI” in PubMed.
- Review any relevant papers found during the search. “Materials and methods” sections of papers are especially important to review for alternatives.
- Determine whether to incorporate any of the search findings into the research plan and corresponding IACUC animal use protocol.
- Briefly describe the search and its outcome; this should be done in a narrative format (*e.g.*, paragraph). If no relevant information was found, state this in the protocol.
- For consultants, the PI must supply the consultant’s name, qualifications, and the date and content of the consult in the IACUC protocol. For conference proceedings, the PI must supply details about the conference proceeding(s) (*e.g.*, name of proceeding, content, and date) in the IACUC protocol.

4.0 Definitions

For the purpose of this directive, the terms below have the following definitions:

Category D: Animals upon which experiments, teaching, research, surgery, or tests will be conducted involving accompanying pain or distress to the animals and for which appropriate anesthetic, analgesic, or tranquilizing drugs will be used.

Category E: Animals upon which teaching, experiments, research, surgery, or tests will be conducted involving accompanying pain or distress to the animals and for which the use of appropriate anesthetic, analgesic, or tranquilizing drugs will adversely affect the procedures, results, or interpretation of the teaching, research, experiments, surgery, or tests.

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.

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.

5.0 Responsibilities



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All individuals to whom this directive applies are responsible for becoming familiar with and following this directive. University supervisors are responsible for promoting the understanding of this directive and for taking appropriate steps to help ensure compliance with it.

6.0 Related Information

The following information complements and supplements this document. The information is intended to help explain this directive and is not an all-inclusive list of policies, procedures, laws and requirements.

6.1 Related University Documents: N/A

6.2 Frequently Asked Questions (FAQs): N/A

6.3 Other Related Information: References

- Animal Welfare Act. United States Department of Agriculture Animal and Plant Health Inspection Service. May 2020. USDA-APHIS

7.0 Document Owner and Contact

7.0 Document Owner: IACUC

7.1 Document Approved by: IACUC

7.2 Subject Matter Contact: Brown University Animal Research Compliance

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8.0 Document History

8.0 Document Effective Date: April 8, 2016

8.1 Document Last Reviewed: December 2, 2022

8.2 Document Update/Review Summary: This Directive is not new; it was converted from the policy format and re-reviewed by the IACUC at its convened meeting on December 2, 2022. Prior version of this directive was:

- Conversion to the University's new SOP template from its original Policy and re-reviewed by the IACUC at its convened meeting on July 10, 2020.
- This document was due for its triennial review and approval: December 1, 2022
- IACUC Policy for Literature Searches for Alternatives, date of IACUC review and approval: July 20, 2017.
- IACUC Policy for Literature Searchers for Alternatives, date of initial IACUC review and approval: April 8, 2016