Meeting the Information Requirements of the Animal Welfare Act

Presented by the
Animal Welfare Information Center (AWIC)
National Agricultural Library
U.S. Department of Agriculture
Objectives

• List the information requirements of the Animal Welfare Act.

• Define the 3 Rs of Alternatives.

• Become familiar with databases and other resources helpful in searching for alternatives.

• Design and run a search for alternatives.
Early History of Animal Protection Legislation in the U.S.

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1641</td>
<td>Puritan’s Body of Liberties</td>
</tr>
<tr>
<td>1828</td>
<td>First state anti-cruelty law passed in New York</td>
</tr>
<tr>
<td>1873</td>
<td>First Federal legislation: “28-Hour Law”</td>
</tr>
<tr>
<td>1958</td>
<td>Humane Methods of Slaughter Act passed</td>
</tr>
<tr>
<td>1965</td>
<td>Disappearance of Pepper and publication of <em>Sports Illustrated</em> article</td>
</tr>
<tr>
<td>1966</td>
<td><em>Life</em> article published: “Concentration Camp for Dogs”</td>
</tr>
</tbody>
</table>
August 24, 1966
Laboratory Animal Welfare Act signed into law


Laboratory Animal Welfare Act of 1966 Public Law 89-544

- Authorized Secretary of Agriculture to regulate transport, sale, and handling of animals pre-research or “for other purposes.”
- Defined animal as dogs, cats, nonhuman primates, guinea pigs, hamsters, and rabbits.
- Established licensing of dog and cat dealers.
Animal Welfare Act of 1970
Public Law 91-579

- Ensured the humane treatment of animals for research or exhibition by regulating their transport, sale, housing, care, handling, and treatment in commerce, exhibition, and all stages of experimentation.

- Clarified the definition of animals as all warm-blooded vertebrates excluding
  - Horses not used in research and
  - Farm animals used for improving animal nutrition, breeding, management, production efficiency, and the quality of food and fiber.
Animal Welfare Act of 1970
Public Law 91-579

- Defined regulated and non-regulated institutions:
  - Regulated: research facilities, dealers, and exhibitors.
  - Non-regulated: retail pet stores, state and county fairs, rodeos, purebred dog and cat shows, and agricultural exhibitions.
Animal Welfare Act of 1976
Public Law 94-279

• Refines regulations on transport and commerce.
• Requires health certification prior to transport and commerce.
• Discusses licenses, methods of payments, penalties.
• Outlaws interstate or foreign transport of animals used in fighting ventures.
Food Security Act of 1985
Subtitle F, Animal Welfare, Public Law 99-198
Improved Standards for Laboratory Animals Act

“…the farm bill contains legislation dealing with the humane treatment of animals. The main thrust of the bill is to minimize pain and distress suffered by animals used for experiments and tests. In so doing, biomedical research will gain in accuracy and humanity. We owe much to laboratory animals and that debt can best be repaid by good treatment and keeping painful experiments to a minimum.”

Sen. R. Dole
Congressional Record
Senate
17 December 1985
Food Security Act of 1985
Subtitle F, Animal Welfare, Public Law 99-198

Improved Standards for Laboratory Animals Act

- Clarifies humane care to include specific criteria such as sanitation, ventilation, and housing.
- Directs the Secretary of Agriculture to establish regulations for
  - exercise for dogs and
  - a physical environment adequate to promote the psychological well-being of primates.
- Specifies that animal pain and distress must be minimized (veterinary care, anesthesia, analgesia, tranquilizers, and euthanasia).
Food Security Act of 1985
Subtitle F, Animal Welfare, Public Law 99-198
*Improved Standards for Laboratory Animals Act*

- Specifies that principal investigators must consider alternatives to any procedure likely to cause pain or distress.
- Establishes the Institutional Animal Care and Use Committee (IACUC).
- Explains penalties for the release of trade secrets.
- Establishes an information service at the National Agricultural Library.
The Secretary shall establish an information service at the National Agricultural Library. Such service shall, in cooperation with the National Library of Medicine, provide information--

(1) pertinent to employee training;

(2) which could prevent unintended duplication of animal experimentation as determined by the needs of the research facility; and

(3) on improved methods of animal experimentation which could--
   (A) reduce or replace animal use; and
   (B) minimize pain and distress to animals, such as anesthetic and analgesic procedures.
Public Law 101-624

- Establishes a five-day holding period requirement for dogs and cats at shelters and other holding facilities.
- Requires dealers provide written certification about each animal’s background to recipients.
- Describes mechanisms of enforcement, injunctions, and penalties for violations.
Farm Security and Rural Investment Act of 2002 (*Farm Bill*)
Public Law 107-101

- Modifies the definition of animals to exclude rats, mice and birds bred for use in research.
- Makes it illegal to knowingly sponsor or exhibit an animal in a fighting venture, if any animal was moved in interstate or foreign commerce and increases fines.
Animal Fighting Prohibition Enforcement Act of 2007
Public Law 110-22

• Makes it unlawful to sell, buy, transport, or deliver in interstate or foreign commerce a knife, a gaff, or any other sharp instrument attached, or designed to be attached, to the leg of a bird for use in fighting.

• Increases criminal penalties for fighting ventures.
Food, Conservation, and Energy Act (Farm Bill) of 2008
Public Law 110-246

- Increases fines for violations of the Animal Welfare Act from $2500 to $10,000 (per violation, per animal, per day)

- Prohibits the importation of dogs for resale, unless
  - In good health
  - Received all necessary vaccinations
  - At least 6 months old

  (Exemption for research purposes, medical treatment)
Food, Conservation, and Energy Act (Farm Bill) of 2008
Public Law 110-246

- Addresses the use of cats and dogs in Federal research
  - NIH was asked to seek an independent review of the use of Class B dogs and cats
  - USDA is required to review this review
  - Submit a report to Congress on how any recommendations in this review may be applied
Food, Conservation, and Energy Act (Farm Bill) of 2008
Public Law 110-246

- Adds additional prohibitions on Animal Fighting Ventures
  - Added prohibitions on possession and training
  - Added prohibitions on advertising animals or sharp instruments for use in animal fighting
  - Increased criminal penalties to 5 years imprisonment
Code of Federal Regulations
Title 9, Chapter I, Subchapter A, Animal Welfare

• Specifies how to comply with the Animal Welfare Act and its amendments.
  – Definitions: “Animal” excludes Rattus, Mus, and birds bred and raised for use in research.
  – Regulations: Specific requirements for facility licensing, veterinary care, records, stolen animals.
  – Standards: Facilities and operations, health and husbandry, transportation.
  – Rules of Practice: Scope, application, administrative procedures.
Painful Procedure, Sec. 1.1

...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.
Twenty-two members of the research or scientific community commented that when pain is relieved through anesthesia, a procedure should not be considered painful. The 1985 amendments to the Act refer repeatedly to the use of pain-relieving drugs and anesthetics in conducting painful procedures and practices (see, e.g., 7 U.S.C. 2143(a)(3)(C)(ii) and 2143(e)(3)(B)). Therefore, under the Act, a procedure in which pain is relieved is still considered to be a painful procedure, and the provisions of the Act which address the conduct of painful procedures apply. We are not adopting the commenters’ suggestions.
(ii) The principal investigator has considered alternatives to procedures that may cause more than momentary or slight pain or distress to the animals, and has provided a written narrative description of the methods and sources, e.g., the Animal Welfare Information Center, used to determine that alternatives were not available;

(iii) The principal investigator has provided written assurance that the activities do not unnecessarily duplicate previous experiments.
[The] IACUC shall determine that...

(iv) Procedures that may cause more than momentary or slight pain or distress to the animals will:

(A) Be performed with appropriate sedatives, analgesics or anesthetics, unless withholding such agents is justified for scientific reason, in writing, by the principal investigator and will continue for only the necessary period;
[The] IACUC shall determine that…

(x) No animal will be used in more than one major operative procedure from which it is allowed to recover unless:

(A) Justified for scientific reasons by the principal investigator in writing.

(B) Required as routine veterinary procedure.

(C) Approved by the Administrator of APHIS.
“The principal investigator must provide a written narrative of the sources, such as biological abstracts, Index Medicus, the Current Research Information Service (CRIS), and the Animal Welfare Information Center that is operated by the National Agricultural Library. We believe that in fulfilling this requirement Committee members will discuss these efforts with the principal investigator in reviewing the proposed activity. We also believe that considerations of alternatives will be discussed during Committee meetings where proposed activities are presented for approval, and made part of the meeting minutes…”
Animal Care Policy #12
Written Narrative for Alternatives to Painful/Distressful Procedures: March 25, 2011

• “..APHIS continues to recommend a database search as the most effective and efficient method for demonstrating compliance with the requirement to consider alternatives to painful/distressful procedures.”

• The database search narrative must, at a minimum, include
  – Names of the databases searched (“one database is seldom adequate”)
  – Date the search was performed
  – Time period covered by the search
  – The search strategy (including scientifically relevant terminology) used.

“Alternatives should be considered in the planning phase of the animal use proposal”. …

“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 protocol), the IACUC may and should ask the PI to explain why an alternative that had been found was not used”.

Animal Care Policy #12
Written Narrative for Alternatives to Painful/Distressful Procedures: March 25, 2011
Other Policies and Guidelines

- Public Health Service Policy on Humane Care and Use of Laboratory Animals
  [Link](http://grants1.nih.gov/grants/olaw/references/phspol.htm)

- Guide for the Care and Use of Laboratory Animals
  [Link](http://www.nap.edu/catalog.php?record_id=12910)

- Guide for the Care and Use of Agricultural Animals in Agricultural Research and Teaching
  [Link](http://www.fass.org/page.asp?pageID=216)

  [Link](https://www.avma.org/KB/Policies/Documents/euthanasia.pdf)
Federally Mandated IACUC Functions Under the AWA

- Review, at least once every six months, the research facility’s program for humane care and use of animals, using title 9, chapter 1, subchapter A—Animal Welfare, as a basis for evaluation.

- Inspect, at least once every six months, all of the research facility’s animal facilities, including animal study areas, using title 9, chapter 1, subchapter A—Animal Welfare as a basis for evaluation. Areas where animals are housed for more than 12 hours are defined as “study areas.”

- Prepare reports of its evaluations (using CFR Title 9, chapter 1, A – AWR) and submit to the IO. …no member wishing to participate in any evaluation [can be] excluded. Reports must distinguish significant deficiencies from minor deficiencies and must contain a reasonable and specific plan and schedule with dates for correcting. Notify APHIS and Federal funding agencies if uncorrected by scheduled date.

- Review and investigate legitimate concerns involving the care and use of animals at the research facility resulting from public complaints and from reports of non-compliance received from facility personnel or employees.
Federally Mandated IACUC Functions Under the AWA

- Make recommendations to the IO regarding any aspect of the research facility’s animal program, facilities, or personnel training.

- Review and approve, require modifications in (to secure approval), or withhold approval of those components of proposed activities related to care and use of animals.

- Review and approve, require modifications in (to secure approval), or withhold approval of proposed significant changes regarding the care and use of animals in ongoing activities.

- Suspend an activity involving animals when necessary; take corrective action and report to funding agency and USDA.
Federal Criteria for Granting IACUC Approval

**Activities**
Must be in accord with USDA Regulations.

**Pain/Distress**
Must avoid/minimize discomfort/distress/pain. If pain/distress is caused, appropriate sedation, analgesia, or anesthesia will be used. Attending veterinarian must be involved in planning. Use of paralytics without anesthesia is prohibited. Animals with chronic/severe unrelievable pain will be painlessly euthanized.

**Surgery**
Must meet requirements for sterile surgery and pre/post operative care. Cannot use one animal for more than one major operative procedure from which it will recover, without meeting specified conditions.

**Euthanasia**
Must be consistent with USDA Regulations/AVMA recommendations.
Federal Criteria for Granting IACUC Approval

**Housing/Health**

The animals’ living conditions will be appropriate for their species (see part 3 of the regulations) and contribute to their health and comfort. The housing, feeding, and nonmedical care of the animals will be directed by the attending veterinarian or other scientist trained and experienced in the proper care, handling, and use of the species being maintained or studied. Medical care for animals will be available and provided as necessary by a qualified veterinarian.

**Alternatives**

Must provide written narrative description of methods and sources used to determine that alternatives were not available.

**Animals**

A proposal…must contain the following: (1) Identification of the species and approximate number of animals to be used; (2) A rationale for involving animals, and for the appropriateness of the species and numbers of animals to be used…

**Duplication**

Must provide assurances that activities do not unnecessarily duplicate previous efforts

**Qualifications**

Personnel must be appropriately qualified for procedures and species.

**Deviations**

Must be justified for scientific reasons, in writing.
Required Contents for an Institutional Training Program

(1) Humane methods of animal maintenance and experimentation, including:
   (i) The basic needs of each species of animal;
   (ii) Proper handling and care for the various species of animals used by the facility.
   (iii) Proper pre-procedural and post-procedural care of animals; and
   (iv) Aseptic surgical methods and procedures.

(2) The concept, availability, and use of research or testing methods that limit the use of animals or minimize animal distress.

(3) Proper use of anesthetics, analgesics, and tranquilizers for any species of animals used by the facility.

(4) Methods whereby deficiencies in animal care and treatment are reported, including deficiencies in animal care and treatment reported by any employee of the facility. No facility employee, committee member, or laboratory personnel shall be discriminated against or be subject to any reprisal for reporting violations of any regulation or standards under the Act.

(5) Utilization of Services (e.g., National Agricultural Library, National Library of Medicine) available to provide information;
   (i) On appropriate methods of animal care and use;
   (ii) On alternatives to the use of live animals in research;
   (iii) That could prevent unintended and unnecessary duplication of research involving animals; and
   (iv) Regarding the intent and regulation of the Act.
Alternatives and the 3Rs
Definition of Alternatives

• Russell and Burch (1959) – *The Principles of Humane Experimental Technique*

  – Full text available online at AltWeb: [http://altweb.jhsph.edu/pubs/books/humane_exp/het-toc](http://altweb.jhsph.edu/pubs/books/humane_exp/het-toc)

• Development of the concept of the 3Rs:
  – Reduction
  – Refinement
  – Replacement
Alternatives
The 3Rs of Russell and Burch

**Reduction** - Minimize the number of animals used.

**Refinement** - Employ techniques that reduce pain and distress.

**Replacement** - Substitute animal with nonanimal methods or lower organisms.
Why Consider Alternatives?

- Regulatory
- Social
- Humane
- Economic
- Scientific
Regulatory

- Comply with the Animal Welfare Act.
- Comply with the PHS Policy.
- Maintain AAALAC International accreditation.
Social

• Respond to social pressures to
  – Change to non-animals as soon as possible and
  – Make research pain free.
Humane

• Ask ethical questions such as
  – Should animals be used in research?
  – When should animals be used?
  – How should they be used?
Economic

• Reduce the expense of animal use in:
  – Specialized facility infrastructure costs—such as caging, building design, and equipment
  – Purchase costs
  – Maintenance costs
  – Personnel costs and
  – Occupational health and safety costs.
Economic

- Animals lower on the phylogenetic scale may be cheaper and more plentiful.

- Non-animal models
  - May be cheaper to use and
  - Could possibly increase the number of compounds that can be tested.
Scientific

• Keep current in area of research.
• Become aware of research from unfamiliar resources.
• Reduce duplication in research.
• Screen more compounds and predict their effects (computer automated structure evaluation system).
• Find opportunities for less painful and invasive procedures.
• Learn insights into totally new approaches.
• Determine appropriate numbers.
• Identify possible collaborators.
• Reduce stress through proper handling, training, enrichment, group housing, etc.
Group Exercise: The 3Rs
Alternatives: *Reduction*

*The Principles of Humane Experimental Technique* (1959)

- Quality literature search
- Appropriate statistical design
- Pilot studies
- Sharing animals, tissues, or organs
- New methods in testing
  (e.g. limit test, local lymph node assay, etc.)
3Rs—Reduction/Refinement

- Emerging Technologies
  - Imaging Devices for Use in Small Animals
    - positron emission tomography
    - single-photon emission computed tomography
    - computed tomography
    - magnetic resonance imaging
    - ultrasound
    - optical imaging with fluorescent and bioluminescent tracer technology

In vivo imaging modalities, within the context of animal welfare concerns, are seen as **technical refinements** in that they are much less invasive than older diagnostic and monitoring techniques. In addition, animal imaging devices now offer the possibility of **reduction of animal sacrifice** through longitudinal study that uses animals as their own controls, thereby also **simultaneously improving science** by the use of the improved statistics of paired observations.

Imaging

PET system for small animals
http://zmbe.uni-muenster.de/institutes/izb/stemres_de.htm
3Rs—Reduction/ Refinement

• New animal models
  - One problem limiting development of therapeutic interventions is that the relevance of rodent models to human spinal cord injury is not clear. Progress in developing therapies would be better facilitated by a valid, humane non-human primate model that would allow testing of potentially efficacious pharmacological treatments. This brief report addresses the feasibility of this concept. In human spinal cord injury, the primary impairment is the inability to control the limb to perform functional tasks such as walking, grooming, feeding, etc. However, to propose a primate model of acute spinal cord injury that induce significant hind limb and/ or forelimb limb paralysis would be unacceptable. As well, extensive lesions of the spinal cord could result in bowel and bladder dysfunction. To appropriately address the animal welfare issues, this spinal cord injury model is predicated on a monkey’s tail being the ‘fifth limb’. As such, this model focuses on creating a selective, small lesion on one side of the sacral spinal cord that partially impairs movement of the tail.
3Rs—Reduction/ Refinement

• Telemetry
  – Affect welfare in several ways
    • Can be used to reduce stress by capturing data without increased handling
    • Can be used to capture data to determine if experimental methods are stressful
Searching Pubmed - Telemetry

- **Useful Terms**
  - telemetry
  - species
  - data to be collected

- **Example**
  - telemetry and mice

  - Sample citation—shows both reduction of numbers/ refined procedure that minimizes stress


- Reactogenicity often represents a major hurdle to the clinical use of new substances. Yet, **irrespective of its importance, this parameter has remained difficult to screen for, owing to a lack of sensitive small animal models with a capacity for high throughput testing**. Here we report that continuous telemetric measurements of heart rate, heart rate variability, body core temperature and locomotor activity in laboratory mice **readily unmasked systemic side-effects of vaccination, which went undetected by conventional observational assessment and clinical scoring**. Using only limited numbers of mice, this method allows for their automated evaluation, differentiation and selection without sizeable risk for investigator-related bias.
Alternatives: Refinement

The Principles of Humane Experimental Technique (1959)

- Knowledge of species physiology and normal and abnormal behavior
- Proper use of anesthetics and analgesics
- Modifications in restraint, handling, blood collection
- Increased sensitivity of monitoring devices and chemical assays
- Proper training of personnel
Social Housing
Cage Design
Handling and Training
Environmental Enrichment
Alternatives: **Replacement**

*The Principles of Humane Experimental Technique* (1959)

- **Relative replacement** - some animal involvement
  - Isolated cell and nerve preparations
  - Use of tissues from slaughter house or grocer
  - Computer simulations based on in vivo data
3Rs - Replacement

• Emerging Technologies
  – Artificial Organs/Tissue Engineering
    • Liver on a chip
    • Organ/tissue printing technology

Virtual Alternatives

Virtual dissection:

1. Stretch the colon and cut it along its longitudinal axis similar to the pathologist’s table.

The Virtual Pig Dissection

1. Salivary Gland
2. Rib Cage
3. Diaphragm
4. Liver
5. Intestines
6. Bulbourethral Gland
7. Testicle with Epididymis

External Anatomy
Respiratory System
Circulatory System
Digestive System
Reproductive (male)
Reproductive (female)
Non-animal Models Used in Teaching
Alternatives: *Replacement*

*The Principles of Humane Experimental Technique* (1959)

- **Absolute replacement** – no animal involvement
  - Endoparasites, plants, microorganisms
  - Computer automated structure evaluation systems
  - Human tissue culture
Alternatives to Animal Testing – In Song
William Russell
http://www.youtube.com/watch?v=3ShQdc7Kbmo
Where Can I Find the Information?

AWIC Services and Databases
AWA Defines Service at NAL
(7 U.S.C. 2142, Sec. 13, Subsection e)

- AWIC provides information
  - For employee training
  - To prevent unintended duplication
    and
  - About the 3Rs:
    - Reduce or replace animal use
    - Minimization of pain and distress
Animal Welfare Information Center

AWIC

• Serves as a comprehensive resource.
• Suggests search terms, strategy, and databases.
• Provides access to resources that you might not have.
• Refers you to experts at other institutions.
• Alerts you to additional information resources.
Animal Welfare Information Center

Services

• Reference and referral
• Workshops and presentations
• Conference exhibits
• Committee members
• Website and social media tools
  http://awic.nal.usda.gov

Twitter: @AnimalWelfareIC
Animal Welfare Information Center
Publications

- Bibliographies
- Information Resource Guides
- AWIC Bulletin
- Collaborations on articles, proceedings, book chapters, etc.
Databases

Biomedical and Biological

- CAB Abstracts
- ToxNET
- EMBASE
- BIOSIS
- Zoological Record
- PsycINFO
- ASFA
- Pascal
- SciSearch
- Current Contents
- Scopus and ScienceDirect
- Web of Science
Databases

Pharmaceutical and Technological

- Pharmaceutical News Index   file 42
- Intern’l. Pharmaceut. Abstracts file 74
- NTIS                        file 6
- INSPEC                      file 2
- Ei Compendex                file 8
- Gale Group Computer Database file 275
Databases
Federally-funded Research

- CRIS
  http://cris.nifa.usda.gov
- NIH RePORTER
  http://projectreporter.nih.gov/reporter.cfm
- NTIS
- FEDRIP

file 6
file 266
Databases

Law and Legislation

- Gale Legal Resource Index
- LexisNexis
- Congress.gov (replaces Thomas)
  - [http://congress.gov](http://congress.gov)
- State Statutes
  - [http://www.law.cornell.edu/statutes.html](http://www.law.cornell.edu/statutes.html)
- GPO’s Federal Digital System (FDsys)
  - [http://www.gpo.gov/fdsys/search/home.action](http://www.gpo.gov/fdsys/search/home.action)
Databases

Education

- ERIC  http://www.eric.ed.gov
- InterNICHE (International Network for Humane Education)  http://www.interniche.org
  http://www.interniche.org/en/alternatives
  http://www.interniche.org/en/studies
- Norwegian Reference Centre for Laboratory Animal Science & Alternatives
  http://oslovet.veths.no/NORINA/
  http://oslovet.veths.no/teaching/materials.html
  http://oslovet.veths.no/textbase/
## Subject Coverage of Selected Databases

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<thead>
<tr>
<th>AGRICOLA</th>
<th>ASFA</th>
<th>BIOSIS</th>
<th>CAB</th>
<th>ERIC</th>
<th>MEDLINE</th>
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<tr>
<td>General agriculture</td>
<td>Aquaculture</td>
<td>General agriculture</td>
<td>General agriculture</td>
<td>Adult, career, voc.</td>
<td>Clinical med.</td>
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<td>Aquatic</td>
<td>Aerospace biology</td>
<td>Animal sci. &amp; production</td>
<td>Education monographs</td>
<td>Experimental medicine</td>
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<tr>
<td>Chemistry &amp; biochemistry</td>
<td>Biology &amp;</td>
<td>Biochemistry &amp; anatomy</td>
<td>Crop science</td>
<td>Info. resources</td>
<td>Pharmacology</td>
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<tr>
<td>Microbiology</td>
<td>Ecology</td>
<td>Bacteriology (microbiology)</td>
<td>Forestry</td>
<td>Science, math &amp;</td>
<td>Microbiology</td>
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<tr>
<td>Cytology</td>
<td>Policy</td>
<td>Cell biology</td>
<td>Pest control</td>
<td>Teacher ed.</td>
<td>Administration</td>
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<tr>
<td>Human &amp; animal nutrition</td>
<td>Pollution</td>
<td>Botany</td>
<td>Human nutrition</td>
<td>Education management</td>
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<tr>
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<td>Biotechnology</td>
<td>Higher ed.</td>
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<td>Physiology</td>
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<td>Physiology</td>
<td>Pesticides</td>
<td>Tests &amp; testing</td>
<td>Anat. &amp; physiol.</td>
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<td>Wildlife</td>
<td>Acoustics and optics</td>
<td>Pathology</td>
<td>Machinery and buildings</td>
<td>Occupational medicine</td>
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<td>Zoology</td>
<td>Fisheries</td>
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<td>Economics</td>
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<td>Toxicology</td>
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<td>Entomology</td>
<td>Diving</td>
<td>Toxicology</td>
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<td>Other med. topics</td>
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## Subject Coverage of Selected Databases

<table>
<thead>
<tr>
<th>EMBASE</th>
<th>CURRENT CONTENTS</th>
<th>ZOOLOGICAL RECORD</th>
<th>PASCAL 63% Eng., 12% Fr</th>
<th>INSPEC</th>
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<td>Experimental medicine</td>
<td>Life sciences</td>
<td>Behavior &amp; communication</td>
<td>Tropical medicine</td>
<td>Computer applications</td>
</tr>
<tr>
<td>Pharmacology, drugs, potential drugs</td>
<td>Engineering tech. &amp; applied sciences</td>
<td>Physiology, immunology</td>
<td>Energy</td>
<td>Computer hardware</td>
</tr>
<tr>
<td>Biochemistry</td>
<td>Physical chem. &amp; earth sciences</td>
<td>Biochemistry</td>
<td>Metals/metallurgy</td>
<td>Control applications</td>
</tr>
<tr>
<td>Developmental biology</td>
<td>Social and behavioral sciences</td>
<td>Disease</td>
<td>Earth science</td>
<td>Control systems</td>
</tr>
<tr>
<td>Forensic med.</td>
<td>Arts &amp; humanities</td>
<td>Evolution</td>
<td>Build. &amp; public works</td>
<td>Systems &amp; contr. theory</td>
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<tr>
<td>Health econ.</td>
<td>Genetics</td>
<td>Information science</td>
<td>Information science</td>
<td></td>
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<tr>
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<td>Histology</td>
<td>Biomedicine</td>
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</tr>
<tr>
<td>Toxicology</td>
<td>Taxonomy</td>
<td>(no animal husbandry)</td>
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<tr>
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<td>Life cycles/develop.</td>
<td>(no odontology)</td>
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# Sources of Information for Selected Databases

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Databases

Vendors

- ProQuest DIALOG  http://www.dialog.com/
- OVID  http://www.ovid.com/
- EbscoHost  http://www.ebscohost.com

Additional Databases

Available on the Web

• NC3Rs Blood Sampling Microsite
  http://www.nc3rs.org.uk/bloodsamplingmicrosite/
• Best Practices for Common Procedures
  http://www.procedureswithcare.org.uk/
• Altweb
  http://altweb.jhsph.edu/
• AltBib: Bibliography on Alternatives to Animal Testing
Additional Databases

Available on the Web

- Animal Welfare Institute (AWI) Enrichment and Refinement Databases
  http://www.awionline.org/lab_animals/index.htm

- PrimateLit
  http://primatelit.library.wisc.edu/ (last updated November 30, 2010, but still useful)

- CCAC Three Rs Microsite
Additional Databases

Available on the Web

- AnimAlt-ZEBET
  http://www.dimdi.de/static/en/db/dbinfo/zt00.htm
- AltTox.org
  http://alttox.org/
- Go3R
  http://www.go3r.org/
- TSAR: Tracking System for Alternative test methods Review, Validation and Approval in the Context of EU Regulations on Chemicals
  http://tsar.jrc.ec.europa.eu/
Organizations

- Interagency Coordinating Committee for the Evaluation of Alternative Methods (ICCVAM) and its supporting center, NICEATM (the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods)
  

- European Centre for the Validation of Alternative Methods (ECVAM)
  

- Johns Hopkins Center for Alternatives to Animal Testing (CAAT)
  
  [http://caat.jhsph.edu/](http://caat.jhsph.edu/)
Organizations

- National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs)
  http://www.nc3rs.org.uk/

- Fund for the Replacement of Animals in Medical Experiments (FRAME)
  http://www.frame.org.uk

- Australian and New Zealand Council for the Care of Animals in Research and Teaching (ANZCCART)
  http://www.adelaide.edu.au/ANZCCART/

- **Norecopa** – Norwegian consensus platform for replacement, reduction and refinement of animal experiments
  - [http://oslovet.norecopa.no](http://oslovet.norecopa.no)
  - Film and Slide Shows: [http://film.oslovet.norecopa.no/](http://film.oslovet.norecopa.no/)
Searching for Alternatives:
Introduction to Search Strategies, Mechanics

3Rs
AWIC’s Approach to Meeting the Information Requirements

- Approach the search in two phases.
- Analyze the protocol to determine where alternatives might be used and for terminology.
- Decide where to go for the information.
  - Databases
  - Websites
- Link terminology appropriately for best search results.
- Evaluate the search results.
Searching for Alternatives

- Consists of three types of terms:
  - Scientific terms related to the research protocol;
  - Alternative (3Rs) terminology; and
  - Search terminology: Boolean operators, limits, truncations, years, types of materials…
Searching for Alternatives

Tips

• Description of protocol and area of study
• Species being used
• Organ systems involved
• Acronyms (CNS, BSE, MAb)
• Spelling (behavior, behaviour)
• Names of hormones, enzymes, CAS#, trade names (xylazine = rompun)
• Authors in the field including the PI
• Is the PI aware of any possible alternatives?
• Previous searches with keywords, years and databases searched
Searching for Alternatives

Search Strategy

Two Phases

• *Phase I*: Reduction and refinement - citations pertinent to PI’s field of study.

• *Phase II*: Replacement - use of nonanimal or alternative animal models.
Searching for Alternatives
Alternative Terms: *Refine and Reduce*

- analgesic or analgesia or painkiller
- technique or method or procedure
- anesthetic or anasthetic or anaesthetic
- monitor or evaluate or supervise
- restrain or immobilize or restrict
- positive reinforcement or animal training
- housing or facility or caging

*Note: Most search terms are obtained from the protocol and area of study.*
Searching for Alternatives

Alternative Terms: *Replacement*

- artificial or vitro or culture
- tissue or cell or organ
- insect or arachnid or invertebrate
- fish or mollusc or cephalopod
- simulation or digital image or interactive
- mannequin or manikin or model

*Animal Use Alternatives Thesaurus*

Searching for Alternatives
Terminology Examples

sedative    virtual surgery
animal testing alternative    virtual reality
environmental enrichment    cadaver
bacteria    plastinate
software    anxiolytic
cadaver    euthanasia
plastinate    pain or distress
anxiolytic    virus
video display    amphibian
welfare
well-being
assay
# Searching for Alternatives

## DIALOG Commands

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<tr>
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<th>Abbreviation</th>
<th>Example</th>
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<td>\textit{logoff}</td>
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<td>Ends the session</td>
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Searching for Alternatives
DIALOG Print Formats

Free (6) - Title and Publication Year
Short (8) - Title, Indexing, and Publication Year
Medium (3) - Bibliographic Citation
Long (7) - Bibliographic Citation and Abstract
Full (9) - Full Record
KWIC - Key Word in Context

*Note: Format Numbers are used in the type command.*

t s2/6/1-5 = type search set #2, title format, citations 1-5
Searching for Alternatives

DIALOG Commands

• **?** Truncation
  s behav? = behave, behaves, behaviour, behavior, etc.

• **OR** Select at least ONE word from set.
  s swine or pig or pigs or porcine

• **AND** Select more than one word from set.
  s swine and euthan?

• **NOT** Eliminates a search term or group of search terms.
  s (pig or pigs or swine or porcine) not guinea

• **TI,DE,ID** Limit terms to title, descriptors, or identifiers.
  s (dog or dogs or cani?)/ti,de,id  *use “/” before ti,de,id

Note: Use of parentheses is very important!
Searching for Alternatives

DIALOG Commands

- **(W)** With - Keep words adjacent and the order specified.
  
  s lethal\textit{(w)}dose = lethal dose
  
  s route\textit{(1w)}administration = route of administration

- **(N)** Near - Keep words adjacent but in either order.
  
  s blood\textit{(n)}sampl? = blood sample or sampling blood
  
  s blood\textit{(2n)}sampl? = blood sample, blood plasma sample, sampling of arterial blood
Alternatives Search Examples
Searching for Alternatives
Sample Search #1 - Osteomyelitis

Objective/Hypothesis
The environment of an open fracture can be manipulated in both a salutary and degratory fashion with respect to the establishment of acute osteomyelitis. L-fucose should decrease and arachidonic acid should increase the propensity toward infection in comparison with controls.
Searching for Alternatives
Osteomyelitis Search Background

Military Relevance

Contaminated trauma through open fractures due to high velocity missile wounds are common military combat injuries. An inexpensive method of prevention of chronic osteomyelitis would be useful in the field and hospital setting.
Searching for Alternatives
Osteomyelitis Search Information

Materials and Methods

- Animals: Albino Sprague-Dawley rats will be used.

- Bacteria: Strain SMH of *Staphylococcus aureus*. 
Searching for Alternatives
Osteomyelitis Search Information

Technical Methods

Pain Alleviation:
The rats will be anesthetized with a cocktail of 1.5 ml ketamine and 1.5 ml xylazine and 0.5 ml acepromazine given at a dosage of 0.5 to 0.7 ml/kg. If the plane of anesthesia is too light as determined by a positive toe pinch reflex, one half the original cocktail dose or isoflurane may be given. Buprenorphine will be given up to 3x/day if the animal shows signs of pain.
Establishment of infection

Tibia exposed and wound created in the bone with dental burr. Wound inoculated with *S. aureus* or *S. aureus* with L-fucose or arachidonic acid, allowed to incubate and rinsed with sterile saline. Wound is closed and animals sampled at various times to track development of osteomyelitic lesions.
Searching for Alternatives
Osteomyelitis Search Information

The search will be developed to find answers to questions such as:

• Are there alternatives to the painful or distressful procedures being employed in the research on the effects of L-fucose or arachidonic acid in the establishment of acute (trauma-induced) osteomyelitis caused by S. aureus in rats?

• Are there other animal models that may be more suitable for testing potential therapeutics or that more closely resemble the human condition?

• Is there useful information on the proposed model that might allow the use of fewer animals or might reduce the pain suffered by the animals?

• Are there any in vitro methods that might allow for early screening of potential therapeutics?

• Do the proposed anesthetics, analgesics, or α 2-adrenergic antagonist (yohimbine) pose a confounding influence on the outcome?

• Anything missing?
Searching for Alternatives
Osteomyelitis Search Strategy

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### Searching for Alternatives

**Osteomyelitis Search Strategy**

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<td>S4</td>
<td>RD (unique items)</td>
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Synergy of HBO2 and a local antibiotic carrier for experimental osteomyelitis due to Staphylococcus aureus in rats.
Mendel V; Simanowski H J; Scholz H Ch
Undersea & hyperbaric medicine - journal of the Undersea and Hyperbaric Medical Society, Inc Winter 2004, 31 (4) p407-16

A standard rat model of Staphylococcus aureus-induced osteomyelitis was used to compare the effect of HBO2, a local antibiotic carrier (gentamicin-containing collagen sponge) and the combination of HBO2 with a local antibiotic carrier. For the induction of osteomyelitis, a defined Staphylococcus aureus suspension was inoculated into the medullary cavity. Arachidonic acid was used as sclerosing agent. With that procedure an infection rate of more than 95 percent was attained.
Arachidonic acid facilitates experimental chronic osteomyelitis in rats.
Rissing JP; Buxton TB; Fisher J; Harris R; Shockley RK
Infect Immun (UNITED STATES) Jul 1985, 49 (1) p141-4

Arachidonic acid was used as a facilitating agent in experimental rat Staphylococcus aureus osteomyelitis and compared with the more commonly used agent, sodium morrhuate. The injection of arachidonic acid or sodium morrhuate and S. aureus into rat tibiae caused increased quantitative bacterial bone counts, gross bone pathology, roentgenographic changes, and weight loss. The doses required to produce these changes appeared to be lower for arachidonic acid.
Binding of a Staphylococcus aureus bone pathogen to type I collagen.
Buxton T B; Rissing J P; Horner J A; Plowman K M; Scott D F; Sprinkle TJ; Best G K
Microbial pathogenesis Jun 1990, 8 (6) p441-8.

We contrasted the collagen-binding potential of the experimental osteomyelitis pathogen, Staphylococcus aureus strain SMH, to several other strains. These included Cowan 1 (binder), Wood 46 (non-binder) and six capsular variants. These measurements were made using an 125I-collagen binding assay. These data suggest that the prototype bone pathogen binds to the major protein component of bone's extracellular matrix. Collagen-binding is promoted by protein adhesin(s), not capsule. The latter, in fact, appeared to interfere with this interaction. Binding was inhibited by solutions containing the simple monosaccharide, L-fucose.
# Searching for Alternatives

## Osteomyelitis Search Strategy

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The multifactorial nature of bone injuries in modern warfare and emergency trauma patients warrants enhancement of existing models. To develop a more appropriate model, rat tibiae (n = 195) were mechanically injured, divided into 2 groups (with or without thermal injury), and contaminated with a range of Staphylococcus aureus (Cowan 1) inocula. In some experiments, S. aureus inocula also contained Escherichia coli or foreign bodies (sand or soil). The primary outcome measure was the amount of S. aureus remaining in the tibia (tibial bacterial load) 24 h after contamination, reported as log(10) cfu/g bone. S. aureus showed ID50 and ID95 values of 72 and 977 cfu, respectively. Sand, added as a foreign body, increased tibial bacterial load. Combined mechanical and thermal trauma of the tibia is associated with increased S. aureus tibial bacterial loads, increasing the risk of acute osteomyelitis. Understanding the interplay of mechanical and thermal injuries, bimicrobial contamination, and foreign bodies may improve our understanding of traumatic bone injuries and the pathogenesis of osteomyelitis.

Subasi M; Kapukaya A; Kesemenli C; Kaya H; Sari I
Archives of orthopaedic and trauma surgery *( Germany )  2001 ,  121(3) p170-3.

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a cytokine that affects the various developmental steps of hematopoietic cells and enhances the phagocytic activity of these cells. The effect of GM-CSF on acute osteomyelitis, developed in rats, was investigated. For this purpose, osteomyelitis was firstly developed through the direct inoculation of Staphylococcus aureus into rat tibial metaphysis. Twenty-four rats in which diagnosis of osteomyelitis was histopathologically established were divided into two groups. Antibiotic only was given to the first group, and antibiotic as well as GM-CSF to the second group. Rats were followed up for 3 months with plain radiographs and scintigraphic methods using 67Ga-citrate.
A model was developed to identify and compare the local wound factors that induce acute osteomyelitis in a prospective, controlled investigation. When compared with wounds containing either virulent bacteria or dead bone, statistical analysis disclosed a significant increase in the incidence of osteomyelitis when virulent bacteria and dead bone were combined. The incidence of osteomyelitis in wounds containing an inoculated, hematoma-filled dead space was significantly less when compared with wounds containing dead bone and virulent bacteria. The incidence of osteomyelitis is significantly less when a nonvirulent strain of bacteria is substituted for a virulent strain. Although rigid internal fixation increased the incidence of osteomyelitis to 100% and long-term antibiotic therapy decreased the incidence, these changes were not statistically significant. These data allow the authors to predict the relative risk of osteomyelitis when these wound factors are present. The prevention of osteomyelitis depends on the clinical identification and modification of these local wound factors.
## Searching for Alternatives

### Osteomyelitis Search Strategy

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Daptomycin and Gentamicin Show Limited Activity in a Novel In Vitro Model of Osteomyelitis
Sweeney E (Reprint); Nelson S; Lovering A; Bowker K; Macgowan A
Washington, DC, USA 20081025,
*Sponsor: * Infect Dis Soc Amer
*ISSN: *0733-6373
*Document Type: * Meeting; Meeting Poster
*Record Type: * Citation
Searching for Alternatives
Osteomyelitis Search Strategy

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<tr>
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<td>S14 AND S15</td>
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Establishment of a real-time, quantitative, and reproducible mouse model of Staphylococcus osteomyelitis using bioluminescence imaging.

Funao, H., et al.

Department of Orthopaedic Surgery, School of Medicine, Keio University, Shinjuku, Tokyo, Japan.

Abstract

Osteomyelitis remains a serious problem in the orthopedic field. There are only a few animal models in which the quantity and distribution of bacteria can be reproducibly traced. Here, we established a real-time quantitative mouse model of osteomyelitis using bioluminescence imaging (BLI) without sacrificing the animals. A bioluminescent strain of Staphylococcus aureus was inoculated into the femurs of mice. The bacterial photon intensity (PI) was then sequentially measured by BLI. Serological and histological analyses of the mice were performed. The mean PI peaked at 3 days, and stable signals were maintained for over 3 months after inoculation. The serum levels of interleukin-6, interleukin-1β, and C-reactive protein were significantly higher in the infected mice than in the control mice on day 7. The serum monocyte chemotactic protein 1 level was also significantly higher in the infected group at 12 h than in the control group. A significantly higher proportion of granulocytes was detected in the peripheral blood of the infected group after day 7. Additionally, both acute and chronic histological manifestations were observed in the infected group. This model is useful for elucidating the pathophysiology of both acute and chronic osteomyelitis and to assess the effects of novel antibiotics or antibacterial implants.
(68)Ga-DOTAVAP-P1 PET imaging capable of demonstrating the phase of inflammation in healing bones and the progress of infection in osteomyelitic bones.


Abstract:
Differentiation between bacterial infection and nonbacterial inflammation remains a diagnostic challenge. Vascular adhesion protein 1 (VAP-1) is a human endothelial protein whose cell surface expression is induced under inflammatory conditions, thus making it a highly promising target molecule for studying inflammatory processes in vivo. We hypothesized that positron emission tomography (PET) with gallium-68-labeled 1,4,7,10-tetraazacyclododecane-N',N''',N'''''-tetraacetic acid-peptide targeted to VAP-1 ((68)Ga-DOTAVAP-P1) could be feasible for imaging the early inflammatory and infectious processes in healing bones.

MATERIALS AND METHODS:
Thirty-four Sprague-Dawley rats with diffuse Staphylococcus aureus tibial osteomyelitis and 34 rats with healing cortical bone defects (representing the inflammation stage of healing) were PET imaged using (68)Ga-DOTAVAP-P1 as a tracer. In addition, peripheral quantitative computed tomography and conventional radiography were performed. Bone samples for quantitative bacteriology and specimens were also processed for histomorphometry of inflammatory and infectious reactions. Quantitative bacteriology confirmed infection in all osteomyelitic animals in our study. Induced infection is primarily localized in the medullary area and its adjacent bone, thus minimizing the impact on the affect for the general well-being of the animal.

CONCLUSIONS:
The current study showed that PET imaging with the new (68)Ga-DOTAVAP-P1 is capable of accurately demonstrating the phase of inflammation in healing bones and the progress of bacterial infection in osteomyelitic bones. Consequently, this novel imaging agent allowed for the differentiation of bone infection due to S. aureus and normal bone healing as soon as 7 days after onset.

Animals, Disease Progression, Gallium Radioisotopes/diagnostic use*, Male, Organometallic Compounds/diagnostic use*, Osteitis/radionuclide imaging*, Osteomyelitis/radionuclide imaging*, Positron-Emission Tomography/methods*, Rats, Sprague-Dawley, Recovery of Function, Reproducibility of Results, Sensitivity and Specificity, Staphylococcal Infections/radionuclide imaging*
A different perspective for radiological evaluation of experimental osteomyelitis.

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INTRODUCTION:
Radiological scoring systems used in experimental osteomyelitis combine several factors into a single score. Because response of bone tissue to infection is a dynamic process, such systems have limited ability to differentiate between treatment groups. The analyzing of radiological criteria separately at different stages of the disease may be superior to a general score.

METHODS AND METHODS:
Osteomyelitis was induced with Staphylococcus aureus in the left tibiae of 72 adult Wistar albino rats. The rats were assigned to one of six different treatment groups. Their radiographs were graded (1) by the use of previously published general scoring systems and (2) by the evaluation of periosteal reaction, bone deformation, diaphyseal widening, osteolysis, soft tissue swelling, bone mineral content (BMC) and bone mineral density (BMD), separately. The assessments were performed 3 weeks after induction as well as 3 weeks and 6 weeks after treatment. RESULTS: Periosteal reaction and diaphyseal widening demonstrated significant differences within 3 weeks of treatment, contrary to the general scores. After 6 weeks of treatment, individual criteria, including diaphyseal widening, osteolysis and BMC but only one of the general grading scores, were able to differentiate between treatment groups. CONCLUSIONS:
For differentiation of treatments in experimental osteomyelitis individual assessment of radiological criteria is superior to previously published general scoring systems.
Group Exercise

Develop a search strategy for the following teaching protocol.

Goals:

1. Determine which databases and online resources to search
2. Determine the most appropriate search terminology to use
3. Determine the most appropriate strategy
4. Explain your process to the class
Dr. Stan Breager uses pigs and dogs in his advanced trauma life support training course. All procedures are conducted on anesthetized animals. When the training session is complete, all animals are euthanized. His IACUC has requested that he search for any potential alternatives to the use of animals.
Search Evaluation
The PI Role

• Check terminology, strategy, sources, and dates of search.
• Review the search before completing the protocol.
• Assess and evaluate the alternative possibilities.
• Be prepared to support the use or non-use of any alternatives in writing.
• Keep a copy of strategy, databases searched, and years of search for future use.
Search Evaluation
The IACUC Role

- Review the protocol form. Are the questions asked in a clear way to gather the information needed?
- Review the
  - Databases searched,
  - Terminology used *and*
  - Years of coverage.
- Review the search strategy.
- Ask about the order of search and protocol writing.
- Have an information provider on the committee as a resource.
Search Evaluation

Red Flags

• Search completed at the last minute.
• Only 1 database searched.
• Terms only for painful aspects.
• The term “alternative” used alone with no other alternative terms.
• Keywords listed not relevant to protocol.
• Keywords and concepts linked in an incorrect manner (e.g. wrong Boolean operators).
• Search doesn’t cover adequate time period (5-10 years).
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