Experimental Endpoints and Humane Alternatives

I. Introduction:

The importance of minimizing discomfort, pain or distress that animals may experience during the conduct of biomedical research is well recognized and is the primary force behind the animal welfare regulations governing the humane and ethical use of animals in research.

Principal investigators are responsible for considering alternatives to the use of potentially painful procedures in animals, and for determining whether these alternatives are feasible for the study. Consultation with the attending veterinarian or other experts in the specific animal models is recommended. A discussion of alternatives to painful or distressful procedures must be included in the animal use protocol application for review by the Institutional Animal Care and Use Committee.

II. Definitions: See below

III. Guidelines:

Most experimental animal use protocols involve the euthanasia of study animals at a predetermined endpoint, even when the animals may be clinically healthy. However, in the event that animals become ill, debilitated, or experience unrelieved pain or distress, either as a result of spontaneous disease or as a result of experimental procedures, the criteria below must be utilized in deciding whether euthanasia is the most humane option. Animals experiencing one or more of the criteria listed below must be euthanized. Exceptions are permitted only if specifically approved by the IACUC (for example, if clinical signs listed below are expected as part of the experiment and appropriate measures are taken to minimize pain or distress). Diagnostic tests may also be used to define endpoints (for example, vital signs, hematology, serum chemistry, imaging).

If DARS personnel identify animals exhibiting one or more of the conditions listed below, they will attempt to contact the principal investigator or another responsible person. If a responsible person cannot be located, the attending veterinarian will authorize euthanasia. Researchers must comply with the veterinarian's recommendations for treatment or euthanasia.

1. Weight loss: In adult animals, loss of > 20 percent of body weight compared to the pre-study weight or to age-matched controls; in growing animals, or in animals whose body weight has not been recorded, or in tumor studies, weight loss must be assessed by body condition scoring.

2. Decrease in appetite: Complete anorexia for 24 hours in small rodents, up to 5 days in large animals; partial anorexia (less than 50% of normal caloric requirement) for 3 days in rodents, 7 days in large animals.

3. Weakness/inability to obtain feed or water: Inability or extreme reluctance to

stand which persists for 24 hours (assuming that the animal has recovered from anesthesia).

4. Moribund state: An animal found to be in a state of dying with little likelihood of recovery, showing some or all of the following symptoms: severe depression, lack of movement, complete anorexia, hypothermia.

5. Infection: Infection (either overt or indicated by abnormal body temperature or WBC parameters) which fails to respond to therapy within an appropriate time.

6. Tumor growth: Solid tumors estimated to exceed 10% of normal body weight; loss of body condition indicating that tumor growth is being supported by body and/or metabolic resources; tumor growth that impedes an animal's ability to ingest food or water or perform other normal bodily functions or to move about the cage or remain clean and dry; tumors that appear to be causing the animal pain or distress that cannot be relieved with analgesics or other palliative measures; evidence of tumor necrosis or ulceration indicating that the tumor has outgrown its blood supply; evidence of organ dysfunction and/or failure from either the primary or metastasized tumors.

7. Unrelieved pain/distress: Signs of significant pain and/or distress which are unresponsive to analgesics/anesthesia, or as determined by DARS staff in conjunction with the attending veterinarian.

8. Organ system dysfunction/failure, including but not limited to:
    a. Respiratory: Labored breathing, cyanosis
    b. Cardiovascular: Acute blood loss resulting in shock or anemia; cardiac failure
    c. Gastrointestinal: Severe vomiting or diarrhea; rectal prolapse; intestinal obstruction
    d. Urogenital: Renal failure characterized by elevated BUN or creatinine; urinary tract obstruction; ruptured bladder; uroperitoneum; vaginal, uterine, or penile prolapse
    e. Nervous: CNS depression; frequent or continuous seizures; severe paralysis; neurological conditions which impede movement or the animals' ability to eat or drink
    f. Musculoskeletal: Muscle or bone damage resulting in severe pain or inablility to use a limb.
    g. Integumental: Non-healing wounds or severe burns covering more than 10% of the body; self-mutilation; severe autophagia

Humane Endpoints for Studies with Expected Morbidity or Mortality

In most studies, animals must be humanely euthanized if they experience unrelieved pain or distress, based on the criteria described in the section above. Studies with death as an endpoint (also known as survival duration studies, LD50 etc.) are not approved by the UC

Merced Institutional Animal Care and Use Committee unless this endpoint is scientifically justified in the animal use protocol. The justification must include, at minimum:

- A clear and detailed description of the clinical signs that are expected as animals enter a moribund state and approach death
- An explanation for why animals cannot be euthanized as soon as such signs present themselves
- Discussion of what additional information may be gained in the interval between the first sign of moribund symptoms and actual death
- The method used to determine the minimum number of animals required to achieve statistically valid results.

At all times during this process, the well-being of the research animals must be balanced against the requirements of the study. If the study is approved with expected morbidity or death as an endpoint, investigators must monitor animals at least daily, including weekends and holidays, and keep detailed records of any observations and treatments.

IV. References:

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