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STANDARD OPERATING PROCEDURE

ADVERSE EVENT (AE) REPORTING IN ANIMALS USED IN BIOMEDICAL RESEARCH PROJECTS AT THE UNIVERSITY OF PITTSBURGH

Approval(s):

_____	_____
Director, DLAR	Date
_____	_____
Chair, IACUC	Date
_____	_____
Executive Director, IACUC	Date

A. PURPOSE. This SOP defines the concept of "adverse event(s)" in animals used in approved biomedical research manipulation at the University of Pittsburgh and lists the institutional requirements and methods to document such problems. The reporting of adverse events, review of circumstances surrounding them and subsequent determination as to whether procedural changes are necessary to prevent additional problems (via completion of the Adverse Event Reporting Form) has been designed to be an interactive process with the DLAR Veterinary staff. It is not intended as a punitive action against investigators, but an effort to facilitate research effectiveness and improve animal welfare

B. BACKGROUND. The National Research Council's Guide for the Care and Use of Laboratory Animals and the Animal Welfare Act require as part of adequate veterinary care: 1) effective programs for the management of protocol-associated disease, disability, or other sequelae (1) and 2) the timely and accurate communication of information on problems of animal health, behavior and well-being (2). In addition to the required proactive measures taken in protocol design and review to assure welfare, these requirements are met in large part by the ongoing daily observation, treatment and care of manipulated research subjects by both the research staff and Division of Laboratory Animal Resources (DLAR). However, the experimental manipulation of animals in research, testing or teaching activities occasionally results in serious unanticipated clinical consequences. Associated with recommendations specifically made to the University of Pittsburgh by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC) – "increasing the monitoring of unexpected animal deaths . . ." (3) and in light of the expanding standards routinely required in numerous areas of research, policies related to the formal reporting of serious or unanticipated adverse events are considered necessary within this Institution to fully comply with federal regulatory expectations.

1) Guide for the Care and Use of Laboratory Animals, National Academy Press, 2011, Chapter 4 (Veterinary Medical Care), p105.
2) Animal Welfare Act – title 9 C.F.R, Section 2.33 – Attending Veterinarian and Adequate Veterinary Care, b-3.
3) AAALAC correspondence, University of Pittsburgh, March 8, 2005

C. DEFINITIONS. Adverse events in the context of this SOP refer to unexpected or excessive, unfavorable clinical outcomes to research manipulation resulting in either:

a) levels of mortality exceeding by 10% or greater that anticipated in the approved protocol* (This includes both spontaneous animal deaths and animals being euthanized due to reaching either study-specified or other humane end-points)
b) mortality due to complications unanticipated in the approved protocol
c) high levels of "cluster" mortality**

Adverse events in the context of this SOP are general associated with animal deaths. However, investigators should also report animal morbidity occurring either in frequency or severity beyond that anticipated in the approved protocol. In particular, morbid complications leading to unanticipated animal discomfort – especially those creating difficult to manage levels of pain and distress or situations of uncontrollable pain or distress (i.e. - Category E conditions), should be reported.

* In many studies, initial mortality may be higher than that experienced later in the project – a "learning/experience curve" effect. Although adverse event reporting is not definitively required until animal losses in absolute terms exceeds that predicted in the protocol, it is considered advantageous to report unexpectedly high levels of early, relative mortality (i.e. mortality to date divided by animals used to date).

** Cluster mortality is defined as a grouping of animal deaths occurring closely together, significantly above anticipated study loss levels

D. APPLICABILITY. The requirements specified in this SOP for reporting Adverse Events apply to all vertebrate animal species used at the University of Pittsburgh, including those not covered by the Animal Welfare Act. In some protocols, proactive project status reporting – including mortality accountability has been required by the IACUC as a condition for project approval. Any such conditions mandated, as part of the approval process in such protocols will supercede requirements specified in this SOP.

E. RESPONSIBILITIES. I) INVESTIGATOR: Filing Adverse Event reports is the responsibility of the Principal Investigator (PI) (or his/her designee) on whose Institutional Animal Care and Use protocol those animals were listed. Adverse Event Reporting forms are available for download at the DLAR website: https://web.dlar.pitt.edu/Forms.aspx. Investigative consultation with DLAR veterinary services personnel is encouraged prior to the completion and submission of this form (648-8950) – especially with respect to the development of an appropriate corrective action plan (CAP).

II. DLAR: A) The DLAR veterinary staff will 1) acknowledge the receipt of the AE report in a timely fashion, 2) work with the investigative group as appropriate in helping identify the pathogenesis of the reported event(s) and formulating or refining the formulation of an acceptable corrective action plan and 3) provide to the investigative group any feedback as to further action(s) necessary. Adverse Event report summaries will be reported to the IACUC by the DLAR veterinary staff on a monthly basis along with the corrective action plans established. B) Normal clinical surveillance monitoring and problem reporting as conducted by the DLAR veterinary services and animal care staffs will serve as an adjunct means to notify both the PIs and DLAR veterinarians of high or excessive levels of animal morbidity or mortality – see Death and Illness reporting SOPs at:
https://www.iacuc2.pitt.edu/sop/restricted/DeathIllnessLargeAnimal.pdf
https://www.iacuc2.pitt.edu/sop/restricted/DeathIllnessSmallAnimal.pdf

III. IACUC: The IACUC will review monthly DLAR summaries of all Adverse Event Reports filed. The committee maintains the final right of approval of proposed corrective action plans, and/or may require any further action(s) deemed necessary – such as additional formal follow-up reporting, specific mandated protocol refinement through modification to address concerns, or even ordering a temporary cessation of animal use pending further review & information. Any actions taken or requirements made on the part of the committee as a result of Adverse Event review will be reported to the Principal Investigator by representatives of the IACUC.

F. PROCEDURES. The PI (or his/her designee) should report Adverse Events as defined in section C by electronically filing a completed Adverse Event Reporting Form with the DLAR Veterinary Services unit at (vetserve@pitt.edu). If direct prior communications concerning such problems have already occurred with a specific DLAR veterinarian, the completed form may be sent by e-mail to that individual. Questions as to whether events qualify as reportable should be directed to the DLAR Veterinary Service staff – generally to site team members assigned to the specific facility in which the losses occurred. If an Adverse Event Report is submitted, the PI should also summarize the incident in their next required filing of an Annual Renewal Application for Approval to Use Vertebrate Animals in Research submission, under the Problems/Adverse Events Section. If levels of morbidity or mortality (M&M) cannot be maintained at protocol specified levels with the implementation of the corrective action plan, a protocol modification reflecting this and justifying new M&M standards/levels along with other appropriate procedural adjustments should be submitted to the IACUC office.

Appendix A: Adverse Event Reporting Form

Adverse Event (AE) Reporting Form
For Animals Used In Biomedical Research Projects
at the University of Pittsburgh

For detailed information concerning the definition of an adverse event, as well as procedures and responsibilities associated with the reporting process, please refer to the Adverse Event (AE) Reporting in Animals Used in Biomedical Research Projects at the University of Pittsburgh SOP located on the IACUC Policies page, under the Compliance Reporting section, http://www.iacuc.pitt.edu/policies.

Consultation with your DLAR Facility Veterinarian is encouraged prior to the completion and submission of this form, especially with respect to the development of a corrective action plan. Please electronically submit the completed form to the DLAR Veterinarian with whom there has been previous discussions regarding the problem. Call (412) 648-8950 for assistance in contacting your facility veterinarian.

Today's Date: _____

Individual Initiating This AE Report (if different from the principle investigator)

Name:	Title:
Email:	Phone:

Protocol #: _____

Protocol Title: _____

Principal Investigator:

Name:	Email:	Phone:

Reason for submission:

- ☐ Levels of mortality experienced are ≥ 10% that anticipated in the approved protocol.
- ☐ Mortality due to unanticipated complications involving the approved protocol.
- ☐ High "cluster" mortality (Cluster mortality is defined as a grouping of animal deaths occurring closely together, significantly above anticipated study loss levels).
- ☐ Morbidity/non-fatal complications significantly beyond that anticipated in the approved protocol, especially those creating difficult to manage levels of pain and distress.
- ☐ Other (please list):

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Briefly summarize the excessive or unanticipated mortality or morbidity being reported including:

a) Species involved.

b) Number of animals impacted.

c) Animal identification number(s) or CAMS number.

d) Date or date range of incident(s).

e) Describe the adverse event(s) that occurred and compare to the expected frequency/rate of morbidity or mortality in the protocol.

f) Please list the preliminary etiology for the adverse event(s).

g) Please list any pending diagnostics or other reports that may explain the cause(s) of the adverse event(s).

h) Any additional information, extenuating circumstances or other details that may be helpful in reviewing this matter.

Has there been prior communication or consultation with the DLAR veterinary staff concerning this or similar adverse events? ☐ Yes ☐ No If yes, please provide details.

Please describe the proposed Corrective Action Plan (CAP) to reduce or prevent future morbidity or mortality.

Please note in conjunction with adverse event filing:

a) *Events listed in this form should be summarized and included in the in the PI's next Annual Renewal Application for Approval to Use Vertebrate Animals in Research submission, under the Problems/Adverse Events Section.*
b) *If levels of morbidity or mortality (M&M) cannot be maintained at protocol specified levels with the implementation of the corrective action plan, a protocol modification reflecting this and justifying new M&M standards/levels along with other appropriate procedural adjustments should be submitted to the IACUC office.*
c) *All Adverse Event report summaries are reviewed by the full IACUC and the committee maintains the right of final approval of the CAP and may require additional stipulations in the project.*
d) *Proactive feedback to the DLAR on the success of the CAP in reducing or eliminating additional M&M is encouraged.*

DLAR Use Only

Plan approved: ☐ Yes ☐ No

Additional Comments:

Date: _____

DLAR Veterinary signature: _____