DEATH AS AN ENPOINT

Purpose/Scope

The purpose of this Standard Operating Procedure (SOP) is to outline the IACUC's policy regarding investigators using death as an endpoint in experiments.

References

Institutional Animal Care and Use Committee Guidebook, OPPR and ARENA, 2nd edition, pages 103-107.

Montgomery, C.A., Jr. Oncological and Toxicological Research: Alleviation and Control of Pain and Distress in Laboratory Animals. Cancer Bulletin; 42(4):230-237, 1990.

Background

Legal, regulatory, and moral guidelines require that animal pain and/or distress be minimized in any experiment. The *routine* use of death as an endpoint should be discouraged. For these reasons, investigators are encouraged to administer euthanasia in death as an endpoint experiments before the actual death of the animals if experimental validity will not be compromised. Endpoints other than death must always be considered and should be used whenever the research objective makes it possible. Investigators must be able to judge and perform euthanasia on moribund rodents based on objective signs of dying, depending on experience with the animal model, professional judgment, and the experimental protocol. Some of the known signs of illness or dying that may be applied are listed below to assist investigators in decision-making. The use of this information is encouraged with the understanding that the combination of signs indicating time for euthanasia may vary with experimental end points. Animals found moribund should be euthanatized. If death itself is the required end point of an experiment, the investigator may receive approval to conduct such studies by providing appropriate justification to the IACUC. Inconvenience or increased cost are not justifiable reasons. Investigators are expected to make a good faith effort to justify their end points, or assure that they can evaluate animals found moribund and agree to perform euthanasia.

Terms

"Death as an endpoint" refers to projects in which the animals' non-experimentally induced death is required as a measured data point. It does not refer to projects in which the animals will be euthanatized prior to non-experimentally induced death for tissue collection or project termination. "Moribund" is defined as "in the state of dying" or "at the point of death." Animals are considered to be moribund if they evidence unconsciousness or show no response to external stimuli such as a toe pinch withdrawal test. A moribund condition may be an appropriate humane experimental endpoint for some studies where there is the induction of severe disease states and high rates of mortality.

Signs of Morbidity (disease/illness) in rodents:

1. Rapid breathing rate
2. Breathing rate very slow, shallow, and labored
3. Rapid weight loss
4. Ruffled fur (rough hair coat)
5. Hunched posture
6. Hypothermia or hyperthermia
7. Ulcerative dermatitis or infected tumors
8. Inappetance
9. Diarrhea or constipation

Signs for Judging the Moribund Condition (state of dying) in rodents – signs for morbidity plus any/all of the following:

1. Impaired ambulation (unable to reach food or water)
2. Evidence of emaciation
3. Any obvious prolonged signs such as lethargy (drowsiness, aversion to activity)
4. Lack of physical or mental alertness
5. Prolonged inappetance
6. Bleeding
7. Difficulty breathing
8. Central nervous system disturbances
9. Chronic diarrhea or constipation
10. Ataxia

Procedure

If killing a moribund animal would invalidate the study, the scientific justification for using death as an endpoint must be provided in writing as part of the animal care protocol and must be approved by the Mississippi State University IACUC.

The following points should be discussed in the protocol justification:

1. Why should death be used as an endpoint instead of morbidity?
2. What alternatives were considered?
3. Is any additional information learned between the moribund condition and death?
4. The number of animals in survival duration protocols should be clearly stated, as well as the statistical techniques used to estimate the numbers in the study groups.

Investigators who receive approval from the IACUC to use death as an experimental endpoint must also agree to the following:

1. Written records of all monitoring sessions, indicating the time of the observations, the person observing the animals, and any observations such as the number of animals evidencing clinically abnormal behavior and the number of animals found dead, must be maintained and made available to the Office of Laboratory Animal Care and the IACUC.
2. Animals must be monitored twice daily (including weekends and holidays), and any animals evidencing clinically abnormal behavior must be removed from group housing situations and housed individually with easy access to food and water to avoid competition between animals.
3. Use the minimum number of animals necessary to achieve statistical significance and use alternative endpoints other than death whenever possible.

4. Drugs or techniques to alleviate pain or distress preceding death must be used unless they would interfere with the scientific objectives of the study. If the investigator is foregoing the use of anesthetics, analgesics, or tranquilizing drugs the animal care and use protocol must contain extensive justification. It should be stated clearly why alternatives are not appropriate.
5. Protocols which utilize death as an endpoint and which forego the use of anesthetics, analgesics, or tranquilizing drugs to alleviate pain and distress in experimental animals will be assigned to the highest pain level category, "D," on all protocol forms and regulatory papers.

Federal law authorizes the veterinary staff to euthanatize animals in states of unauthorized or uncontrolled pain or distress. The Institutional Animal Care and Use Committee Guidebook includes examples of humane endpoints for studies with potential lethality. The investigator is encouraged to work closely with the MSU laboratory animal veterinarian in cases where this situation may arise.