	UCSD INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE POLICY MANUAL	POLICY # 14.03
	Death as an Endpoint	Originally Issued: 2/10/98 Revised: 11/17/2004 Revised: 6/20/2018

I. Background and Purpose

This policy defines the term 'Death as an Endpoint' and is provided to assist researchers in fulfilling their ethical responsibilities to minimize animal pain and distress. The University of California is committed to the improvement of human and animal health and the advancement of science. The IACUC upholds statements specified in the Guide for the Care and Use of Laboratory Animals, the PHS Policy and the Animal Welfare Act, regarding the care and use of animals, especially those that may experience pain and distress. When pain or distress is a necessary part of the study, animals must not be allowed to suffer beyond the point where justifiable scientific objectives have been achieved.

II. Who Should Read This Policy

All personnel engaged in or responsible for studies involving death as an endpoint in animals.

III. Definitions

Term	Definition
Humane Endpoint	The earliest scientifically justified point at which pain or distress can be minimized, terminated, or relieved, while still meeting the scientific aims and objectives of the study.
Death as an Endpoint Study	A study that requires any animal to die without humane euthanasia in order to meet specific scientific objectives.
	The following are Not considered to be death as an endpoint: • longevity studies in which animals are held until they are aged, clinical signs of disease are treated according to recommendations by veterinary staff, and animals are euthanized when they become moribund • spontaneous mortality, when death is not the intended outcome • any study in which animals are euthanized when experimental or humane endpoints are reached as described on the protocol
Experimental Endpoint	The point in a study when scientific aims and objectives have been reached.
Moribund	A severely debilitated condition that immediately precedes death.

IV. Policy

1. Death as an endpoint studies are only approved by the Institutional Animal Care and Use Committee when the PI has provided rigorous scientific justification for why earlier endpoints cannot be used.

2. The scientific justification for use of death as an endpoint must include:
    a. what humane endpoints were considered and why morbidity or moribundity cannot be used in place of death
    b. what additional information is gained in the interval between moribund condition and death
    c. 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
    d. consideration of pain-relieving drugs and non-pharmaceutical methods (e.g., softer bedding, nesting material, supplemental heat or fluids, moist food)

3. Monitoring must be performed as appropriate to the model and must be described on the animal protocol.
    a. The monitoring schedule must take into account the expected onset and progression of disease and whether timely retrieval of animal carcasses is required for scientific data.
    b. Monitoring must be documented. Records of monitoring must be kept in the animal housing room and must be readily accessible to inspectors.
    c. The cages of animals that are subject to death as an experimental endpoint must be labeled to indicate that death or moribundity of the animal is expected.

V. Related Documents

UCSD Documents	IACUC Policy 26 Minimizing Pain and Distress IACUC Policy 13 Euthanasia
Other Documents and References	PHS Policy on Humane Care and Use of Laboratory Animals Animal Welfare Act and Regulations Animal Care Policy Manual Guide for the Care and Use of Laboratory Animals

VI. Additional information

1. Regulatory agencies, including the Interagency Research Animal Committee (IRAC), Food and Drug Administration (FDA) and the Environmental Protection Agency (EPA), highly discourage the use of conventional LD50 testing and recommend alternatives be used that greatly reduce the number of animals and when possible, use signs of morbidity (e.g. hypothermia following venom exposure or septicemia) rather than

mortality as the endpoint. The preferred alternative protocol is the Up-and-Down Procedure (UDP). Other methods include the Limit Test, Fixed Dose Procedure (FDP), Acute Toxic Class (ATC) method, Dose-Probing Test, and Pyramiding Test.

a. The Up-and-Down Procedure (UDP), also referred to as the staircase method, involves dosing one animal at a time, beginning with the anticipated LD50 or one step below. Each subsequent animal is then given a higher or lower dose depending upon the previous animal's survival or probable survival. The total number of animals used is typically 6-10. The EPA provides free software to assist in calculating the recommended sequential doses, estimated LD50 and confidence intervals. When using humane endpoints with UDP, it may be possible to incorporate survival assays such as Kaplan–Meier, when duration of survival is needed in addition to mortality.

b. The Limit Test examines the effects of a single dose on 5 to 10 animals.

c. The Fixed Dose Procedure (FDP) is similar to the Limit Test. However, depending upon the results of the first dose, a second or third dosage may be tested in subsequent groups.

d. The Acute Toxic Class (ATC) Method utilizes a similar step procedure but includes three fixed starting doses and only three animals per dose. Depending on the morbidity or mortality observed, additional steps may be necessary.

e. In the Dose-Probing Test, three widely spaced dosages are each tested on one or two animals.

f. In the Pyramiding Test, two animals are given increasing doses on alternate days until a specific limit is reached or morbidity is observed.

2. If the funding agency in support of the proposed research will not accept the use of humane endpoints, please include the agency's verbiage in your IACUC protocol to aid in providing sufficient justification for using death as an endpoint.

3. Cage card information: "Special Instruction" tags are placed on cages in studies with Death as an Endpoint. These tags must specify what the endpoint is, and instructions for ACP or lab staff. These instructions need to include what monitoring is required, whether to remove the dead animals or not, who to contact when animals are found dead, etc.