POLICY

The experimental endpoint of a study occurs when the scientific aims and objectives have been reached. This involves the euthanasia or other final disposition at a predetermined endpoint, even when the animals may be clinically healthy. The humane endpoint is the point at which pain or distress in an animal is prevented, terminated, or relieved.

Animals that become ill, debilitated, or experience unrelieved pain or distress, either as a result of spontaneous disease or as a result of experimental procedures, must be provided standard veterinary treatment or be immediately euthanized, unless doing so would interfere with, or compromise the scientific goals of the experiment. Withholding pain relief (treatment or euthanasia) is only permitted if specifically reviewed and approved by the IACUC.

In the event that an animal is found to be exhibiting clinical signs of disease, illness, or unrelieved pain or distress that has not been documented and justified in the approved protocol, reasonable attempts will be made to contact the PI for consultation. If the PI is unavailable, the Attending Veterinarian (AV) or designee has the authority to use appropriate treatment measures including euthanasia if necessary.

The criteria below are clinical signs of illness or disease that indicate a humane endpoint has been reached. Exceptions to the following endpoints are only approved by the IACUC as part of the protocol review process.

Humane Endpoints: The following clinical signs of illness or disease, that constitute a humane endpoint include, but are not limited to:

- **Weight loss**: Loss of 20% body weight compared to the pre-study weight or to age-matched controls. With some disease processes or in growing animals, body weight is a poor indicator, thus body condition (e.g. muscle atrophy or emaciation is more useful).
- **Inappetance**: Complete anorexia for 24 hours in small rodents. Up to 5 days in large animals. Inappetence may be "normal" for immediate post-surgical patients. Partial anorexia (less than 50% of caloric requirement) for 3 days in small rodents; 7 days in large animals.
- **Inability to obtain feed/water**: Inability to ambulate to reach food or water; lesions that interfere with eating or drinking or reluctance to stand which persists for 24 hours.
- **Infection**: Infection involving any organ system (either clinical infection, or indicated by fever or WBC parameters) which fail to respond to antibiotic therapy within an appropriate time and is accompanied by systemic signs of illness.
- **Tumors**: Tumors which interfere with ability to eat, drink, or move normally. Tumors that exhibit necrosis, ulceration, and/or infection. Tumors that exceed 2 cm in any direction in mice or 4 cm in any direction in rats. Tumors that interfere with a vital physiological functions such as respiration, mastication, swallowing, urination, and/or defecation regardless of size of the tumor.
- **Marked change in behavior/depression**: Lethargy, abnormal vocalization, aggression, recumbency, rough hair coat/hunched posture. Excessive porphyrin staining at the eyes and/or nostrils (rats).
- **Fluid accumulation in body cavities/subcutaneous tissue**: Distended abdomen in conjunction with other clinical signs or conditions that lead to debilitation (e.g neoplasia, liver failure)
- **Signs of severe organ system dysfunction**: Non-responsive to treatment or with a poor prognosis as determined by a clinical veterinarian. Examples include but are not limited to:
  - **Respiratory**: labored breathing, cyanosis, persistent coughing
• **Cardiovascular**: marked dehydration, blood loss or anemia, bleeding from any orifice, cardiac failure
• **Gastrointestinal**: severe vomiting or diarrhea, rectal prolapse
• **Urogenital**: renal failure, urinary tract obstruction, penile prolapse
• **Neurological symptoms**: e.g. circling, head tilt, seizures, paresis, paralysis,
• **Musculoskeletal**: muscle damage or bone fracture resulting in inability to use limb, muscle atrophy
• **Integumentary**: non-healing wounds, repeated self-trauma, progressive dermatitis

**Moribund state** (in a dying state; in a clinically irreversible condition leading inevitably to death): extreme depression, body temperature significantly below normal, nonresponsive or unconscious with no response to external stimuli such as handling or the toe-pinch withdrawal test.

**Death as an Endpoint**

While it is preferable to use the earliest endpoints compatible with the scientific requirements of each study, there are studies that require moribundity or death as an endpoint. In these studies, animals are permitted to continue in a moribund state or die, as a result of the experimental procedures. The continuation of an experimental study to the point where an animal dies without the benefit of intervention or euthanasia is not acceptable without strong scientific justification and review and approval by the IACUC.

**REGULATIONS**

**The Guide for the Care and Use of Laboratory Animals**, ILAR, NAS, Eighth Edition 2011, pg 27

**Experimental and Humane Endpoints**

**The Public Health Service (PHS) Policy**, 2015, IV.C. 1a.”Procedures with animals will avoid or minimize discomfort, distress and pain to the animals, consistent with sound research design”. IV. C. 1e “Medical care for animals will be available and provided as necessary by a qualified veterinarian.”

**U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training, IRAC, 1985, Principle IV** “Proper use of animals, including the avoidance or minimization of discomfort, distress, and pain when consistent with sound scientific practices, is imperative.” **Principle VI.** “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.”

**PROCEDURE**

1.0 To obtain IACUC approval for exceptions to the above defined endpoints, provide the following on the IACUC form:
   1.1 Indicate which of the criteria for which that you are requesting an exception.
   1.2 Scientific justification for the requested exception.
   1.3 Supportive care that will be given to minimize discomfort, distress, or pain.
   1.4 The endpoint that will be used for euthanasia.

2.0 To obtain IACUC approval for use of moribundity or death as an endpoint, provide the following on the IACUC form:
   2.1 Why morbidity (i.e., affected with disease and illness) as an endpoint cannot be used?
   2.2 Whether animals will be euthanized when moribund (i.e. in the state of dying or clinically irreversible condition leading inevitably to death) and if not, what scientific information is to be gained in the interval between moribundity and death, or how it would jeopardize the scientific validity of the study?
   2.3 Will pain relieving measures be used? If not, provide scientific justification for withholding pain relief.
3.0 When moribundity or death is approved as an endpoint, the PI must comply with the following:

3.1 A cage card must be placed on every cage at the onset of experiments indicating “moribundity or death as an endpoint” as applicable.

3.2 Animals will be monitored daily by research personnel experienced in recognizing signs of pain, distress and morbidity. The frequency of observation will be increased to at least twice daily when animals exhibit signs of pain or distress.

3.3 If signs of pain or distress are detected, designated personnel, including a veterinarian, should be notified promptly to assess the animals’ condition and establish a plan of action.

3.4 Animals are to be removed from group housing to individual cages when their condition deteriorates to the point that injury from other animals is likely, and/or access to food and/or water becomes difficult.

3.5 Promptly remove animals upon death.

3.6 Written records must be made of monitoring sessions indicating the protocol number, the date and time of observation, the person performing the observation, any interventions performed, and any findings such as number of animals demonstrating pain and/or distress, number of dead animals, etc. These records must be kept on file and available for review by regulatory bodies.