Humane Endpoints

**Policy:** Humane experimental endpoints that minimize pain, distress, or discomfort by choosing the earliest endpoint that is compatible with the scientific objectives of the research project must be identified within UofL Institutional Animal Care and Use Committee (IACUC) Proposals.

**Rationale:** The UofL IACUC is responsible for evaluating and ensuring that research projects are conducted in accordance with the Animal Welfare Act and Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals. These regulations and policies require that any research, testing and teaching that uses animals must be performed in such a way as to minimize discomfort, distress and pain consistent with sound research design. Some experimental studies may involve procedures that cause clinical symptoms or morbidity in animals. Studies that cause pain and/or distress are categorized as Class II or Class III studies. Further, the investigator and the IACUC must consider the selection of the most appropriate endpoints. This requires careful consideration of the scientific requirements of the study, the expected an possible adverse effects the research animals may experience (pain, distress, illness, etc.), the most likely time course and progression of those adverse effects, and the earliest most predictive indicators of present or impending adverse effects. The effective use of endpoints requires that properly qualified individuals perform both general and study-specific observations of the research animals at appropriate time points. Optimally, studies are terminated when animals begin to exhibit clinical signs of disease if this endpoint is compatible with meeting the research objectives. Such endpoints are preferable to death or moribundity since they minimize pain and distress.

**Procedures, Guidelines, and Exceptions:**

1. *Proposals* that include morbidity as an endpoint or that include animal procedures that have the potential to cause adverse sequella should address the following:
   a. Criteria that establish when the endpoint has been reached.
      1) There are several examples in the literature that might be considered, including:
         a) Evaluation of five aspects of an animal's condition as described by Morton and Griffiths. These are body weight, physical appearance, measurable clinical signs, unprovoked behavior and response to external stimuli.
         b) Clinical observations used in cancer research and toxicological studies as described by Montgomery. Parameters include changes in general appearance, skin and hair, eyes, nose, mouth and head, respiration, urine, feces and locomotion.
         c) Body condition scoring as described by Ullman-Culleré and Foltz.
      2) The clinical signs, depending on severity and duration, that may constitute an endpoint include, but are not limited to:
         a) Rapid weight loss.
         b) Rapid breathing rate.
         c) Diarrhea, or constipation if debilitating.
         d) Progressive dermatitis.
         e) Rough/ruffled hair coat, hunched posture, lethargy or persistent recumbency.
         f) Coughing, breathing rate very slow, shallow, and/or labored, nasal discharge.
g) Jaundice and/or anemia.

h) Inappetance.

i) Neurological signs.

j) Bleeding from any orifice.

k) Self-induced trauma, ulcerative dermatitis.

l) Any condition interfering with eating or drinking (e.g. difficulty with ambulation).

m) Excessive or prolonged hyperthermia or hypothermia.

n) Any animal found unexpectedly to be moribund, cachectic, or unable to obtain food or water.

3) Additional signs in neoplasia studies that may constitute an endpoint include, but are not limited to:

a) A tumor burden greater than 10% body weight, and in an adult mouse, a mean tumor diameter exceeding 20 mm or in an adult rat, a mean tumor diameter exceeding 40 mm. Formulas for calculating tumor size can be found in the literature (see tumor size references).

b) Tumors that ulcerate, become necrotic or infected.

4) A plan for monitoring the animals both before and after a change in any of the above aspects, providing care if appropriate, and increasing the level of monitoring. Certain procedures/experiments may require monitoring weekly, or several times per day. Monitoring or clinical care on weekends and holidays may require involvement of the investigative staff to supplement that provided by the animal care and veterinary staff.

5) Identification of personnel responsible for evaluation, record keeping, notification of the investigator and/or veterinarian and persons responsible for euthanasia.

2. Moribund is defined as “in a dying state.” Animals are considered to be moribund if they manifest any of the signs of morbidity plus any/all of following clinical signs and recovery is not expected (e.g., recovery would be expected with anesthesia):

a. Inability to ambulate that prevents the animal’s easy access to food and/or water.

b. Inability to maintain itself in an upright position.

c. Prolonged (greater than 48 hours) inappetence and/or clinical dehydration.

d. Agonal breathing and cyanosis; chronic diarrhea, vomiting, or constipation.

e. Hematologic or biochemical parameters that indicate organ failure incompatible with life.

f. Unconsciousness with no response to external stimuli such as a toe-pinch withdrawal test.

g. Evidence of muscle atrophy or other signs of emaciation (body weight always proportionate).

h. Uncontrolled bleeding.

i. Unexpected central nervous system disturbances (e.g., intractable seizures).

3. Scoring Systems

a. The use of a system for scoring the animal’s condition provides an objective format for deciding which observations are important, ensures that specific observations are not overlooked and provides a blueprint for training individuals involved in the research project. A score sheet system allows each member of the team to make and judge observations in a uniform manner. A checklist or score sheet system should be prepared specifically for each scientific procedures since the expected sequelae of experiments can vary greatly. For example, the effects of an abdominal surgical procedure will differ significantly from a cranial implant. Qualitative signs such as limping may be assigned scores according to severity. Score sheets provide a method to obtain an overall impression of well-being and should be considered as a part of the IACUC proposal review process.
b. Score sheet systems may be simple or complex depending on the research proposal. Score sheet systems have been published by Morton and Griffiths 1985, Morton 1990, Morton and Townsend 1995, and Workman et al., 1998. The veterinary staff is available for individual consultation and development of score sheet systems; an example may be found in the IACUC Information Sheet: “Pain Scoring using Response Variables.”

References:
2. Canadian Council on Animal Care (CCAC) guidelines on: choosing an appropriate endpoint in experiments using animals for research, teaching and testing. 1998.
11. The Office of Animal Care and Use, National Institutes of Health. 2007. ARAC Guidelines for Endpoints in Animal Study Proposals