LITERATURE SEARCHES FOR ALTERNATIVES

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Background

Federal regulations mandate that an investigator must consider alternatives to the use of animals and any procedures that may cause pain and distress. Alternatives refer to methods or approaches which result in:

- Replacement of animals with a non-animal model, such as:
    - Computer simulations
    - Non-living systems, such as chemical techniques and mechanical models for training
    - Organ, tissue or cell culture techniques
    - Using phylogenetically lower species (e.g., mice instead of monkeys)

- Reduction in the number of animals used

- Refinement of procedures which minimize pain and distress to the animals (Russell & Burch, 1959).

According to the US Department of Agriculture (USDA):

- 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" (9CFR §1.1). Examples include surgeries, use of Freud's Complete Adjuvant, and ocular or dermal toxicity testing.

- Distress means "a state in which an animal cannot escape from or adapt to the external or internal stressors or conditions it experiences, resulting in negative effects upon its well-being." Examples include food and/or water deprivation or restriction, paralysis and forced exercise ([9CFR §1.1](#)).

The Animal Care and Use Committee (ACUC) require this information be presented in the form of a literature search and updated at the de novo review and with every revision that uses potentially painful procedures. The purpose of this guideline is to provide assistance on how to appropriately [conduct a literature search](#) for alternatives.

Identifying Important Concepts & Developing a Search Question

Think about the procedures that you are proposing in your protocol.

- What is your general area of study (e.g., cardiology, neurology, toxicology, etc.)?
- What species are you currently working with (e.g., rats, dogs, swine, etc.)?
- What is your experimental protocol?
- What specific systems or parts of the anatomy are involved (e.g., central nervous system, brain stem, parabrachial nucleus)?
- What hormones, enzymes, or chemical agents are you studying?
- Have you conducted any other searches? If so, what databases were used (e.g., MEDLINE, AGRICOLA, BIOSIS)?
  - What keywords were used (e.g., kidney, parathyroid hormone)?
  - What years were searched (e.g., 1997-present)?
- Do you know of any prominent authors in your area of research? Have you published any previous literature that relates to your current study?

Replacement

- Have any computer simulation models or statistical models been developed that relate to the study?
- Can the product, enzyme, or tissue be tested or raised in culture?
- If not, are there any alternative animal models (e.g., invertebrates, protozoa, etc.)?
- Are there any other in vitro techniques that may reduce or replace the number of animals used?
- Is there literature on proper experimental design that may assist the researcher in utilizing animals more effectively or in reducing the number of animals?

Refinement

- Can you replace a technique, compound/drug, etc. with a less painful or distressing alternative and still get the desired effect?

- Are you using anesthetics, analgesics and/or sedatives to alleviate pain/distress without jeopardizing the scientific results?

- Do the pharmacological compounds that you are using have any adverse effects?

- Are the compounds tolerable when administered in the suggested location on the body? Using that route of administration? In that species or strain?

- Is there an alternative compound with fewer side effects or is more tolerable?

- Are there any alternative humane endpoints?

- Is there another researcher doing the proposed technique from whom you can receive training?

Reduction

- Will a pilot study be necessary to evaluate whether further studies are justified?

- Are you using the appropriate species?

- How do you know that the proposed number of animals, animals per group and replications will give you statistically significant results? Has another researcher found statistically significant results with your proposed numbers?

- Can you reduce experimental variability (e.g., using transgenic animals instead of pharmacological agents) or reducing confounding variables (e.g., stress)?

Your search question determines the appropriate keywords that you will need to answer your questions.

Keywords

Problems often arise in choosing keywords and search strategies that will yield the most pertinent information. A good literature search will use general biology terms for replacement, reduction, and refinement as well as words that are specific to your research. The key words for alternatives must specifically address anything in the protocol that is potentially painful or distressful.

Appendix 1 outlines example general terms that can be combined with terms specific to your anticipated research. Use synonyms, related terms, different word spelling, acronyms, and interchangeable drug names in your search for alternatives.   A general thesaurus (e.g., Agricultural Thesaurus or Canadian Literacy Thesaurus) or one specific to a database (e.g., MeSH or Medical Subject Headings) may be helpful for this task.

Appropriate Database Examples

Once you have a search question and some keywords, you can begin your search. Note that a Google search or artificial intelligence (AI) query is not a replacement for an appropriate database search, but may return keywords or other information that you hadn't considered. Below are several appropriate databases that can be used for the literature searches. Refer to the Resources section of this guideline for additional links.

- [Agricola – The National Agricultural Library Catalog](#)

- [Agris – International Information System for the Agricultural Sciences and Technology](#)

- [ALTBIB – Resources for Alternatives to the Use of Live Vertebrates in Biomedical Research and Testing](#) (US National Library of Medicine)

- [Alternatives to Laboratory Animals (ATLA) Journal](#)

- [AWIC – Animal Welfare Information Center](#)

- [Ecotox Database](#)

- [Embase Biomedical Answers](#)

- [Fishbase](#)

- [MEDLINE](#)

- [NORINA Database – Norwegian Inventory of Alternatives](#)

- [National Center for the 3Rs](#)

- [North American 3Rs Collaborative](#)

- [Norway's National Consensus Platform for the Advancement of the 3Rs (Norecopa)](#)

- [PUBMED – National Library of Medicine (includes UC-eLinks)](#)

  - If you sign up with [National Center for Biotechnology Information (NCBI)](#), you can save your literature searches, receive email alerts regarding new articles that fit into your keyword search criteria, filter results and more.

- [Web of Science](#)

- [Zfin](#)

General Search Strategies

- Ask a [librarian](#). UC Berkeley librarians host [workshops, presentations, and classes](#) on everything from how to do a literature search to saving your searches on the Endnote program.

- Utilize different [databases](#)

- Get to know the database. Databases treat symbols, operators, and search strategies and terms differently. Before starting your search, look for tutorials, "Help" links, Frequently Asked Questions (FAQs), or advanced search options.

- Use the database thesaurus to find better terms and phrases. Some databases come with their own "thesaurus", like PubMed's [Medical Subject Headings](#) (MeSH; National Library of Medicine). **NOTE**: MeSH has to be manually

updated, so the most recent terms, phrases or concepts may not be in the database yet.

- Start out searching more broadly and then slowly narrow your results by adding keywords one at a time.

- Add more and/or unique terms to your search statement

More Specific Search Strategies

- Use the "explosion" feature if it is not done automatically. This feature will likely increase the number of relevant citations by searching for more specific and broader words associated with your specified term.

- Use syntax (truncation, quotation marks, etc.)

- Find and use synonyms, related terms, commonly used acronyms, different drug names (trade, brand and generic names)

- Use symbols* for:

  - Plural variation (e.g., stud+ will find study, studying, or studies)

  - Truncation (e.g., comput* will find computers, computer, computed, computing, etc.)

  - Wildcard (e.g., leuk*mia will find leukemia or leukaemia)

- Vary the spelling of words (e.g., tumor and tumour) and prefixes (e.g., prenatal, pre natal, pre-natal)

- Use Boolean logical operators*

Logical Operator	Purpose	Effects on the Search	Examples
"AND"	Find a connection between words	Narrows the search because the citation must contain both words	Cancer AND p53
"OR"	Search for similar terms, such as synonyms, scientific vs. common species name, trade/brand name vs. generic name, etc.	Broadens the search because the citations will contain at least one of the words	Ozempic OR semaglutide
"NOT"	Find one term but not the other	USE WITH CAUTION: Narrows the search by eliminating citations with the second word	Dementia NOT Alzheimer's Disease
"AND NOT"			benzodiazepine AND NOT Xanax

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* May vary by database

- Use Boolean expressions[*] to link words and logical operators together
  - Quotations
    - Best if you are looking for a specific phrase or title
    - Example: "X is not Y"
  - Parentheses
    - Best if you are looking for different combinations of words and/or phrases
    - Can be used in conjunction with Boolean logical operators and quotations
    - Examples
      - ("X is not Y") OR ("Y is not X") will search for one of the two phrases word for word
      - (dermatoses NOT erythema) AND photochemotherapy will search for photochemotherapy and different dermatoses except erythema
      - (8-methoxypsoralen OR 8MOP OR xanthotoxin OR ammoidin) AND "Ammi majus" will find citations with the plant "Ammi majus" and one of the four terms that are synonymous with the drug, methoxsalen
- Use appropriate search filters and limit options (e.g., an "advanced" search).
- Use proximity operators[*] (e.g., Nx or Wx) to find words that are in close proximity to each other.
  - Near operators ("Nx") find citations with the words that are "x" words apart _regardless of the sequence_. For example, "Nicotine n2 addictive" will result in citations that have the words "nicotine" and "addictive" up to 2 words apart. Therefore, "nicotine is addictive" or "addictive drug nicotine," would appear, but "nicotine, similar to that of cocaine, is considered highly addictive" would not.
  - Within operators ("Wx") find citations with the words that are "x" words apart _in the order searched_. For example, "John w2 Booth" will result in citations that have the words "John" and "Booth" up to 2 words apart. However, "John Wilkes Booth" and "John Booth" would appear but not "Wilkes John".

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[*] May differ by database

Things to Avoid

- Using the word (or variations of the word) "alternative" or the phrase "animal testing alternatives" as the only strategy to retrieve information. Not all databases use this word or term (e.g., BIOSIS).

- Keywords that are irrelevant to your protocol

- Range of years covered by the search that is not large enough (e.g., 2023-2024 instead of 2000-2024)

- Searching for too many keywords at one time

- Using too many limiting options or search filters

Save Your Searches

Save your searches for future references. UC Berkeley Public Health library outlines several [web-based options](#), including [EndNote](#), [Mendeley](#), [Zotero](#), and [BibTex](#), to help you document your literature searches.

Written Narrative

- This description must include the databases searched, date of the search, years covered, keywords, methods of searching (e.g., what did you type in search bar to get those results?), and a summary of your findings.

- Summarizing your findings

    o Did you determine that there are any alternatives for the procedures/species/strains that you are proposing to do/use? If a database search or other source identifies a bona fide alternative method (one that could be used to accomplish the goals of the animal use proposal), the written narrative should scientifically justify why this alternative was not used. If you did not find an appropriate or plausible method, indicate that this is the only technique available for that particular purpose.

    o Example

        ▪ Procedures – "Based on my years of experience in this field and periodic consultation of bibliographic sources outlined above, I believe there is no alternative to performing [insert the potentially painful/distressful procedure] in order to achieve the scientific objectives of this research. Therefore, based on the aforementioned references, this procedure is the most appropriate for conducting my research."

        ▪ Species/Strain – "Based on the periodic consultation of bibliographic sources outlined above, I believe there is no alternative to using (insert species/strain)] in order to achieve the

scientific objectives of this research. Therefore, this (insert species) is the most appropriate species to use in my research."

- This information must be updated with every revision that uses potentially painful procedures and at the *de novo* review.

Examples of Literature Searches on Alternatives

- Portland VA Medical Center. "Research and Development Service – Alternatives for Animal Use: Search Example 1". Retrieved 02 December 2024. Portland VA Medical Center. "Research and Development Service – Alternatives for Animal Use: Search Example 2". Retrieved 02 December 2024.

- Portland VA Medical Center. "Research and Development Service – Alternatives for Animal Use: Search Example 3". Retrieved 02 December 2024.

Resources for Conducting Literature Searches for Alternatives

- Animal Welfare Institute. "Refinement Databases". Retrieved 02 December 2024.

- Colorado State University. "IACUC Alternatives Search Help". Retrieved 02 December 2024.

- National Institutes of Health Library. "Searching for Alternatives to Painful Procedures Used on Research Animals". Retrieved 02 December 2024.

- US Department of Agriculture. "Alternatives and the Animal Welfare Act" brochure. Retrieved 02 December 2024

- US National Library of Medicine, National Institutes of Health. "PubMed Tutorial". Retrieved 02 December 2024.

References

- Animal Plant Health Inspection Service (APHIS). United States Department of Agriculture (USDA). "*Institutional Animal Care and Use Committee (IACUC)*", *Code of Federal Regulations*, Title 9, Chapter 1. Part 2. Subpart C. Section 2.31. Retrieved 02 December 2024.

- Institute of Laboratory Animal Research (ILAR). National Research Council. (2011). *Guide for the Care and Use of Laboratory Animals* (8th edition). Washington, D.C.: The National Academies Press. Retrieved 02 December 2024.

Appendix 1 – Example Keywords

Example Keywords for Replacement		
AI	culture (cell, tissue, organ)	model[]
algae	digital imag[]	plant
Alternat[]	expert system	procedur[]
amphibian	fish	protozoan
animal testing alternative	fungus	QSAR
animal use alternative	hydra	replac[]
artificial[]	interactive	reptile
artificial intelligence	insect	simulat[]
assay[]	isolated (cell, tissue, organ)	Software
autopsy	Invertebrat[]	surrogate
bacter[]	in vitro (AND method, model, technique	technique
biopsy	mannequin or manikin	theoretical model[]
cadaver	mathematical model[]	video[]
cephalopod	method[]	virtual (surgery, reality)
computer	microorganism	yeast

Example Keywords for Reduction and Refinement		
advers[]	environment[]	pain[]
analges[]	enrich[]	procedur[]
anasthe[]	Environmental enrichment	reduc[]
anaesthe[]	euthanasia	refin[]
anesthe[]	euthanize[]	restrain[]
anxiolytic	handl[]	restrict[]
assay[]	hous[]	sedative
cag[]	husbandry	stress[]
device	immobil[]	technique
distress[]	method[]	tranquiliz[]
enhancement	monitor[]	welfare