



CARE 402.01 Humane Intervention Points

The intent of this standard operating procedure (SOP) is to provide instructions on how to set points for humane intervention (see definitions) for animal research models while maximizing the opportunity to achieve the scientific objectives of the research. This SOP is designed for use by research and veterinary personnel, and the Cornell Institutional Animal Care and Use Committee (IACUC). This procedure is approved by the IACUC and the Cornell Center for Animal Resources and Education (CARE). Any exemption must be submitted for approval by the IACUC prior to its application.

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1. Introduction

a. Definitions

- i. Humane intervention points: clear criteria set to define the point at which humane interventions must be implemented to prevent or relieve unnecessary distress and/or pain to a research animal.
- ii. Humane interventions: actions/instructions including but not limited to the following:
 - Provide adequate veterinary treatment, analgesia and/or supportive therapy to the animal(s)
 - Terminate painful procedures
 - Remove the animal(s) from the study
 - Modify the experimental procedures to minimize the discomfort to the animal(s)
 - Increase the frequency of animal observations
 - Modify the housing and husbandry practices to improve the comfort of the animal(s)
 - Perform euthanasia
- iii. Pilot study: a preliminary study used to determine the intervention points in cases where the course of disease, the experimental effects or the indicators of discomfort are otherwise unknown.
NOTE: An IACUC protocol is required to perform a pilot study.
- iv. Scoring system: a method of animal evaluation in which objective values are assigned to specific clinical signs or animal observations. These values are used to calculate a numerical score for each animal at any given time point during an experiment. Humane interventions are implemented based on

specific, predetermined numerical scores (see section 4 for additional details on designing scoring systems).

b. Requirements

Ensuring appropriate intervention points involves the combined efforts of the principal investigator, the IACUC and CARE to carry out the following instructions:

- i. Determine the humane interventions that are appropriate for the study.
- ii. Ensure that humane intervention points are clearly defined in the protocol.
- iii. Ensure all personnel responsible for making animal observations have been adequately trained to observe and recognize the intervention points in the approved protocol.

2. Materials NA

3. Procedures

a. Instructions for research personnel

- i. Review literature and perform web based searches of established models and alternative methods. Implement the alternatives whenever possible.
- ii. Consult with CARE veterinarians on study refinements designed to minimize pain and distress.
- iii. Establish all responsible parties and a clear chain of consultation for dealing with unanticipated events. Include this information in the animal use protocol.
- iv. Schedule regular animal observations at an appropriate frequency to ensure early detection of signs of pain and discomfort.
 - Keep records of all observations including specific measurements or data (e.g., body weight).
 - Increase the frequency of observations and measurements in response to a decline in the animal's condition and during pre-determined critical periods during the study.

b. Instructions for CARE veterinary personnel

- i. Provide clinical evaluations of animals on study.
- ii. Liaise with scientists to provide guidance and consultation for choosing appropriate endpoints.

c. Instructions for IACUC

- i. Review intervention points in protocol.
- ii. Approve appropriate intervention points in the protocol.
- iii. Refer the principal investigator to the CARE veterinarians for consultation if the intervention points in the protocol need revision prior to approving them.

d. General guidelines for choosing humane intervention points

- i. Use experimental, non-subjective data whenever possible, to designate the points at which intervention occurs. For example:
 - Percent body weight loss
 - Targeted level of liver enzyme in the blood
 - Targeted tumor growth rate
- ii. Use quantitative terms and scoring systems to assign objective values to animal observations. Refer to instructions below on designing scoring systems:

1. Refer to literature searches, previous experiments or pilot studies to determine the criteria that are the best indicators of distress relevant to the study.
 2. Assign each of these observations a numerical score, e.g., provide a range of scores from 0 (normal to mildly affected) to 5 (severe changes from normal).
 3. Monitor and record all scores at regular time points as predetermined through literature searches and pilot studies.
 4. Add the scores for all designated observations and observe the cumulative rating as an indicator of the level of pain and distress level of each animal.
 5. Use the cumulative ratings as predictors of further deterioration and indicators for intervention.
- iii. Avoid use of general or ambiguous terminology and phrases, such as “analgesia will be administered as needed.” Use phrases such as “analgesia will be administered every 8 hours for 48 hours post operatively.”
 - iv. Whenever the experimental effects, course of the disease or indicators of discomfort are unknown, perform a pilot study to establish the clinical signs and time points at which intervention is necessary.
 1. Use the results from the pilot study to establish humane intervention point criteria and scoring systems for future research in similar areas.
 2. Use the minimum number of animals/groups necessary to gather the information for the pilot study.
 3. Ensure the evaluation methods dictate an adequate frequency of observation for early detection of points.
 - v. Refer to the following list of clinical observations and examples as a guideline for setting intervention points. An example of an end point scoring system for in vivo tumor induction can be found [here](#).

4. Safety NA

5. Contingencies NA

6. References

CARE 411.01 Monoclonal Antibody Production

<http://www.research.cornell.edu/care/documents/SOPs/CARE411.pdf>

CCAC guidelines on: choosing an appropriate endpoint in experiments using animals for research, teaching and testing. Canadian Council on Animal Care:

http://www.ccac.ca/en/CCAC_Programs/Guidelines_Policies/GDLINES/ENDPTS/APPOPEN.HTM (accessed: Jan. 2006).

University of Michigan Medical School, Tumor Burdon Scoring System SOP:

<http://www.ulam.umich.edu/sops/ULAM%20SOP%20Tumors.pdf>

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Wendy Williams, April 2003, June 2005	Feb. 2006	April 2008	N/A	CARE 402.01

7. Appendices

Clinical Observations	
<p>Observe for Changes in Behavior</p> <ul style="list-style-type: none"> • Response to external stimuli (e.g., exaggerated response or lack of response when the animal is gently touched) • Changes in the frequency of behaviors that might occur as a result of pain or discomfort (e.g., vocalizations, licking, guarding, biting) • Adverse behaviors relevant to the problem being studied (e.g., for an arthritis study in rodent, lameness and swelling) • Non-specific behaviors (i.e., change in frequency of sniffing, food hoarding, grooming, resting, sleeping, eating, drinking) <p>Observe for Changes in Appearance</p> <ul style="list-style-type: none"> • Loss of body condition • Postural changes (e.g., hunched posture) • Missing anatomy (e.g., tail sloughing, digit missing) • Obvious tissue swelling or masses • Rectal or vaginal prolapse • Sunken eyes indicative of advanced dehydration • Head tilt • Piloerection (hair coat raised) <p>Monitor for Changes in Weight</p> <ul style="list-style-type: none"> • Begin interventions such as nutritional supplements when there is weight loss of 10% or greater. • Perform euthanasia when the weight loss is greater than 20% of the original body weight. • Always consider weight loss in relation to: <ul style="list-style-type: none"> ▪ Attitude ▪ Weight record at time of arrival ▪ Age ▪ Concurrent muscle wasting in comparison to animals of similar age, sex, and physiological status <p>NOTE: An increased frequency of measurements may be required to catch rapid weight loss.</p> <p>Monitor for Inappetence and Clinical Dehydration</p> <ul style="list-style-type: none"> • Intervene if there is complete anorexia for 24 hours in small rodents, up to 5 days in large animals • OR if there is partial anorexia (i.e., consumption of less than 50% of caloric requirement) for 3 days in small rodents or 7 days in large animals • Decrease in the observed and/or measured amount of food and water intake 	<ul style="list-style-type: none"> • Observe for weakness and inability to obtain food and water (e.g., inability or reluctance to stand) assuming that the animal has recovered from anesthesia • Inability to ambulate that prevents the animal's easy access to food and/or water • Inability for the animal to maintain itself in an upright position <p>Monitor for Changes in Body Temperature</p> <ul style="list-style-type: none"> • Hypothermia • Hyperthermia <p>Moribund State</p> <ul style="list-style-type: none"> • Near death • Depression coupled with: <ul style="list-style-type: none"> ▪ Body temperature below 99° F ▪ Non-responsive to stimulation, assuming that the animal has recovered from anesthesia ▪ Unresponsive to external stimuli (i.e., toe pinch withdrawal test) ▪ Evident unconsciousness <p>Observe for Signs of Infection</p> <ul style="list-style-type: none"> • Overt signs such as purulent or mucoid discharge • Less obvious signs such as: <ul style="list-style-type: none"> ▪ Increased body temperature ▪ Elevated WBC parameters ▪ Failure to respond to antibiotic therapy within an appropriate time ▪ Systemic signs of illness <p>Respond to Signs of Pain</p> <ul style="list-style-type: none"> • Sudden pain or distress unalleviated by the use of analgesics, sedatives, or tranquilizers • Signs of severe organ system dysfunction non-responsive to appropriate therapy, or with poor prognosis as determined by a CARE veterinarian <ul style="list-style-type: none"> ▪ Severe medical conditions that cannot be controlled with appropriate therapy (e.g., severe systemic infections, kidney or liver failure, heart disease) ▪ Hematological or biochemical parameters that indicate organ failure incompatible with life; measurable clinical signs (e.g., changes in heart rate, respiratory rate and nature)

Special Conditions: Criteria for the determination of humane intervention points for animals with tumors	
<p>Tumor Size and Location</p> <ul style="list-style-type: none"> • >2 cm for mice • >10 cm for rats • Affecting normal bodily functions (e.g., ambulate, eat or drink) • Causes pain or distress • Tumor weight exceeds 10% of body weight or weight loss exceeds 20% <p>Ulcerated Tumor</p> <ul style="list-style-type: none"> • Ulceration or necrosis of superficial tumors NOTE: these are not always the best indicators of pain and distress 	<p>Behavioral Effects</p> <ul style="list-style-type: none"> • Interference with normal gait or movements • Interference with normal feeding and drinking behaviors • Causing persistent self trauma <p>Study Requirements</p> <ul style="list-style-type: none"> • Principal investigator must determine the degree of tumor development that is required to meet scientific objectives of the research protocol. • Determine whether the extent of tumor growth can be minimized. • Prevent death as a result of excessive tumor growth as this may result in unnecessary pain and distress and in the loss of animals from the study (i.e., negating tissue or blood collection).
Special Conditions: Death as an endpoint	
<p>NOTE: This table refers to those protocols in which death has been approved by the Cornell IACUC as an endpoint of the study.</p>	
<p>Death as an Endpoint</p> <ul style="list-style-type: none"> • Use humane intervention points other than death whenever possible. • Use the minimum number of animals necessary to achieve statistical significance. • Ensure justification has been made to the IACUC in special circumstances in which death as an endpoint is necessary. • NOTE that any approved use of death as an experimental endpoint will be noted on all protocol forms and regulatory papers as being the highest pain level category “E,” indicating that no analgesic or anesthetics are provided to alleviate pain or distress in the experimental animals. • Always do a search for alternatives to keep abreast of recent literature because rapid developments of alternatives are possible. 	<ul style="list-style-type: none"> • Reduce the need to use death as an endpoint by using the following clinical indices: <ul style="list-style-type: none"> ▪ Increase the frequency of observation whenever there is a lack of clear criteria known to indicate when death may occur. Increased observation frequency may improve the ability to catch the events that may occur outside of regular working hours. ▪ Keep written records of all monitoring sessions including the time of the observation, the person making the observation, and entries regarding the condition of the animal as described in the Clinical Observations table. ▪ House individually and provide easy access to food and water for any animals with clinically abnormal behavior.
Special Conditions: Criteria for the determination of humane intervention points for animals with ascites	
<p>Ascites</p> <ul style="list-style-type: none"> • Weight of animal and ascites should not exceed greater than 20% normal body weight • Ascites that exceed the size of normal pregnancy mass 	<p>A maximum of two taps of the ascites fluid are allowed with the second tap being a terminal procedure performed after euthanasia.</p> <p><i>Further endpoint criteria for mice used to produce ascites are discussed in CARE SOP 411.01 Monoclonal Antibody Production.</i></p>