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VA PORTLAND HEALTH CARE SYSTEM

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE POLICIES

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INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE
STANDARD OPERATING PROCEDURES AND GUIDELINES

1. PURPOSE

This document sets forth the principles and standard operating procedures (SOPs) that govern research, testing, and teaching activities involving laboratory animals at the VA Portland Health Care System (VAPORHCS).

2. BACKGROUND

Animal research contributes immeasurably to advancements in medical science. As recognized by principle #3 of the Nuremberg Code of 1947, it is often a moral imperative to perform research or testing on animals before subjecting humans to new procedures, pharmacologics, or devices. Most research and testing involving human patients continue to be based on the results of animal experimentation. To provide hope for veterans suffering from diseases that currently lack cures or effective treatments, the VA actively supports the use of animals in research, teaching, and testing. However, the use of animals in VA research is a privilege granted with the understanding and expectation that such research is conducted according to the highest ethical and legal standards. The basic principles governing animal research in the VA are found in the United States (US) Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training, which include the following imperatives:

- A.** Animal experiments are undertaken only after due consideration of their relevance for human or animal health and the advancement of biological knowledge.
- B.** The fewest number of animals needed to achieve scientific objectives is to be used.
- C.** The least sentient species that will permit the attainment of research objectives is to be used.
- D.** The least painful or distressful procedures needed to meet research objectives are to be used, and all reasonable measures to minimize pain and distress should be utilized.
- E.** When planning and conducting studies, the principles of replacement, reduction, and refinement always need to be considered.
- F.** Procedures that would be considered painful in a human need to be considered to be painful in an animal.
- G.** The best possible living conditions need to be maintained for animals kept for research, training, or testing purposes. Animal care needs to be supervised by a veterinarian experienced in laboratory animal medicine. Housing needs to ensure that the general health of animals is safeguarded and that undue stress is avoided, with appropriate attention paid to environmental factors such as temperature, ventilation, and humidity.

H. Personnel need to have appropriate qualifications, training, and experience when conducting procedures on animals. Opportunities for hands-on training will be provided as needed by the veterinary medical unit (VMU).

3. DEFINITIONS

A. **American College of Laboratory Animal Medicine (ACLAM).** ACLAM is the specialty certification board for laboratory animal veterinarians, recognized by the American Veterinary Medical Association.

B. **American Veterinary Medical Association (AVMA).** AVMA is the principal professional organization for veterinarians engaged in any specialty of the practice of veterinary medicine.

C. **Animal.** The term “animal” is defined as any live vertebrate animal used or intended for use in research or research training. An animal for purposes of compliance with the Animal Welfare Act Regulations is any live or dead cat or dog, non-human primate, guinea pig, hamster, rabbit, or any other warm-blooded animal which is being used, or is intended for use in research or teaching

D. **Animal Research.** Animal research refers to any use of laboratory animals in research or training.

E. **Association for Assessment and Accreditation of Laboratory Animal Care, International (AAALAC).** AAALAC is the accrediting body for animal research programs recognized by the VA.

F. **Animal Component of Research Protocol (ACORP).** The ACORP, the official VA animal protocol form, is the set of questions that must be considered during a review of animal protocols. It must be used by the VA Institutional Animal Care and Use Committee (IACUC) when a project involving animal research is being considered for use in research to be conducted at the VA.

G. **Director.** The highest ranking administrative official at the VAPORHCS, who also serves as the Institutional Official (IO). The Director appoints members to the IACUC and appoints the Research Compliance Officer.

H. **Chief Research and Development Officer (CRADO).** The CRADO is the VA Central Office research administrator given the authority and the responsibility for managing all human, animal, and laboratory VA research activities.

I. **Chief Veterinary Medical Officer (CVMO).** The VA Central Office veterinarian given the primary responsibility for formulating VA animal research policy, advising senior VA administrators on animal research issues, and providing support and guidance as needed to field research personnel conducting animal research. Veterinary medical and laboratory animal concerns and issues are the purview of the CVMO.

J. **Institutional Animal Care and Use Committee (IACUC).** The IACUC is the local committee charged with reviewing and conducting continual oversight of laboratory animal

research conducted at the VAPORHCS to ensure ethical treatment of animals and compliance with animal research regulations and guidelines. The IACUC is responsible for monitoring the animal care and use program and the facilities utilized to house and work with animals, and for working with the Institutional Official to correct any problems that have been identified. The IACUC is organized administratively as a subcommittee of the Research and Development Committee.

K. Institutional Official (IO). The Institutional Official (IO) is the legally authorized Signatory Official for a research program who provides all official communications to external agencies and ORO. Facility Directors are the IOs for VA facility research programs.

L. Research Compliance Officer (RCO). A Research Compliance Officer (RCO) is an individual who reports directly to the facility Director and whose primary responsibilities are auditing documentation related to facility research projects and informing the facility Director and research review committees about compliance concerns. The RCO may serve as a non-voting consultant to the IACUC on an as needed basis, which means that the RCO may attend meetings only when requested by the IACUC. The RCO may not serve as a voting or non-voting member of the IACUC per VHA Handbook 1058.01.

M. Office of Laboratory Animal Welfare (OLAW). OLAW is the PHS Office responsible for administering PHS Policy on Humane Care and Use of Laboratory Animals.

N. Office of Research Oversight (ORO). ORO serves as the primary Veterans Health Administration (VHA) office in advising the Under Secretary for Health on all matters of compliance and assurance regarding human subjects' protections, animal welfare, research safety, and research misconduct.

O. Public Health Service Assurance (PHS Assurance, or Animal Welfare Assurance). PHS Assurance is the documentation submitted to the OLAW (USDA), by an institution that pledges that the institution will comply with PHS Policy.

P. Public Health Service Policy on Humane Care and Use of Laboratory Animals (PHS Policy). PHS policies require institutions to establish and maintain proper measures to ensure the appropriate care and use of all animals involved in research and research training supported by PHS.

Q. Reduction. Reduction is minimizing the number of animals needed for research, testing, or training. Reduction may include optimizing a study to utilize animals as their own controls, gathering a maximum amount of data from each animal subject (e.g., by gathering data for more than one experiment concurrently, or designing experiments to prevent the need for duplicate control groups), and using more sophisticated measuring techniques to improve precision and to reduce the sizes of the groups needed.

R. Refinement. Refinement is modification of experimental protocols to minimize pain or distress, whenever possible. Examples include:

1. Identifying ways to prevent or relieve pain or distress likely to be caused by experimental procedures;
2. Setting the earliest possible endpoints for the research;
3. Using more appropriate analgesics and anesthetics for potentially painful

procedures as they become available; and

4. Increasing the effectiveness of post-surgical care with new technology.

S. Replacement. Replacement usually refers to the use of *in vitro* techniques or computer simulations in place of procedures on animals. Sometimes the term is applied to the use of less sentient species, such as invertebrates, birds, and reptiles, in place of more sentient animals such as mammals.

T. Research and Development (R&D) Committee. The R&D Committee is charged with overseeing and approving all research projects at the Medical Center and for maintaining high standards throughout the facility's research program.

U. Subcommittee for Research Safety (SRS). SRS is the subcommittee of the R&D Committee that reviews and approves the use of hazardous substances in VA research.

V. United States Department of Agriculture (USDA). USDA is charged with enforcing the Animal Welfare Act Regulations and Standards (henceforth known as USDA AWAR). The USDA Animal Care Section in the Animal and Plant Health Inspection Service is the administrative unit given the responsibility for monitoring compliance with USDA AWAR.

W. Veterinary Medical Unit (VMU). The VMU consists of the animal research facility plus the husbandry and veterinary technical personnel assigned to care for animals.

4. INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE

According to the USDA AWAR (9 C.F.R. §2.37) and PHS policy, each VA Medical Center with a program of research involving use of live vertebrate animals must establish an IACUC. The Director is responsible for providing adequate administrative support for the IACUC, including personnel to support the review and record-keeping functions of the IACUC (to include timely preparation of minutes and timely preparation of investigator correspondence and other documents).

A. Membership, Composition, and Terms of Service. The R&D Committee approves nominees for the IACUC. The Director must officially appoint members in writing, and the letter must specify the length of the appointments.

1. **Composition.** The composition of the IACUC must meet existing requirements set forth in the Animal Welfare Act and PHS Policy. A minimum of five members are required to serve as voting members to constitute an IACUC. Only a properly constituted IACUC may conduct official business. The required voting members include a Chairperson, the Attending Veterinarian, one scientist with animal research experience, a nonaffiliated member, and a nonscientist member (who must not be involved in animal research). If needed, the nonaffiliated and the nonscientist person can be the same member, although this practice is discouraged.
2. At least one member of the IACUC needs to be a member of the R&D Committee.
3. **Length of Terms:**
 - a. Chairperson. The IACUC Chairperson must be appointed by the Director

annually, without a lapse in service. There is no limit to how many times a chairperson may be reappointed.

- b. Membership. Members other than those who are designated *ex officio* (appointed on the basis of their position, such as the institutional veterinarian) may serve terms of up to three years, on staggered appointments. Members may be reappointed without lapse in service to the IACUC, and there is no limit to the number of times that a member may be reappointed.

B. VA-Affiliate IACUC Interactions

1. The VAPORHCS will maintain an IACUC separate from the affiliate IACUC. If an agreement for partial or full protocol reciprocity is in place, records must be kept at the VAPORHCS for protocols reviewed under such agreements.
2. No IACUC member may participate in the IACUC review, or in the approval of a research project in which the member is personally involved in the project, except to provide information requested by the IACUC. The IACUC member is excused from the meeting during the discussion and deliberation of the project. The IACUC is responsible for ensuring that the protocol review process is not compromised by conflicts of interest arising from members participating in animal research reviewed by the IACUC.
3. IACUC members should not participate in the IACUC review or approval of a research project in which the member has a financial conflict, except to provide information requested by the IACUC prior to the deliberations. The IACUC member is excused from the meeting during the discussion and deliberation of the project.

C. Functions of the VA IACUC. The VA IACUC must perform the review and oversight functions required by PHS Policy, the Guide, the Animal Welfare Act, the USDA AWAR, VA policy, and any other Federal regulations that impact IACUC function.

1. **Semi-Annual Evaluation of the IACUC Program and Facilities.** The VAPORHCS IACUC must perform an evaluation of the program of animal care and research use, and an inspection of the animal facilities and husbandry practices at least every six months. This evaluation must be conducted using the standards established in the most current Guide, PHS Policy, the Animal Welfare Act, and USDA AWAR.
 - a. The semi-annual evaluation must include all facilities and investigator areas where laboratory animals are used in procedures or housed longer than 12 hours.
 - b. Random review of IACUC records is no longer required.
 - c. The compliance items found in the VA Semi-annual Evaluation of the IACUC Program and Facility Checklist must be covered by the IACUC. The checklist incorporating all the elements needs to be completed within a month of the evaluation.
 - d. A list of IACUC members present during the semi-annual evaluation with the name, the degree(s) held, and the IACUC role (veterinarian, scientist with animal

research experience, nonscientist member, nonaffiliated member) of each member should be included. At least three IACUC members (including the veterinarian) need to conduct the program and facilities evaluation, unless exceptional circumstances prevent such attendance. All members of the IACUC are strongly encouraged to participate in the semi-annual evaluation; however, the review team must include at least two voting members of the IACUC.

- e. A majority (of all voting IACUC members) must vote to approve the evaluation report; each member must indicate approval by a signature next to the typed name and committee role. Then the report must be discussed with the Director by the IACUC Chairperson, veterinarian, and one or more research administrators. The Director then must sign the report, indicating that the report has been reviewed. Once the Director has signed the report, it must be sent to the CVMO through the Director within 60 days of the self-review date. A copy needs to be sent to the local R&D Committee for review, but R&D Committee approval is not needed before the document is sent to the CVMO.
- f. The report must be retained on file for at least three years by the research office.

2. **Research Proposal Review at Convened IACUC Meetings.** The IACUC must review and approve, require modifications in (to secure approval), table, or withhold (disapprove) approval of all research proposals involving species and activities included within the definition of an “animal” (see 3.C.). All research projects involving animals must be approved by the IACUC and then by the R&D Committee prior to commencement of any activities involving the use of animals. To review proposed research at a convened IACUC meeting, a quorum (a majority of voting members) must be present. In order for the research to be approved, it must receive the approval of a majority of those voting members present at the meeting. A quorum must be maintained for each vote to occur. If a quorum is not maintained, the proposal must be tabled, although suggestions for review may be recorded and communicated to benefit the investigator.

- a. Evaluations. The IACUC needs to consider the following topics in the preparation and review of animal care and use protocols:
 - 1) Rationale and purpose of the proposed use of animals and a clear and concise sequential description of the procedures involving the use of animals.
 - 2) Justification of the species and number of animals requested. Whenever possible, the number of animals requested should be justified statistically.
 - 3) Availability or appropriateness of the use of less-invasive procedures, other species, isolated organ preparation, cell or tissue culture, or computer simulation.
 - 4) Adequacy of training and experience of personnel in the procedures used, which includes verification of whether annual CITI training is up-to-date.
 - 5) Unusual housing and husbandry requirements.

- 6) Appropriate sedation, analgesia, and anesthesia.
 - 7) Unnecessary duplication of experiments.
 - 8) Conduct of multiple major operative procedures.
 - 9) Criteria and process for timely intervention, removal of animals from a study, or euthanasia, if painful or stressful outcomes are anticipated.
 - 10) Post-procedure care.
 - 11) Method of euthanasia or disposition of the animal.
 - 12) Use of hazardous materials and the safety of the working environment for personnel.
 - 13) Adequacy of training and experience of personnel in the procedures used.
- b. Pre-review. After submission to the IACUC, the Veterinary Medical Officer (VMO) performs a pre-review of each protocol, which is focused on administrative (form) issues, identification of sections where inadequate information is provided, and animal welfare issues (proper endpoints, use of anesthesia and analgesia, clarity in procedures being conducted). Training status for listed staff is also assessed. If time allows, investigators are given five business days to address pre-review concerns if they so elect.
- c. Meeting Materials are provided to IACUC members approximately one week but no later than three business days prior to the IACUC meeting. This includes an agenda with all business items listed, including reviewer assignments for all new protocols and continuing reviews.
- 1) The meeting materials contain a copy of the agenda, the previous month's minutes, information relevant to discussion of old or new business, and protocols and continuing reviews that the member was assigned to review. Electronic copies of all protocols are provided to all members by email; VA policy stipulates that all IACUC members receive complete copies of all protocol forms.
 - 2) Each new protocol is assigned to at least two voting committee members for detailed review. These members serve as the primary and secondary reviewers, and are expected, with the nonscientist or nonaffiliated member and VMO, to lead a discussion of the protocol. All committee members have the opportunity to comment on the protocol.
- d. Use of Parliamentary Procedures During IACUC Meetings. Consistent parliamentary procedures must be used to conduct business. The parliamentary system used needs to allow for discussion of each item, motions, seconds to motions, and official votes tallied by yeas, nays, and abstentions. To protect anonymity, the identity of the members making a motion, seconding a motion, and voting yea, nay, or abstaining should not be recorded. A motion must be seconded for a vote to occur. For a motion to pass, a majority of a quorum present must vote affirmatively.
- e. Approval Process. The IACUC may approve the protocol as written, require modification to secure approval, withhold approval, or table the protocol for review

at the next IACUC meeting (in the event that the IACUC believes that inadequate information is provided to assess animal welfare). When the IACUC votes that a protocol requires modifications to secure approval, the designated member review system is used. The Chairperson will assign two IACUC members to be the designated member reviewers of the revised protocol after ensuring that all IACUC members agree to designated member review of the required modifications. The Chairperson will also assign an alternate designated member reviewer in case one of the two designated member reviewers is not available to expediently review the revised protocol.

- 1) If approved as written, a letter informing the investigator that they may begin the proposed work is forwarded to the Research and Development office, where it is held until all grant and additional committee (R&D, SRS, IRB, et cetera) requirements are met. Once all appropriate approvals are obtained, the Investigator is notified by the ACOS for R&D that the project can begin.
- 2) If approved pending modifications (i.e., requiring modifications to secure approval), one of the following two processes occurs: 1) If all members of the IACUC are present at a meeting, the committee may vote to require modifications to secure approval and have the revised research protocol reviewed and approved by designated member review, or returned for full committee review at a convened meeting; 2) If all members of the IACUC are not present at a meeting, the committee may use designated member review subsequent to full committee review according to the following stipulations: all IACUC members agree in advance in writing that the quorum of members present at a convened meeting may decide by unanimous vote to use designated member review subsequent to full committee review when modification is needed to secure approval. However, any member of the IACUC may, at any time, request to see the revised protocol and/or request full committee review of the protocol. The investigator is notified in writing of the required modifications, which are agreed upon by the reviewers, given the names of the designated member reviewers of the IACUC to contact for additional details on the modifications, and reminded that the proposed work may not begin until final approval has been granted. The investigator must submit a memo detailing their response to the required modification(s) with a revised copy of the protocol to the IACUC office. At least two members review the modifications (typically the designated member reviewers) and notify the IACUC Coordinator (who then notifies the IACUC Chair) when it is ready for approval. A letter informing the investigator that they may begin the proposed work is forwarded to the Research and Development office, where it is held until all grant and additional committee (R&D, SRS, IRB, et cetera) requirements are met. Once all appropriate approvals are obtained, the Investigator is notified by the ACOS for R&D that the project can begin.
- 3) If approval is withheld (protocol disapproved), a letter detailing the committee's rationale, the protocol's required modifications, and a contact person on the committee (typically at least one designated member reviewer) is provided to the investigator, who is encouraged to modify the protocol and resubmit.
- 4) If the protocol is tabled, a letter detailing the committee's rationale, the

protocol's required modifications, and a contact person on the committee (typically at least one designated member reviewer) is provided to the investigator, who is encouraged to modify the protocol and resubmit.

3. **Amendment process.** Changes or modifications to an approved protocol require IACUC approval. The Principal Investigator will submit an amendment to the IACUC in the VA Innovation and Research Review System (VAIRRS). Review of amendments to approved ACORPs fall into three categories, depending on whether the changes are viewed as minor or significant (see Appendix A for details). Minor changes can be reviewed administratively. All significant changes to currently approved animal use protocols will be reviewed through one of three methods: Designated Member Review (DMR), Full Committee Review (FCR) or Veterinary Verification and Consultation (VVC). Each week, a description of the submitted amendment(s), the amendment document(s), and any supporting document(s) will be circulated to all IACUC members via email. Members will recommend DMR, FCR, or VVC within three business days. If the veterinarian feels that the VVC process is appropriate for the amendment, they will reply to the e-mail notifying the other IACUC members that the amendment could proceed through the VVC process. Other IACUC members may recommend VVC; however, if the veterinarian does not agree with that recommendation, the amendment will proceed through DMR or FCR. If the IACUC Coordinator does not receive a response from a member within three business days, the amendment review will proceed based on the recommendations of the other members. If any committee member requests full committee review, the amendment will be held until the next convened IACUC meeting. If the amendment is recommended for DMR and there are no requests for FCR, the IACUC Chair will assign two designated member reviewers to review the amendment. The designated member reviewers may approve, require modifications to secure approval, or refer the amendment to the full committee for review. If the designated member reviewers require modifications to secure approval, the same two designated member reviewers will review identical copies of the revised amendment. If one of the two designated member reviewers is not available to expediently review the revised amendment, the IACUC Chair will assign an alternate designated member reviewer. The designated reviewer outcome to approve must be unanimous.

Alternate designated reviewers: If both the IACUC Chair and the Alternate Chair are in conflict with an amendment and must recuse themselves, the VMO will be asked to either, 1) conduct administrative review, if the amendment qualifies, or 2) assign two designated member reviewers, if the amendment qualifies for DMR. If the VMO is not available, the IACUC Coordinator will ask another IACUC member to perform these tasks..

4. **Expedited Review.**

a. Protocols. In most cases, animal protocols will be reviewed during convened IACUC meetings. However, an expedited review process is available if circumstances such as grant funding receipt call for it. The IACUC Chair or Alternate Chair will determine whether the circumstance warrants expedited review. In the case of expedited review, an electronic copy of the protocol is provided to all members by email, and IACUC members are requested to agree within three business days that the protocol can be reviewed via designated member review or full committee review. When all IACUC members recommend designated member review or three business days have passed with a quorum recommending designated member review and no recommendations for full committee review, the process of review will follow that

described previously in 4.C.3. If any committee member requests full committee review, an attempt will be made to convene a properly constituted IACUC meeting with a quorum of voting members. If this is not possible, the protocol will be held for review until the next regularly scheduled convened IACUC meeting.

b. Annual Review. In most cases, annual review of animal protocols will be reviewed during convened IACUC meetings. However, an expedited review process is available if circumstances are warranted. The IACUC Chair or Alternate Chair will determine whether the circumstance warrants expedited review. In the case of expedited review, the IACUC members are polled via e-mail and asked to agree within three business days that the annual review can occur via designated member review or full committee review. If all IACUC members recommend designated member review or three business days have passed with a quorum recommending designated member review and no requests for full committee review, the process of review will follow that described in 4.C.3. If any committee member requests full committee review, an attempt will be made to convene a properly constituted IACUC meeting with a quorum of voting members. If this is not possible, the annual review will occur during the next regularly scheduled convened IACUC meeting.

5. Annual Review of Protocols.

a. Annual Review. The IACUC reviews the conduct of USDA species animal protocols annually, prior to the date of the initial approval. At least 60 days prior to the first and second anniversary dates of protocol approval, the investigator is sent an email notifying them the continuing review is due. The continuing review requires that the investigator provide the current basic information on the protocol, such as ACORP number, VAIRRS (aka IRBNet) ID number, title of project, staff, conflict of interest, number of approved animals, and a description of approved amendments or any adverse events. The investigator is asked to complete the continuing review form and submit it, as well as a revised abstract, in VAIRRS by a date that will ensure IACUC review prior to the anniversary date. If the work has been completed, the investigator should complete an IACUC ACORP Finalization form in VAIRRS requesting that the protocol be closed. Prior to each monthly IACUC meeting, the IACUC Chairperson will assign an IACUC member to review each continuing review form and abstract. The IACUC reviewer will complete a form that documents the assessment for continued IACUC approval and will make a recommendation to the IACUC (approval of study to continue for another 12 months; approval of the study for another 12 months with the following minor changes; table until further information is submitted; or disapproval). The recommendation by the IACUC reviewer will then be voted on by the IACUC. In the event that modifications are required to secure approval, one of the following two processes occurs: 1) If all members of the IACUC are present at a meeting, the committee may vote to require modifications to secure approval and have the revised research protocol reviewed and approved by designated member review, or returned for full committee review at a convened meeting; 2) If all members of the IACUC are not present at a meeting, the committee may use designated member review subsequent to full committee review according to the following stipulations: all IACUC members agree in advance in writing that the quorum of members present at a convened meeting may decide by unanimous vote to use designated member review subsequent to full committee review when

modification is needed to secure approval. However, any member of the IACUC may, at any time, request to see the revised protocol and/or request full committee review of the protocol. The investigator is notified in writing of the required modification(s) and asked to submit a memo detailing their response, along with a revised copy of the protocol, to the IACUC office. The IACUC reviewer will serve as the designated member reviewer of the recommended modification(s) and will notify the IACUC Coordinator (who then notifies the IACUC Chair) when it is ready for approval. Training status of listed staff is reviewed annually by the VMO.

- b. Third Annual Review. The initial protocol review provides approval for animal work for a total of three years. Continued work on the protocol requires re-review of an updated protocol. Prior to the third anniversary of the initial protocol approval, the IACUC must conduct a complete re-review of the protocol. At 60 days prior to the third anniversary date of the protocol, the IACUC Coordinator sends an email to the investigator reminding them of the anniversary date of the protocol and the fact that a new protocol must be submitted for IACUC approval prior to the anniversary date in order for work to continue on that protocol. Another reminder is sent at 30 days prior to the third anniversary date. The investigator is asked to submit a new protocol, utilizing the latest version of the ACORP forms. The new protocol will be reviewed at the next IACUC meeting, as described in Item 4.C.2.

D. Recording and Reporting Requirements

1. **Preparation of the IACUC minutes.** IACUC minutes will be written and published within three weeks of the meeting date, and will include:
 - a. At the top of the first page, on separate lines in a large typeface, place the bolded name of the facility and facility number, the official address, the official committee name, and the date of the meeting. Subsequent pages are to be numbered.
 - b. List all voting members present and absent (non-voting members may be listed separately). For each voting member, note the voting member's appointed role on the committee to establish that the IACUC is properly constituted (see Item 4.A.1. for required voting members). Use the term "ex-officio" only when the member's office or legal role (such as the institutional veterinarian) dictates a member's presence on the committee.
 - c. Indicate if a quorum is present. A quorum is defined as a majority (more than 50 percent) of voting members.
 - d. Arrange the minutes into at least three sections: review of previous minutes, old business, and new business. At each meeting, a review of semi-annual review schedules for correction needs to be conducted to monitor progress toward completing corrections of deficiencies previously identified.
 - e. Business items need to be retained under old business in subsequent minutes until the final approval is given by the IACUC, the project is disapproved by the IACUC, or the project is withdrawn from consideration by the investigator. The final disposition of each project needs to be clearly stated in the minutes.
 - f. For each project under consideration, list the first and last name of the

principal investigator, and the complete name of the project.

- g. For each new project, the motion passed by the committee (approval, require modifications to secure approval, tabled, disapproval) must be recorded with the exact vote, which must include the number voting for the motion, the number voting against, and the number abstaining (or the number excused). The IACUC members assigned as designated member reviewers also should be noted.
 - h. In the event that the IACUC Chairperson must be excused during the discussion of a project, the Alternate Chairperson will assume responsibility for the deliberations. In the event that the IACUC Chairperson and Alternate Chairperson both are excused during the discussion of a project, the IACUC Chairperson will assign another IACUC member as temporary Chairperson, so that they can assume responsibility for the deliberation of the project.
 - i. Committee deliberations on each project must be reflected in the minutes so that an outside observer can understand the issues discussed and recognize the specific revisions and clarifications requested for each protocol under consideration. Discussion of all Category E protocols must include deliberations regarding whether the omission of pain relief was acceptable or whether it required revision. Following the IACUC meeting, the IACUC members provide their review comments in VAIRRS. Experience has shown that when IACUC members provide written or electronic copies of their reviews, their comments can be used to document deliberations and greatly streamline the process of writing the minutes as well as communicating IACUC decisions in writing to investigators.
 - j. The minutes must note which members have recused themselves from project(s) to prevent conflicts of interest.
 - k. If they are important to understanding the conduct of business, copies of any internal or external reports or correspondence with outside agencies referenced in the minutes need to be attached to the minutes.
2. **Review of IACUC minutes.** At the next convened IACUC meeting, members vote to approve the previous month's minutes or to require minor modifications for approval. Once IACUC minutes are approved, they are signed by the IACUC Chairperson. The R&D Committee needs to review a copy of the signed minutes as an item of business. However, R&D Committee approval is not necessary prior to sending minutes to ORD for review, i.e., if ORD requests a copy for review.

E. Mandated Reporting of Deficiencies. As a condition of extending the privilege of conducting animal research to individual Medical Centers, the IACUC and institutional administrators will avoid any appearance of hiding or suppressing deficiencies. The IACUC will ensure the proper reporting of problems in research as directed by VHA Handbook 1058.01 (§8). In general, there is a five day standard for reporting. That is, five days to report the initial incident in writing to the IACUC, then five days for the IACUC's determination to be provided to the Director or IO (if the IACUC deems that the incident is reportable), then five days for the Director to report the incident to ORO. Per the ORO, reportable events for animal research include the following:

1. **Unanticipated loss of animal life.** Apparent unanticipated loss of animal life includes loss due to physical plant deficiencies, engineering failures, worker errors, or other mishaps. Losses associated with experimental manipulations that are within the range of expected outcomes described in the IACUC approved protocol do not need to be reported. Occasional loss of animals (e.g., in large breeding colonies, from housing incompatible adult animals) need not be reported *beyond* the IACUC *if* the IACUC determines that the incident was an expected or isolated event *and* was not the result of improperly trained study personnel, inadequate veterinary care, inadequate monitoring, or protocol noncompliance.
2. **Animal theft or potentially dangerous escape.** This includes any theft or potentially dangerous escape of animals (e.g., infected). The occasional escape of an animal within the primary holding facility that is resolved without incident is not considered significant or reportable.
3. **Work-related or research-related injuries involving animal research.** Any apparent work-related injury to animal research personnel (or any apparent injury to other personnel related to animal research) that is reportable, is one that requires more than minor medical intervention (i.e., basic first aid), requires extended surveillance of the affected individual(s), or leads to serious complications or death.
4. **Reportable incidents under applicable federal standards.** Incidents reportable under applicable Federal standards include, but are not limited to, VHA Handbooks on laboratory animal welfare and research safety, NIH OLAW requirements, the PHS policy on Humane Care and Use of Laboratory Animals, the Guide for the Care and Use of Laboratory Animals, and USDA Animal Welfare Act Regulations (see Item 4F, below, for examples).

F. Examples of categories of deficiencies under applicable federal standards that must be reported to outside authorities and the elements needed in the report are:

1. **Any serious or continuing non-compliance** (including any serious deviation or continuing non-compliance with the provisions of the Guide, as required by the PHS Policy), USDA AWAR, or ORO (VHA Handbook 1058.01). The report needs to include:
 - a. When and how the IACUC became aware of the problem.
 - b. When the investigation was performed to determine facts and detail the circumstances that led to the non-compliance.
 - c. The results of that investigation, and
 - d. What corrective actions the IACUC approved to stop the noncompliant activity and prevent future recurrences.
2. **Suspensions** of protocols previously approved or suspensions of procedures or studies never given approval. The report needs to include:
 - a. When and how the IACUC became aware of the problem.
 - b. When the investigation was performed to determine facts and detail circumstances that led to the non-compliance.

- c. The results of that investigation.
 - d. When the IACUC convened a quorum to suspend the activity.
 - e. What corrective actions the IACUC approved to prevent recurrences.
3. **Failure to correct a significant deficiency** (identified during a semi-annual IACUC program or facility self-assessment review) according to the schedule approved by the IACUC. The report needs to include:
- a. The date when the IACUC identified the deficiency.
 - b. The timetable and plan approved for correction.
 - c. Why the correction(s) could not be completed according to the timetable.
 - d. The revised timetable.
 - e. The plan to finish the correction(s).

G. Suspension of Projects. The IACUC may suspend an activity that it previously approved if it determines that the activity is not being conducted in accordance with the description of that activity provided by the Principal Investigator (PI) and approved by the IACUC. It may also suspend any animal procedures not approved by the IACUC. Unless the IO has granted additional authority, the IACUC may suspend an activity only after review of the matter at a properly convened IACUC meeting and with the suspension vote by a majority of a quorum.

H. Investigation of Allegations of Improper Animal Care or Use. All internal and external allegations of improper animal care and use (including those as defined in VHA Handbook 1058.01, see Item 4E, above) must be reviewed promptly by the IACUC and investigated, if warranted. A written report of the review or investigation needs to be approved by a majority of a convened IACUC quorum and sent to the Director through the ACOS for R&D.

I. Semi-Annual Evaluation of IACUC Program and Facility. Semi-annual evaluation must be prepared by the IACUC as described in 1200.7, subparagraph 8d(1). No later than 60 days after the self-assessment review date, a copy of the approved report signed by a majority of IACUC members and the Director must be forwarded to the CVMO's office through the ACOS for R&D and the Director.

J. Mandatory Training. Through IACUC oversight, all personnel involved with animal research must receive training to perform their duties related to animal research competently and humanely. This extends to IACUC members, veterinarians, veterinary technicians, husbandry staff, research technicians, investigators, and all others that perform procedures or manipulations on laboratory animals. Prior to approving any protocol, the IACUC must ensure that all staff listed on the protocol have been adequately trained. At a minimum, investigators and research staff who utilize laboratory animals must complete "Working with the IACUC" and the appropriate species-specific course on www.CITprogram.org. IACUC members must additionally take the "Essentials for IACUC Members" course and be trained on topics pertinent to their committee

tasks. These web-based training courses must be completed every three years to demonstrate compliance with Federal animal research training mandates. Hands-on animal use and surgical training will be provided by the VMO or by VMU personnel that are assigned by the VMO.

5. REFERENCES

- a. Animal Welfare Act, Public Law 89-544 as amended; codified at 7 U.S.C. 2131-2159.
- b. USDA Animal Welfare Act Regulations and Standards, 9 CFR Parts 1, 2, 3, and 4.
- c. The Health Research Extension Act of 1985, Public Law 99-158, as amended, "Animals in Research," codified at 42 U.S.C. Section 289d.
- d. PHS Policy on Humane Care and Use of Laboratory Animals. NIH, Office of the Director. Revised September, 1986, and reprinted October, 2000, 2002, and 2015.
- e. U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training. Prepared by the U.S. Interagency Research Animal Committee, and originally published Federal Register, May 20, 1985, Vol. 50, No. 97, by the Office of Science and Technology Policy.
- f. Guide for the Care and Use of Laboratory Animals. National Research Council, 2011 (or most recent edition).
- g. AVMA Guidelines for the Euthanasia of Animals. 2020 Edition (or most recent edition).
- h. Biosafety in Microbiological and Biomedical Laboratories. CDC and NIH. 6th edition (or most recent revision)
- i. NIH Guidelines for Research Involving Recombinant DNA Molecules. NIH, 1994, and as subsequently amended.
- j. CDC, Title 42 Code of Federal Regulations (CFR) 73, Possession, Use, and Transfer of Select Agents and Toxins.
- k. AAALAC, International. "Rules of Accreditation," updated July 2020.
- l. Nuremberg Code of 1947.
- m. VHA Handbook 1108.1, Controlled Substances.
- n. VA Handbook 0730, Security and Law Enforcement.
- o. Title 38 United States Code, Part V, Chapter 73, Section 3707, Functions of Veterans Health Administration: Research Programs.
- p. National Research Council. National Need and Priorities for Veterinarians in Biomedical Research. 2004.
- q. Potkay S, NL Garnett, JG Miller, CL Pond, DJ Doyle. "Frequently Asked Questions about the Public Health Service Policy on Humane Care and Use of Laboratory Animals,"

Laboratory Animal 24:24-26, 1995.

r. USDA Animal and Plant Health Inspection Service, Animal Care Section. Animal Care Policy Manual, Policy #10: Licensing and Registration of Producers of Antibodies, Sera and/or Other Animal Parts and Pregnant Mare Urine (PMU). April 14, 1997.

s. Potkay S, NL Garnett, JG Miller, CL Pond, DJ Doyle. "Frequently Asked Questions about the Public Health Service Policy on Humane Care and Use of Laboratory Animals," Contemporary Topics 36:47-50, 1997.

t. Baker DG. "Natural Pathogens of Laboratory Mice, Rats, and Rabbits and Their Effects on Research," Clinical Microbiology Reviews. 11: 231-266. 1998.

u. VHA Handbook 1108.2, Inspection of Controlled Substances.

v. M-2, Part VII, Pharmacy Services.

w. VA Handbook 5005, Staffing, Part II, Appendix F32.

x. VHA Handbook 1200.6, Control of Hazardous Agents in VA Research Laboratories.

y. VHA Handbook 1200.8, Safety of Personnel Engaged in Research.

z. VHA Handbook 1105.1, Procedures for Management of Radioactive Materials.

aa. VHA Handbook 1058.01, Research Compliance Reporting Requirements.

bb. VHA Handbook 1200.07, Use of Animals in Research.

IACUC Standard Operating Procedure (SOP): Appendix A Modifications to Approved Protocols via Amendment

Definitions: Animal Welfare Regulations use the following terms interchangeably when applying them to modifications to an approved protocol: amendment, change, and modification.

Background: Animal Welfare Regulations require that Principal Investigators receive approval from the IACUC for all significant changes to approved animal research protocols (ACORPs). However, these regulations provide little guidance with respect to the actual criteria for determining whether a change is significant or minor. The goal of this appendix to the IACUC SOP is to describe the process regarding modifications to approved protocols and to distinguish between a minor and a significant change to an approved IACUC protocol.

Levels of Review: Changes or modifications to an approved protocol require IACUC approval. The Principal Investigator will submit an amendment to the IACUC Coordinator who will distribute the amendment to all members of the IACUC. Any member of the IACUC can request full committee review of an amendment, or they can communicate that designated member review of the amendment is acceptable.

Changes to approved protocols fall into three categories:

1. Minor changes by Administrative or IACUC Chair approval
2. Significant changes by Designated Member Review by at least two members of the IACUC or by VVC
3. Significant changes by Full Committee Review

Minor vs. Significant Modification:

Those items considered to be minor modifications include, but are not limited to, the following changes:

- In research personnel (addition or deletion) other than the Principal Investigator, but deletion of personnel now can be requested on the continuing review form
- In the location of animal procedures (i.e., adding or changing the location)

According to the Office of Laboratory Animal Welfare (OLAW), National Institutes of Health, the IACUC has some discretion to define what it considers a significant change or to establish a mechanism for determining significance on a case-by-case basis. Because significant changes require IACUC approval, the IACUC must define its policy and mechanism for determining significance.

Items considered to be significant modifications by OLAW and by the VAPORHCS IACUC, and must be approved by FCR or DMR include, but are not limited to, the following changes:

- In objectives of the study, if the overall scope of the work does not change. New objectives, hypotheses, and methods/procedures may require submission of a new ACORP.
- From non-survival to survival surgery
- Resulting in greater discomfort or in a greater degree of invasiveness (e.g., a procedure that increases the pain category)
- In Principal Investigator
- In the addition of a new procedure, including surgery
- Changes in housing and or use of animals in a location that is not part of the animal program overseen by the IACUC

Items considered to be significant modifications may be handled administratively according to IACUC reviewed and -approved policies in consultation with a veterinarian authorized by the IACUC (Veterinary Verification and Consultation process (VVC)) include changes in:

- Anesthesia, analgesia, sedation, or experimental substances
- Euthanasia to any method approved in the *AVMA Guidelines for the Euthanasia of Animals*
- Duration, frequency, type, or number of procedures performed on an animal

The VAPORHCS IACUC adheres to the guidance provided by OLAW on whether an amendment to a protocol is significant and uses the above criteria to make this determination.