

Alleviation of Pain and Distress in Animals Policy

I. Purpose

The purpose of this policy is to ensure, as much as possible, the comfort and safekeeping of animals used in research at Albert Einstein College of Medicine (Einstein).

II. Scope

This policy applies to all research experiments and programs at Einstein.

III. Policy

Einstein follows U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Teaching and the Public Health Service Policy on Humane Care and Use of Laboratory Animals that states:

PHS Policy IV: "Proper use of animals, including the avoidance or minimization of discomfort, distress and pain when consistent with sound scientific practices, is imperative. Unless the contrary is established, investigators should consider that procedures that cause pain or distress in human beings may cause pain or distress in other animals."

PHS Policy V: "Procedures with animals that may cause more than momentary or slight pain or distress should be performed with appropriate sedation, analgesia, or anesthesia [unless the omission of these agents is justified for scientific reasons in writing by the investigator]. Surgical or other painful procedures should not be performed on unanesthetized animals paralyzed by chemical agents."

PHS Policy VI: "Animals that would otherwise suffer severe or chronic pain or distress that cannot be relieved should be painlessly killed at the end of the procedure or, if appropriate, during the procedure."

Furthermore, to comply with the USDA's implementation of the Animal Welfare Act, Principal Investigators (PIs) must document in their written protocols, the methods they have used to explore alternatives to procedures that cause more than momentary or slight discomfort, pain, or distress, and they must provide a written plan for dealing with pain, discomfort, or distress when it is encountered.

In interpreting and implementing these policies and regulations, the Institutional Animal Care and Use Committee (IACUC) has adopted the following specific policies, which apply to all vertebrate species used by Einstein PIs:

III.A. Recognition of Pain and Distress

Certain procedures are always assumed to have the potential for causing pain and distress. These are the basis for the numerous experimental guidelines that are intended to prevent pain or distress. These include:

- Surgery
- Repeated use of large volumes of, or intradermal injections of Freund's complete adjuvant
- Intraperitoneal implantation of ascites-producing hybridomas for monoclonal antibody production
- Prolonged physical restraint
- Malignant neoplasms
- Prolonged food or water deprivation
- Distal tail biopsy in animals over 3 weeks of age (tail snipping)
- Electrical shock or other adverse stimuli that are not immediately escapable
- Paralysis or immobility in a conscious animal
- Inflammatory disease
- Organ failure resulting in clinical signs
- Non-healing skin lesions
- Whole body irradiation at high doses
- Withdrawal of more than 10% of an animal's blood volume
- Studies that require an animal to reach a moribund state or die spontaneously as the endpoint of the study

III.A.1. Surgical Procedures

All surgical procedures are considered to be potentially painful and must be performed under anesthesia.

Whenever possible, pain should be treated pre-emptively (the administration of preoperative and intraoperative analgesia, before the cause) enhancing intraoperative patient stability and optimizing postoperative care and wellbeing by reducing postoperative pain. Analgesic agents become effective before the animal emerges from anesthesia when administered before surgery and re-dosed as needed during the procedure. Local anesthetic/analgesic drugs are not to be used as the sole analgesic for pain. Contact the veterinarian to determine the best form of analgesia for a particular animal/project during the planning phase of the project or when an animal is observed to be in pain.

Analgesics must be provided to all animals following survival surgery to avoid or minimize the discomfort, distress, and pain when consistent with sound scientific practices, unless scientific justification for withholding post-operative analgesics is provided by the investigator and

approved by the IACUC or if a veterinarian examines the animal and determines that analgesic administration is no longer necessary.

III.A.2. Procedures that Can Result in Chronic Discomfort or Distress

Analgesic treatment must be considered in case there are signs of discomfort/distress. Omission of analgesic treatment when signs of pain or distress are observed must be scientifically justified in an approved IACUC protocol. If the withholding of routinely administered intra, post-operative or post-procedural systemic analgesia has been scientifically justified in an IACUC approved protocol, the protocol will be listed as a Category E study (studies in which the animals will experience pain or distress greater than that produced by routine injections or venipuncture and will not receive pain relieving agents). At this time if animals cannot receive systemic analgesia with IACUC approved justification they must be listed in Category E. Special exceptions must include the "3R's with justification from experts.

III.B. Assessment of Pain, Distress, and Discomfort

Pain, discomfort, and distress in humans have a subjective component which makes it difficult to compare pain levels with animals. Furthermore, many laboratory animals, especially prey species such as rodents, have evolved to mask signs of minor to moderate discomfort. Therefore, any outward signs observed in a laboratory animal, probably indicate real discomfort or illness.

III.B.1. Evaluation of Conscious (Awake) Animals

Many of the signs described below are general indications of illness whose expression varies with species. The context (e.g., immediately post-op) accompanied by obvious injury or lesion (e.g., abscess), as well as response to analgesic therapy, will help interpretation. Some signs that may indicate pain or distress in conscious animals include:

- Piloerection (ruffled fur)
- Unkempt fur (failure to groom)
- Hunched or abnormal posture
- Reluctance to move (spontaneously or in response to stimuli)
- Withdrawal (withdrawn from cagemates, hiding in corner, or in nest)
- Protection (withdrawal/avoidance in response to palpation of the affected area or part
- Bruxism (teeth grinding)
- Vocalization (spontaneous or in response to palpation of the affected area or part)
- Decreased appetite, reduced fecal output, weight loss, loss of body condition
- Dehydration, decreased urine output
- Excessive attention to the affected area or part (licking, biting, scratching)
- Abnormal gait
- Persistent struggling during restraint

Grimace scales have been developed to identify and assess pain in several species of awake animals. These useful tools can be found at <u>https://nc3rs.org.uk/grimacescales</u>

III.B.2. Evaluation of Unconscious Patients - Intraoperative Monitoring

All animals undergoing surgical procedures, either survival or non-survival, must be adequately anesthetized. The adequacy of anesthesia must be evaluated periodically during the procedure. Signs of an inadequate level of anesthesia include:

- Responses to toe pinch (withdrawal reflex)
- Responses to corneal or palpebral stimulus (touch) blink response
- Increased respiratory rate, heart rate, and/or blood pressure usually as level of anesthesia is reduced, these will increase as a sign of pain
- Response to surgical manipulation

If the animal is responsive, the PI must stop the procedure immediately and adjust the anesthetic level.

III.C. Monitoring, Evaluation, and Treatment

III.C.1. Responsibility

Even though Einstein and the IACUC are responsible from a regulatory perspective for ensuring that all animals used on campus receive adequate and timely veterinary care, **each PI and his or her staff bear primary responsibility for monitoring, evaluating, and treating their animals.** In most cases, the veterinary staff of the Institute for Animal Studies (IAS) can help PIs make an assessment of animals that are exhibiting signs of discomfort or distress. However, it is not possible for the IAS veterinary staff to monitor all animals at appropriate time intervals to detect the onset of problems. Therefore, the IACUC requires that PIs check their animals regularly as indicated in the protocol. The protocol must also have a written contingency (treatment) plan for dealing with discomfort and distress.

III.C.2. Frequency of Monitoring

All animals owned by PI must be examined by the PI or his/her staff at least once per week, when no experiments have been performed.

When animals are on an experiment or are otherwise likely to develop clinical disease which may cause pain, discomfort or distress, the PI or his/her staff must check animals at least 3 times a week, or as often as specified in the approved protocol.

Animals that have developed clinical signs must be evaluated daily and, in some cases, more frequently. Unless there is strong scientific justification, the IACUC does not permit animals to experience unrelieved pain or distress longer than 12 hours (see below).

III.D. Surgical Recovery and Post-Operative Period

All animals undergoing surgery must be monitored continuously during the surgery and subsequent recovery period, until they are ambulatory. For animals that do not automatically receive an analgesic during the recovery period, an evaluation of pain and distress must be made

once the animal is awake, before it is returned to the animal facility. The IACUC requires that each animal then be checked again within 12 hours and at least once daily thereafter for at least 3 additional days to reevaluate pain and wound healing. Animals that show signs of pain or distress must be monitored at least once daily until they return to normal behavior. More frequent or extended monitoring may be required, as specified in the approved protocol.

III.E. Treatments/Interventions

PIs must have a plan for treatment/intervention described in their approved protocols. The IACUC expects one of the following interventions to be made within 12 hours of detecting pain/distress:

- a. Continue to monitor for up to 12 hours, at which time if signs of pain/distress have not subsided, the animal is euthanized.
- b. Upon detection of signs of pain/distress, administer analgesic medication. Reevaluate at the time the next analgesic dose is recommended, but not more than 12 hours later. Thus, if the recommended dosing interval is every 6 hours, the animals must be reevaluated within 6 hours. Reevaluation includes a decision to either discontinue analgesia, euthanize the animal, continue the same dose, or to adjust the dose. This plan must be followed for the period of time specified in the protocol, after which if the animal is still in pain or distress, it is euthanized.
- c. Analgesic medication can be scheduled to be given routinely for a specific number of treatments during the post-procedural period (fixed plan). The efficacy of the treatment must still be monitored, and any deviations in the prescribed dose or schedule must be justified and documented. This may include reducing the dose, if the animal appears to be free of pain/distress (using the grimace scale C.1. for evaluation), to reduce the occurrence of potential undesirable side effects. A final evaluation of the animal's condition must be made one dosage period after the final treatment.

III.F. Record Keeping/Documentation

To demonstrate compliance with regulatory requirements for adequate monitoring, assessment, and treatment of animals during the operative and post-operative period, or at other times when animals may be experiencing pain or distress, such activities must be documented. The written plan, as approved in the animal use protocol, must be followed explicitly.

III.F.1. For USDA-Regulated Species (all mammals except laboratory rats and laboratory mice)

Individual animal records must be maintained on forms provided by the Institute for Animal Studies (IAS) and kept with the animals until euthanasia. The records must then be returned to the IAS; copies may be made for the PI's own files. The minimum information includes: date, species, animal ID, name of procedure, anesthetic dose and route, an evaluation of anesthetic level prior to starting the procedure, and written statement about level of anesthesia periodically (e.g. every 10 minutes) throughout surgery, including objective monitoring data such as respiratory and heart rates, if any. This record should also include reasons for giving supplemental anesthesia or other drugs. Finally, a statement about the animal's

condition following recovery and an assessment of the need, if any, for post-operative intervention should be provided. Notes must be initialed and dated.

Word for word compliance with the written plan provided in the protocol is demanded by the USDA. The IACUC requires that a copy of the approved protocol be maintained with the laboratory's animal records so that research personnel can cross-check. Decisions to deviate from the written/approved plan must be documented and explained in the animal record.

III.F.2. For laboratory rats and mice and all other non-USDA regulated species

Records to be kept will depend on the procedure, as specified in the approved protocol. They may be documented as group records for a cohort of animals undergoing the same procedure without complication. Records may be maintained in laboratory notebooks but must be kept available in the laboratory for inspection by IACUC personnel or site visitors / inspectors from regulatory agencies at any time.

III.G. Anesthetics, Analgesics, and Sedatives

Lists of recommended agents and doses for mice and rats are available on the IAS website. PIs should consult with the IAS veterinary staff for advice especially when working with USDA covered species.

IV. Definitions

PAIN: A complex experience that typically results from stimuli that damage or have the potential to damage tissue; such stimuli prompt withdrawal and evasive action.

DISTRESS: An aversive state in which an animal fails to cope or adjust to various stressors with which it is presented (page 121 in the Guide).

V. Related documents

AECOM IACUC policies can be found at <u>https://einsteinmed.edu/administration/animal-care-use-</u> committee/default.aspx?id=36005

Public Health Service Policy on Humane Care and Use of Laboratory Animals http://grants.nih.gov/grants/olaw/references/phspol.htm

U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training http://oacu.od.nih.gov/regs/USGovtPrncpl.htm

Guide for the Care and Use of Laboratory Animals (Guide) http://grants.nih.gov/grants/olaw/Guide-for-the-care-and-use-oflaboratory-animals.pdf

USDA Policy #11: Painful and Distressful Procedures http://www.aphis.usda.gov/animal_welfare/policy.php?policy=11 USDA Policy #12: Consideration of Alternatives to Painful/Distressful Procedures http://www.aphis.usda.gov/animal_welfare/policy_php?policy=12

V. Effective Date

Effective as of 1 December 2021

VI. Policy Management and Responsibilities

Einstein's Institutional Animal Care and Use Committee (IACUC) is the Responsible Office under this Policy. The Institutional Official for the IACUC is the Responsible Executive for this policy. The IACUC Chairperson is the Responsible Officer for the management of this policy.

VII. Approved (or Revised)

12/1/21 ERN Institutional Official Date

Revision dates: 11/14/2001, 6/15/2011, 4/29/2014, 2/20/18, 11/22/21