

**Institutional Animal Care and Use Committee
Policy #19
Humane Endpoints regarding Severe or Chronic Pain or Distress**

In concurrence with
TTUHSC El Paso Assurance #D19-01056
and Federal Regulations and Guidelines

This policy provides a guideline of default endpoints for animal research studies, for use by Principal Investigators (PIs) and project personnel, when either anticipated or unanticipated, severe or chronic pain or distress occurs. The PI should identify and justify alternative endpoints in a protocol application. The default endpoints below can be used for protocols that have the potential for pain and distress. If an animal research study involves death as an endpoint, the PI shall include the information required by Section C below in his/her protocol application.

Definitions

Experimental Endpoint: This occurs when the scientific aims and objectives have been reached.

Humane Endpoint: The point at which pain and distress is prevented, terminated, or relieved in an experimental animal.

Moribund: The point at which an animal is in the state of dying. This is frequently seen as an inability to right; hypothermia, unresponsive, unable to walk or some combination thereof.

Death as an Endpoint: Study that requires an animal to die without benefit of intervention or humane euthanasia.

A. Humane Endpoints

Humane endpoints are those endpoints that will remove an animal from a study before the experimental endpoint has been reached. Humane endpoints refer to one or more predetermined physiological or behavioral signs that define the point at which an experimental animal's pain and/or distress is terminated, minimized or reduced by taking actions such as euthanizing the animal, terminating a painful procedure or giving treatment to relieve pain and/or distress. Humane endpoints function as an alternative to death as an endpoint and provide investigators with an effective way to refine their research. The establishment of humane endpoints prior to the start of an experiment allows the investigator to prevent unnecessary animal pain and distress while ensuring accurate and timely data collection.

To be effective, humane endpoints must be clearly defined and based on objective criteria. Non-specific signs of illness such as inactivity, hunched posture or a rough coat are an indication that an animal should be examined more closely. Familiarity with the animal model in use is necessary to select endpoints that are both humane and scientifically sound. As experience with and data collected from a specific animal model accrue, endpoints can be refined or modified. Humane endpoints should be specific to the condition being studied. For examples, see the scoring sheets at the end. While every study does not need a scoring sheet, you can see how these sheets reflect possible clinical conditions and are relevant to the condition being studied.

B. Default Endpoints

Unless a PI identifies and adequately justifies alternative endpoints and the IACUC approves them, endpoints for laboratory animals, including, but not limited to, nonhuman primates, dogs, cats, pigs, sheep, goats, rabbits and rodents, will be triggered by any of the following conditions:

1. 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.



2. Organ failure or major medical conditions that are unresponsive to treatment such as respiratory distress, icterus (jaundice), uremia (loss of renal function), intractable diarrhea, self-mutilation or persistent vomiting.
3. Surgical complications that are unresponsive to immediate intervention; i.e. bleeding, vascular graft/circulation failure, infection, and wound dehiscence (rupture of sutures).
4. Rodents that have complete anorexia for 2 days or non-rodents that display anorexia for 4 days.
5. Other clinical or behavioral signs in rodents or non-rodents that are unresponsive to appropriate intervention. In the case of rodents, these are defined as abnormalities persisting for 24 hours and for non-rodents, for 48 hours.

Abnormalities would include:

- | | |
|----------------------------|--|
| a. inactivity | f. one or more unresolving skin ulcers |
| b. labored breathing | g. abnormal vocalization when handled |
| c. sunken eyes | h. tumors that affect normal function or that become ulcerated |
| d. hunched posture | i. persistent coughing |
| e. piloerection/matted fur | j. excessive scratching or inability to rest due to dermal changes |

The circumstances described above represent a conservative minimum and are not necessarily consistent with pain-and-distress-free research. In his/her protocol applications, the PI must identify endpoints that avoid or minimize discomfort, distress and pain to the animals and that are compatible with experimental objectives.

Appendix 1 and 2 provide examples of alternative assessments that may be used to establish humane endpoints in specific IACUC protocols, depending on how the experimental model affects animal physiology.

If the LARC or laboratory staff identify an animal that displays any of the behaviors described above, the LARC or laboratory staff shall immediately report their observations to the PI and the Institutional Veterinarian (IVet). If the PI identifies an animal as having any of the behaviors described above, he/she shall immediately follow this policy and euthanize the animals, unless an exception to these criteria has been approved in the IACUC protocol. If an animal has any of the endpoints identified above and the PI feels that the animal should not be euthanized, the IVet should be consulted immediately. In this circumstance the IVet will make the final, clinical decision regarding the need to euthanize the animals.

C. Institutional Endpoints

The IACUC upholds statements put forth by the PHS Policy, AWA Regulations and The Guide, regarding the care and use of animals, especially those that may experience pain and distress. Animals must not be allowed to suffer beyond the point where justifiable scientific objectives have been achieved. The IACUC requires very thoughtful scientific rationale and planning for the use of death as an endpoint in studies that cause morbidity, moribundity and mortality. If the protocol involves death as an endpoint, the following shall be included:

Scientific Justification:

1. What specific set of circumstances requires death, what alternatives were considered, and how alternatives will be used whenever possible.
2. Why efforts to relieve pain and/or distress cannot be used.
3. Why the number of animals proposed is the minimum necessary to achieve scientific objectives.
4. What information will be gained by allowing death as an endpoint.
5. Has the LARC veterinarian been consulted on alternatives to death as an endpoint? If not, please do so.
6. Explain why morbidity as an endpoint cannot be used.

Plan:



1. Personnel are trained to recognize signs of morbidity and moribundity of animals on study.
2. Written monitoring records are kept current and available to veterinary staff and IACUC.
3. Monitoring of animals increases with level of morbidity and does NOT stop during weekends or holidays.
4. The veterinarian is promptly notified when animals show signs of morbidity and moribundity that were unexpected, or of greater intensity or duration than those described in the animal protocol.

References

1. Silverman, et al. *The IACUC Handbook*. 3rd edition. CRC press. p. 386.
2. Canadian Council on Animal Care, "Guidelines on: Choosing an appropriate endpoint in experiments using animals for research, teaching and testing". http://www.ccac.ca/Documents/Standards/Guidelines/Appropriate_endpoint.pdf
3. Toth. "Defining the Moribund Condition as an Experimental Endpoint for Animal Research." *ILAR Journal*. 41(2) January, 2000, p. 72.

Appendix I. Example Scoring Systems for Humane Endpoints

The following system parameters should be assessed in the order listed in the table. Evaluation of behavior and neurologic signs requires minor handling. Hydration and weight loss require manipulation of the mice. Care should be taken when manipulating animals with significant compromise.

Clinical scoring system for tumor implantation mice (cranial injection)

Parameter	Description	Score	Category score
Appearance	Normal, sleek appearance	0	
	Scruffy, unkempt	1	
	Scruffy, hunched	2	
Behavior	Normal, active	0	
	Hyperactivity, aggression	1	
	Reduced activity, active when provoked	1	
	Reluctant to move ^a	2	
	Delayed righting response ^b	3	
	Absent righting response	HEP	
Neurologic (scores in this category are additive)	Decreased grip strength ^c	1	
	Clasp response ^d	1	
	Ataxia	2	
	Circling	3	
	Paralysis	HEP	
	Seizure activity	HEP	
Hydration	Normal	0	
	Clinical dehydration	2	
Weight loss	None	0	
	<5%	1	
	5-10%	2	
	10-15%	3	
	>15%	HEP	
Other	Cranial deformity >1cm ^e	HEP	
Total Score			See below

Scoring:

- Reluctant to move**—mouse is easily restrained from the cage floor. Reduced flee response when gloved hand is placed around the mouse.
- Delayed righting response**—the righting response assesses both motor coordination and vestibular function. The mouse is placed in a supine position and the time taken to right (all four limbs placed under the body) is assessed. Normal mice will immediately turn over. Delay to righting of >2sec should be scored as 3.
- Decreased grip strength**—mouse is held at the base of the tail, lowered towards the cage hopper and allowed to grasp the wire bars. The mouse is gently pulled backwards to test ability to maintain grip on the wire bar. Abnormal mice do not grasp the bars or are easily displaced (weak).
- Clasp response**—The mouse is suspended by the base of the tail. Normal mice will elevate the head and extend the limbs in an attempt to place the feet (especially when lowered towards a surface). Abnormal mice clasp the forelimbs, pelvic limbs or both.
- Cranial deformity**—for tumors that result in deformity of the cranium, the distance between the bases of the ears is measured. Significant enlargement in the vertical plane will also be considered an endpoint.

Interventions:

HEP = humane endpoint (euthanasia required)

0-2 = Normal, monitor daily

3-6 = Monitor twice daily, contact veterinarian for treatment options




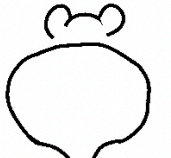

>6 = Euthanasia

If category score for any one category is 3 or more, contact veterinarian for treatment options.

Appendix 2.

Body Condition Scoring for demonstration purposes

(Ullere-Cullere, MH, *Laboratory Animal Science*, **49**, 319 (1999))

	<p>BC 1</p> <p>Mouse is emaciated.</p> <ul style="list-style-type: none"> ◦ <i>Skeletal structure extremely prominent; little or no flesh cover.</i> ◦ <i>Vertebrae distinctly segmented.</i>
	<p>BC 2</p> <p>Mouse is underconditioned.</p> <ul style="list-style-type: none"> ◦ <i>Segmentation of vertebral column evident.</i> ◦ <i>Dorsal pelvic bones are readily palpable.</i>
	<p>BC 3</p> <p>Mouse is well-conditioned.</p> <ul style="list-style-type: none"> ◦ <i>Vertebrae and dorsal pelvis not prominent; palpable with slight pressure.</i>
	<p>BC 4</p> <p>Mouse is overconditioned.</p> <ul style="list-style-type: none"> ◦ <i>Spine is a continuous column.</i> ◦ <i>Vertebrae palpable only with firm pressure.</i>
	<p>BC 5</p> <p>Mouse is obese.</p> <ul style="list-style-type: none"> ◦ <i>Mouse is smooth and bulky.</i> ◦ <i>Bone structure disappears under flesh and subcutaneous fat.</i>

A "+" or a "-" can be added to the body condition score if additional increments are necessary (i.e. ...2+, 2, 2-...)