

Regulatory and Ethical Oversight in Animal Research

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OVERVIEW

Public accountability

Regulatory Oversight: Federal, Baylor College of Medicine

Ethical Consideration: Culture of Care

Moral mandate: Reduce numbers, Replace with other methods, Refine – eliminate pain/distress

Animal rights/liberation movements:

Common political aim – eliminate all human use of animals;

Philosophical principles behind movements: Utilitarianism, Intuitionism, Capabilities Approach; Animal Personhood

Questions:

- How many use animals in medical research?
- How many plan to use parts (tissues, cells) from animals?
- How many have read the animal research protocol allowing animal use in your labs?
- How many have helped write an animal research protocol to submit to the IACUC?
- Why and for what purpose is an IACUC? What powers does it have?
- What regulations govern animal research?
- Does anyone want to challenge the concept that some animals are needed in medical research?
- Should animal research be banned?

Reality at Baylor College of Medicine

Office of Research

- Approximately 100,000 cages
- 300,000 animals - very expensive
- Husbandry (80+) staff, (5+) vet techs, (5+ vets)
- IACUC and office (3+)

Regulations

- USDA Animal and Plant Health Inspection Service (APHIS) - Higher species than mice/rats
- Animal Welfare Act Regulations 1966, 1970, 1976, 1985
- “The GUIDE” – first published 1963, supported by NIH
- Public Health Service (PHS)
 1. Health Research Extension Act, 1985 → public accountability/self regulation
 2. Office of Laboratory Animal Welfare (OLAW) any vertebrate animals (mouse, rat, amphibian, reptiles, fish)
- AAALAC International
- Baylor College of Medicine - assurances, IACUC, record keeping, reporting, grant submission, animal care

Guide for the Care and Use of Laboratory Animals

REGULATIONS, POLICIES, AND PRINCIPLES (SUMMARY)

- Design and performance of procedures on the basis of relevance to human or animal health, advancement of knowledge, or the good of society.
- Use of appropriate species, quality, and number of animals.
- Avoidance or minimization of discomfort, distress, and pain in concert with sound science.
- Use of appropriate sedation, analgesia, or anesthesia.
- Establishment of experimental end points.
- Provision of appropriate animal husbandry directed and performed by qualified persons.
- Conduct of experimentation on living animals only by or under the close supervision of qualified and experienced persons.

ANIMAL CARE AND USE PROTOCOLS

- Rationale and purpose of the proposed use of animals.
- Justification of the species and number of animals requested. Whenever possible, the number of animals requested should be justified statistically.
- Availability or appropriateness of the use of less-invasive procedures, other species, isolated organ preparation, cell or tissue culture, or computer simulation.
- Adequacy of training and experience of personnel in the procedures used.
- Unusual housing and husbandry requirements.
- Appropriate sedation, analgesia, and anesthesia.
- Unnecessary duplication of experiments.
- Conduct of multiple major operative procedures.
- Criteria and process for timely intervention, removal of animals from a study, or euthanasia if painful or stressful outcomes are anticipated.
- Postprocedure care.
- Method of euthanasia or disposition of animal.
- Safety of working environment for personnel.

Guide for the Care and Use of Laboratory Animals cont.

**ANIMAL ENVIRONMENT, HOUSING MANAGEMENT:
FACTORS TO BE CONSIDERED**

- **Species, strain, breed/sex, age, size, behavior, experiences, health**
- **Social group thru sight, smell, single or groups**
- **Design and construction**
- **Suitable enrichments**
- **Ventilation, food, water, illumination, noise**
- **Secure and injury-free site**
- **Goals of project (breeding, testing, teaching, etc.)**

VETERINARY MEDICAL CARE

- **Preventive medicine (physiologic, psychologic, nutritional stabilization)**
- **Diagnosis, treatment, control of disease**
- **Management of protocol-associated disease, disability**
- **Anesthesia, analgesia**
- **Surgery and postsurgical care**
- **Assessment of animal well-being**
- **Euthanasia**

Background Reading

Cohen, C. The Case for the Use of Animals in Biomedical Research. *N. Engl J Med*, 315:865-870, 1986.

Fox, M.A. The Case for Animal Experimentation: An Evolutionary and Ethical Perspective. Berkeley: University of California, 1986.

Regan, T. The Case for Animal Rights. Berkeley: The University of California, 1983.

Singer, P. Animal Liberation, 2nd Edition., New York: Random House, 1990.

Vance, R.P. An Introduction To The Philosophical Presuppositions of the Animal Liberation/Rights Movement. *JAMA*, 268:1715, 1992.

Nussbaum, M. Justice for Animals. The Chronicle of Higher Education Review. Section B6-B8; February 3, 2006.

Glenn, L. When Pigs Fly? Legal and Ethical Issues in Transgenics and the Creation of Chimeras. The Physiologist: 46(No. 5): 251-255, 2003.

Michael, S. Animal Personhood – A Threat to Research? The Physiologist: 47 (No. 6): 47-50, 2004.

Government Publications

Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council, *Guide for the Care and Use of Laboratory Animals*, Washington, DC: National Academy Press; 1996.

Comment: A copy of this publication is available on the National Academy Press website at www.nap.edu/readingroom/books/labrats/

US Department of Health and Human Services (USDHHS), Centers for Disease Control (CDC) and Prevention, and National Institutes of Health (NIH), *Biosafety in Microbiological and Biomedical Laboratories (BMBL)*, 4th ed. Washington, DC: US Government Printing Office; 1999.

Comment: A copy of the BMBL is available on the CDC website at www.cdc.gov/od/ohs/biosfty/bmb14/bmb14toc.htm

Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council, *Occupational Health and Safety in the Care and Use of Research Animals*, Washington, DC: National Academy Press, 1997.

Federal Laws and Regulations

Animal Welfare Act – Public Law 89-544, 1966, as amended, (PL 91-579, PL 94-279 and PL 99.198) 7 U.S.C. 2131 et seq.

Comment: Implementing regulations are published in the Code of Federal Regulations (CFR), Title 9, Chapter 1, Subchapter A, Parts 1, 2, and 3, and are administered by the U.S. Department of Agriculture.

Public Health Service (PHS) Policy on Human Care and Use of Laboratory Animals. Office of Laboratory Animal Welfare (OLAW), National Institutes of Health, Office of Extramural Research, Bethesda, MD amended August, 2002.

Comment: A reprint of this publication is available on the NIH website at <http://grants.nih.gov/grants/olaw/references/phspol.htm>. The document also includes the Health Research Extension Act of 1985, Public Law 158, “Animals in Research” (November 20, 1985), which provides the statutory mandate for the PHS policy, and the US Government Principles of the Utilization and Care of Vertebrate Animals Used in Testing, Research and Training (US Principles). The US Principles were incorporated into the PHS Policy in 1986.

Institutional Animal Care and Use Committee

<https://intranet.bcm.edu/?fuseaction=home.showpage&tmp=/research/oor/iacuc/home>

[Mandatory Training \(BRAIN eCAT\)](#)

[FAQ for Species-Specific Laboratory Animal Online Training](#) [.pdf]

[BCM Guidelines for Animal Care and Use](#)

[BCM Animal Care and Use Handbook](#) [.pdf]

[IACUC Manual](#)

[Documents Needed for Grant Submissions](#)

[Meeting Dates](#)

[Issues Contact List](#) [.pdf]

As a national leader in advancing human health, Baylor College of Medicine (BCM) regards the use of animals in research, teaching and testing to be an essential component for continued progress in gaining scientific knowledge. Adherence of BCM researchers to the highest animal welfare standards and guidelines for animal use in research ensures continued public support and trust.

To assist researchers in complying with federal laws and regulations governing the use of animals in research, teaching and testing and to fulfill its legal obligation, BCM has established an Institutional Animal Care and Use Committee (IACUC) and an IACUC Office. The IACUC provides guidance on animal use, oversees the animal care and use program, and ensures compliance with applicable laws, regulations, and policies.

The Principal Investigator is responsible for ensuring that all personnel listed on an animal protocol have completed the required species specific training module(s) found in the Mandatory Training in the [BRAIN](#) - Electronic Certification and Training (eCAT).

For more information see the FAQs on this page.



BCM Guidelines for Animal Care and Use

https://intranet.bcm.edu/?fuseaction=home.showpage&tmp=/research/oor/animalcare/iacuc_animalpro

- [Rodent – Feeding on the Cage Floor](#) [.pdf]
- [Post-Operative Monitoring of Animals](#) [.pdf]
- [Isoflurane use in Anesthetic Chambers for Rodents](#) [.pdf]
- [Guidelines for Maintaining Mouse Cage Populations](#) [.pdf]
- [Death as an Endpoint](#) [.pdf]
- [Guidelines for Developing Humane Endpoints](#) [.pdf]
- [Guidelines for Toe Clipping](#) [.pdf]
- [Clipping of Mouse and Rat Tail Tissue](#) [.pdf]
- [Counting of Rodents](#) [.pdf]
- [Guidelines for Survival Bleeding of Mice and Rats](#) [.pdf]
- [Guidelines for Justifying Wire Bottom Cage Use for Rodents](#) [.pdf]
- [Guidance on Restraint of Animals](#) [.pdf]
- [Guidelines for Food and Water Restriction](#) [.pdf]
- [Guidelines for Research Projects that Include Multiple Survival Surgery](#) [.pdf]
- [Subcutaneous Tumor Burden in Mice and Rats](#) [.pdf]
- [Removal of Wound Clips or Skin Sutures for Embryo Transfer Recipients](#) [.pdf]
- [Euthanasia and Anesthesia of Late Term Rodent Embryos](#) [.pdf]
- [Euthanasia of Rodents, Rabbits, Fish, Amphibians and Reptiles](#) [.pdf]
- [Euthanasia of Neonatal Rodents – Mice, Rats and Hamsters](#) [.pdf]
- [Terminal Blood Collection for Rodents and Rabbits](#) [.pdf]
- [Environment Enrichment Program for Singly Housed Rodents](#) [.pdf]
- [Analgesic Treatment of Rodents Undergoing Major Survival Surgery](#) [.pdf]
- [Study Areas and Satellite Facilities for Research Animals](#) [.pdf]
- [Anesthesia and Euthanasia of Frogs](#) [.pdf]
- [Multiple Oocytes Collections from Frogs](#) [.pdf]
- [Use Guidelines for Expired Drugs, Medical Materials, and Non-Pharmaceutical-Grade Compounds](#) [.pdf]

[Institutional Animal Care and Use Committee](#)

[Animal Care Forms](#)

[TMF Training](#)

Guidelines for Developing Humane Endpoints

PHS Policy

From the Public Health Service (PHS) policy on Humane Care and Use of Laboratory Animals, [U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training](#):

- Proper use of animals, including the avoidance or minimization of discomfort, distress, and pain when consistent with sound scientific practices, is imperative
 - Unless the contrary is established, investigators should consider that procedures that cause pain or distress in human beings may cause pain or distress in other animals
 - Procedures with animals that may cause more than momentary or slight pain or distress should be performed with appropriate sedation, analgesia, or anesthesia
 - Surgical or other painful procedures should not be performed on unanesthetized animals paralyzed by chemical agents
 - Animals that would otherwise suffer severe or chronic pain or distress that cannot be relieved should be painlessly killed at the end of the procedure, or if appropriate, during the procedure
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Definition of “endpoint”

The term “endpoint” is defined as the point at which an experimental animal’s pain and/or distress is terminated, minimized or reduced, by taking actions such as:

- Killing the animal humanely
 - Terminating a painful procedure
 - Giving treatment to relieve pain and/or distress
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BCM IACUC guidelines

Defining endpoints (termination of animals and/or experimental procedures) for studies that have the potential to result in severe or chronic pain or distress should be part of the consultation process between the principal investigator and the institutional veterinarian.

- The investigator should include clearly defined endpoints for such studies in their protocol submitted to the IACUC for review
 - The committee requires the following for research proposals that include death as an endpoint:
 - Written scientific justification, including discussion of alternative endpoints
 - Justification of the numbers of animals to be included
 - Justification for non-use of analgesics if this is so
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Guidelines for Developing Humane Endpoints, *Continued*

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- Default endpoints** The IACUC has adopted default endpoints which are applied **only if** investigators do not delineate and adequately justify alternative endpoints (see Default Endpoint List below).
- These default endpoints are not necessarily consistent with pain and distress free research
 - In the preparation of applications to the IACUC, investigators are encouraged to develop earlier, more refined endpoints that avoid or minimize discomfort, distress and pain to the animals and that are compatible with experimental objectives

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- Default endpoint list** Default endpoints for laboratory animals including non-human primates, dogs, cats, pigs, sheep, goats, rabbits and rodents are as follows:
- Loss of 20% of body weight from baseline weight when assigned to the protocol. A growth nomogram must be used to adjust the basal weight for growing animals.
 - Major organ failure
 - Medical conditions unresponsive to treatment such as:
 - Respiratory distress
 - Icterus
 - Uremia
 - Intractable diarrhea
 - Self-mutilation
 - Persistent vomiting
 - Surgical complications unresponsive to immediate intervention:
 - Bleeding
 - Vascular graft/circulation failure
 - Infection
 - Wound dehiscence
 - Non-rodent animals that have complete anorexia for 3 days
 - Clinical or behavioral signs in rodents or rabbits unresponsive to appropriate intervention (see Abnormalities below)
 - Abnormalities would include:
 - Inactivity
 - Labored breathing
 - Sunken eyes
 - Hunched posture
 - Piloerection/mattered fur
 - One or more unresolving skin ulcers
 - Abnormal vocalization when handled
 - Tumors that affect normal function or that become ulcerated or that exceed designated size (1.5 cm for mice, 2.0 cm for rats, see [Tumor Burden in Mice and Rats](#))
 - Anorexia

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Guidelines for Developing Humane Endpoints, *Continued*

Useful links

- Defining an Acceptable Endpoint in Invasive Experiments, AWIC
<http://www.nal.usda.gov/awic/newsletters/v6n1/6n1olfer.htm>
- Endpoints in Animal Study Proposals, NIH
<http://www.nal.usda.gov/awic/pubs/IACUC/pain.htm#end>
- Canadian Council on Animal Care Guidelines on: Choosing an Appropriate Endpoint in Experiments Using Animals in Research Teaching and Testing
<http://altweb.jhsph.edu/meetings/pain/wong.htm>
- Humane Endpoints for Animals used in Biomedical Research and Teaching, ILAR Journal
http://dels.nas.edu/ilar_n/ilarjournal/41_2/index.shtml
- Endpoints in Infectious Disease Models
<http://altweb.jhsph.edu/meetings/pain/olfert.htm>

Date of Last Revision/Review 0609/09

Subcutaneous Tumor Burden in Mice and Rats

Guidelines

There are experimental procedures that require tumor burdens.

The following are specific guidelines recommended by the IACUC with regard to tumor burden in rats and mice:

Item	Recommended Guidelines
1	The maximum tumor burden on any one animal should not exceed an estimated 10% of the animal's body weight.
2	The maximum measurable <u>total tumor burden for a solitary mass</u> on any one animal should not exceed a mean diameter of: <ul style="list-style-type: none"> • 1.5 centimeters on a mouse • 2 centimeters on a rat
3	The total tumor burden for multiple masses on any one animal should be calculated by summation of all measurable masses. The maximum measurable <u>total tumor burden for multiple masses</u> on any one animal should not exceed a combined mean diameter for the sum of all masses of: <ul style="list-style-type: none"> • 1.5 centimeters for mice • 2 centimeters for rats
4	A written scientific justification must be submitted with the protocol and approved by the IACUC if an investigator: <ul style="list-style-type: none"> • Requires tumor burdens larger than those specified above • Expects tumors to be partially necrotic and/or ulcerated
5	Investigators should promptly euthanize animals at the committee-approved end points for their protocols.

Tumor position

When injecting cells subcutaneously into mice or rats, the tumor position should be placed at sites that will not compromise the animal's mobility.

Example: Backs and flanks are preferred sites

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Subcutaneous Tumor Burden in Mice and Rats, *Continued*

Monitoring schedule

The monitoring schedule depends on the tumor growth rate as follows:

If growth rate is...	Then...
Predictable	The PI should provide: <ul style="list-style-type: none"> • Data on tumor growth • A monitoring schedule
Not known	The PI should provide a monitoring schedule. Recommendations are as follows: <ul style="list-style-type: none"> • Monitor three times weekly until a palpable tumor nodule is present (0.5-0.75 cm in diameter) • Daily thereafter • If tumor growth is rapid in the few days before termination, twice daily monitoring should be considered

Related standards

USDA 2.32 (a) and (b)
 The Guide
 PHS policy C.1.a.b.f

Date of Last Revision/Review: 12/22/10

Environment Enrichment Program for Singly Housed Rodents

Past designs	<p>Environments of laboratory animals have often been designed on the basis of economic and ergonomic aspects, with less consideration for animal welfare.</p> <p>Result: Laboratory housing conditions can deprive animals the possibility of performing a full repertoire of normal behavior.</p>
Definition: Environmental enrichment	<p><i>Environmental enrichment</i> can be defined as altering the living environment of captive animals in order to provide opportunities to express more of their natural behavioral repertoire.</p>
Advantages	<p>The living conditions and therefore the well-being of captive animals can be improved through environmental enrichment.</p> <p>Allowing animals to perform the widest possible range of behaviors has been shown to reduce stereotypic behavior in captivity.</p>
Background	<p>To meet expectations of legal, regulatory, and accrediting bodies, as well as to better serve the research community, the Institutional Animal and Use Committee (IACUC) has implemented this enrichment program for rodents.</p> <p>To address this housing issue, the IACUC, in consultation with CCM, voted to provide nestlets and/or other appropriate objects such as cardboard rolls to enrich all singly housed rodents.</p> <p>Result: CCM provides nestlets and cardboard rolls at no extra charge and includes a nestlet or roll with each cage change carried out by CCM.</p>
Policy	<p>The environmental enrichment policy follows:</p> <ul style="list-style-type: none"> • Whenever possible, rodents should be housed socially in compatible groups. • Researchers must provide nestlets or rolls as follows: <ul style="list-style-type: none"> – To individually housed rodents – In some circumstances, such as breeding and excessive barbering
Applicability	<p>The environmental enrichment program for singly housed rodents also applies to rodents housed in study areas and satellite facilities.</p>
Nesting	<p>Rodents build nests in the wild.</p>
Justification	<p>Providing nesting material to laboratory rodents is:</p> <ul style="list-style-type: none"> • A relatively simple, cost effective measure that addresses both activity and structural enrichment • Acceptable to accrediting agencies as environmental enrichment to individually housed rodents
Exception	<p>An investigator must fill out a Special Care Instruction Form (SCIF) if he/she does not wish singly housed rodents to participate in the enrichment program.</p>

Philosophical/Ethical Considerations: Defining Our Relationship with Animals

Utilitarianism:	Bentham/Singer	Equal Consideration - Animal Liberation
Intuitionism:	Moore/Regan	Inherent Value – Basic Moral Rights
Capabilities Approach	Nussbaum	Opportunity for Animals to Flourish In Own Way with Dignity
Animal Personhood Property/Legal Issues:	Glenn, Steve Michael	Grant Living, Sentient Beings, Greater Moral Recognition and Legal Status