HUMANE ENDPOINTS

Policy and/or Guidelines on Endpoints for Animals Used for Research or Teaching Purposes

Humane Endpoints:

Animals used in biomedical research may sometimes be subject to pain and/or distress while undergoing experimental procedures. All animal research must be reviewed and approved by the IACUC and must be in accordance with the Animals Welfare Act, The Guide for the Care and Use of Laboratory Animals, and other federal regulations. To be in accordance with these regulations, all research, testing, and teaching that utilize animals must be performed to minimize discomfort, distress, and pain. When laboratory animals experience pain and/or distress they may advance to the moribund condition or death. Although each scientific study is unique, the IACUC has established this set of guidelines to assist principal investigators in looking for clinical signs in rodents indicative of a humane experimental endpoint. However, these guidelines cannot be articulated satisfactorily to cover every research proposal; therefore, the IACUC reserves the right to evaluate protocols on an individual basis.

Federal Guidelines require that endpoints are determined for animals use in research and require the consideration of (4) areas:

1. Anticipated adverse effects the research animals may experience (e.g. pain, distress, illness).
2. Most Likely time course and progression of these adverse effects.
3. Earliest most predictive indicators of present or impending adverse effects.
4. Justification of the humane endpoint to meet the scientific requirements of the study.

Legal regulations and moral guidelines require that animal pain, distress, discomfort and suffering be minimized in any experiment. Conditions or procedures that cause more than momentary or slight pain or distress should be performed with appropriate sedation, analgesia, or anesthesia. Discomfort to animals must be limited to that which is unavoidable for the conduct of scientifically valuable research, and unrelieved pain or distress can continue only for the duration necessary to accomplish the scientific objectives.

Research procedures involving unrelieved pain or distress may receive consideration for approval by providing appropriate scientific justification on the Animal Care and Use Protocol Form. The justification must describe how administration of pain relieving agents would interfere with the scientific objectives of the study and must also be supported by scientific literature.
The Animal Resource Center (ARC) conducts daily rounds and places “health check” cards on cages that need attention. The ARC will then notify the investigators and the veterinarian. Once animals start to display clinical signs of illness, investigators or laboratory personnel must monitor their animals frequently (at least once daily or described in their protocol) to ensure timely identification of moribund animals or animals for which previously defined humane endpoints have been reached (this includes weekends and holidays). The frequency of observations should be increased as the potential for pain and/or distress increases. The protocol should clearly state monitoring frequency and define conditions when frequency will increase as the potential for pain and/or distress increases. Investigators are obligated to make every effort to identify and humanely euthanize moribund animals.

**Humane Experimental Endpoints** – are criteria used to end experiments on individual animals in order to avoid or terminate unrelied pain and/or distress. Once a humane endpoint is reached, the animal should be immediately euthanized or treated as described in the approved protocol.

The presence of one or more of the following criteria below may be indications for euthanasia. The professional judgment and decision of the Consulting Veterinarian will be final. The clinical signs, depending on severity and duration, that may constitute an endpoint include, but are not limited to: *this list is not exhaustive*

- **Hunched posture, lethargy, persistent decumbency, or inability to rise or ambulate** – This condition would indicate that an animal would not be able to reach for food/water. Animals should be euthanized within 24 hours of not being able to rise.

- **Rough or unthrifty hair coat** – healthy rodents fastidiously groom their hair coats.

- **Dyspnea** – labored breathing. A humane endpoint may be reached when animals show an altered respiratory rate and/or effort. Labored breathing is often accompanied by a strong abdominal component to breathing.

- **Dehydration** – as evaluated by skin turgor. Severe dehydration is manifested when an animal’s skin loses elasticity. Skin pinched over the back that does not return to normal is called “tenting” and if this is excessive, it is considered a humane endpoint.

- **Anorexia/Weight loss** – A 20% weight loss over a few days would be considered rapid. This requires frequent monitoring. A gradual weight loss over an extended period of time (weeks to months), which leads to emaciation, would also be grounds for euthanasia. Degree of weight loss and monitoring frequency should be defined and described in the IACUC approved protocol.

- **Tumor size** – Tumor burden should not exceed 10% body weight in an adult rodent and/or 1.5cm diameter in adult mouse or 3cm in an adult rat. Tumor endpoints
should also take into account the location of the tumor and the ability of the animal to ambulate. In addition, an endpoint is reached if the tumor ulcerates or is necrotic.

- **Abdominal Distension** – Animals will have enlarged abdomens and may have a difficult time breathing and/or ambulating.

- **Other clinical signs that may lead to an humane endpoint, depending on severity and duration** – Diarrhea, progressive dermatitis, jaundice and/or anemia, neurologic signs, bleeding from any orifice, self-trauma, circling or head tilt, limb paralysis, any condition interfering with eating or drinking, excessive or prolonged hyperthermia or hypothermia, prolapse of genitals or anus, malocclusion, and not response to external stimuli.

**Other considerations for Establishing a Humane Endpoint**

**Endpoints in Behavioral studies**

In all behavior studies and tests, proposed procedures for monitoring, record keeping and humane intervention must be described in the animal care and use protocol. A baseline behavioral profile of an animal should be established if changes in behavior are going to be used to monitor the animal for distress. An understanding of the species-typical behavior of the animals used in awake, behaving experiments is critical for adequately assessing the animal for signs of stress/discomfort that may be minimized either through an earlier endpoint determination or by modifying experimental procedures. Subtle changes detected in the animal’s demeanor or its willingness to work in a study or sudden changes in performance on behavioral tasks may be the first indicators of a health problem that should be investigated. If such changes are noted, the researcher should promptly notify the Animal Resource Center and the Veterinarian so that the animal can receive further attention.

**Surgery and post-procedural recovery**

Animals recovering from surgery or other stressful procedures usually lose body weight for a shorter or longer period of time. The IACUC will review any procedures or recoveries what would hinder that animal’s ability to reach food and/or water. However, animals which are able to reach food and water may still lose weight due to loss of well-being and accompanying inappetance or due to pain. The investigators will need to address monitoring frequency for post-procedural recovery for potential pain and/or distress increase in animals in animal care and use protocol.

**Pilot Study**

The selection of appropriate humane endpoints requires a detailed knowledge of the impact of the procedures on the animal. The IACUC reserves the right to request a pilot study if these factors are unknown.
Moribund Condition and Death as an Endpoint
Moribund is defined as the condition that occurs immediately prior to death. The moribund state is preferred to death as an endpoint because it is assumed that euthanizing a moribund animal will help reduce terminal pain and/or distress; however defining moribundity is usually subjective. The continuation of a study until an animal dies is almost never acceptable. Strong scientific justification is required for such a study.

References:
1. Southern Illinois University – IACUC Humane endpoints policy
2. Boston University – IACUC Humane Endpoints Policy
3. Tulane University – IACUC policy P6.08
4. University of Pennsylvania Office of Regulatory Affairs
5. University of Medicine and Dentistry of New Jersey Newark Campus IACUC policy.