Proposal Review and Approval

Policy: Any use of live vertebrate animals for teaching or research, including pilot and/or internally funded research, at the University of Louisville (UofL) must be reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) prior to the start of related research or teaching activities. Approval may be granted only after a *Proposal to Use Laboratory Animals in Research and Teaching ("Proposal")* has been submitted by the Principal Investigator and reviewed by the IACUC.

Principal Investigators (PIs) must be University faculty or otherwise meet criteria defined in applicable University policies (*e.g.*, Research Handbook). Current PIs departing UofL must have a gratis appointment at the University of Louisville to continue to meet the criteria for serving as PI on an IACUC *Proposal*. Otherwise, PIs departing UofL are responsible for notifying the IACUC Office or Assistant Vice President for Research Services in advance of their departure date to make arrangements for any current IACUC *Proposals* and animals in-house. All IACUC *Proposals* under a departing, non-gratis PI must be closed and arrangements must be made for the transfer or disposition of animals under the *Proposals* (prior to closure), or the *Proposals* must be transferred to another PI and approved by the IACUC via iRIS. If a PI departs without making prior arrangements, any animals remaining on the departed PI's IACUC *Proposals* will be transferred to the Comparative Medicine Research Unit (CMRU) Holding Protocol and the *Proposals* will be closed within 7 days. If no prior arrangements were made for the disposition of the animals (export, transfer, or euthanasia), their disposition will be determined by the Attending Veterinarian. All expenses incurred while animals are assigned to the CMRU Holding Protocol still remain the responsibility of the department.

Proposal approval expires by the end of three years following the date of approval. A new *Proposal* to use laboratory animals in teaching or research must be submitted for *de novo* review and approval at the end of three years.

Studies characterized by the likelihood of pain or stress will not be considered by the IACUC without comprehensive and explicit scientific justification. Such *Proposals* will be approved only when detailed scientific justification is provided for the purpose of the study and the inappropriateness of less "severe" alternatives. Class III *Proposals* must also detail the incompatibility of pain/distress relief and the goals of the research.

In the *Proposal*, the Principal Investigator must also provide a detailed description of the objective criteria that will be used to determine when an unacceptable level of pain or distress is reached and the intervention that will occur when this threshold, or "humane endpoint" is reached. The Principal Investigator will be responsible for monitoring high-risk animals to ensure that the specified criteria for determining unacceptable levels of pain or distress are met. The CMRU staff will also assist in monitoring high-risk animals. Should the CMRU identify animals requiring immediate attention, attempts will be made to contact the Principal Investigator or a suitable designee. In the event that these

individuals cannot be reached, ***CMRU veterinarians will intervene on behalf of the animal. This intervention may include euthanasia.***

The IACUC also requires a written *Proposal* for the use of vertebrate animal tissue(s), using a form entitled, *Proposal to Use Fresh or Frozen Animal Tissues in Research and Teaching*. The use of plants, bacteria, protozoa, or invertebrate animals is excluded from the IACUC review process. However, in accordance with the Guide for the Care and Use of Laboratory Animals, the IACUC expects that the use of invertebrate animals (*e.g.*, cephalopods) will be conducted using comparable ethical considerations.

Proposals for which the PI has not responded to reviewer(s) comments or resolved safety contingencies for over 12 months will be considered withdrawn from the review process and will revert to the beginning of the review process if a response is received after this time frame.

Rationale: Federal regulations and guidelines require the IACUC to review and approve all anticipated animal use. Review and approval of the *Proposal* form provides this mechanism. During *Proposal* review, the significance of study goals is weighed against the pain and/or distress that may be imposed on animals which serve as models. Decisions involving *Proposal* disposition are made only after consideration has been given to other research methods which may not involve animals and/or cause pain or distress. The Committee gives ethical consideration to animal use as well as to the benefits related to the improvement of animal or human health or other societal good.

Procedures, Guidelines, and Exceptions:

1. Definitions Used

a. *New Proposal*. A new *Proposal* to use animals in research and/or teaching is one that does not have current IACUC approval.

b. *Three-Year Renewals* are previously approved *Proposal*s which have been resubmitted to comply with the IACUC mandate for three-year *de-novo* review.

c. *Modified Proposal*. A modified *Proposal* is one in which the Principal Investigator requests protocol change(s) in a currently approved project. The procedures for reviewing requests to modify existing *Proposal*s are described in "Modification of an Approved Proposal."

d. Experimental groups are categorized based on the anticipated amount of pain and distress associated with the procedure used. Refer to the IACUC policy "Pain and Distress Class Categorization."

2. Submission and Administrative Pre-Review

Incoming *Proposal*s are examined by IACUC Office staff to ensure that the Principal Investigator has provided all pertinent information required for Committee review. IACUC Office staff may also conduct a thorough pre-review to ensure that the *Proposal* is suitable for review.

3. Pre-Review

All *Proposals* are assigned to an CMRU veterinarian for review. The IACUC Office will also assign the appropriate safety unit representative for *Proposals* involving the use of biological, chemical, or physical hazards to review the *Proposal.* One Community Member, a Clinical Librarian if available, will be assigned to review Proposals. Reviewers may require revisions to the *Proposal* ("stipulations") before completing their review and may provide review comments for consideration by the Designated Reviewer.

4. Reviewer Assignment

Proposals will be assigned to a Designated Reviewer and additional Review Consultant(s). Review Consultants are generally IACUC scientific committee members but may also be non-member expert consultants. Review consultants provide review comments for consideration by the Designated Reviewer. The IACUC Chair has delegated the authority to assign the Designated Reviewer to the IACUC office. The Designated Reviewer will be chosen from the voting IACUC scientist membership. Responsibility for serving as a Designated Reviewer, as described in Public Health Service "Policy on Humane Care and Use of Laboratory Animals" and USDA Animal Welfare Regulations, is rotated among scientist members and conflict of interest is avoided. Pain Category E *Proposals* will have at least one Review Consultant assigned to review them in addition to the pre-reviewers and any expert non-member consultants. Other *Proposals* may be assigned to non-IACUC member expert consultants as deemed necessary by the IACUC Chair and/or Attending Veterinarian.

Reviewers and Consultants are notified of assignment automatically by iRIS or via email; all committee members and non-member expert consultants have web-based access to the *Proposal* and other pertinent information submitted by the Principal Investigator and pre-reviewers.

5. IACUC Activity Report and Requests for Full Committee Review

All *Proposal*s undergoing review are listed on an ***IACUC Activity Report***. The report includes information such as the PI, title, species, highest pain/distress category, and Lay Summary and is forwarded at least weekly to all members of the IACUC via e-mail, facsimile, or other expeditious form of delivery. All committee members have access to or may request a complete copy of any *Proposal* should additional information be desired. Furthermore, any IACUC member may request Full Committee Review (FCR) of any *Proposal*. Once requested, final committee action must await FCR.

Committee members are allowed three calendar days following submission of an IACUC Activity Report; lack of a response within three days is considered acceptance of a *Proposal* for Designated Review. If a PI requires approval within three calendar days, a special convened meeting of at least a quorum of the committee must be held for *Proposal* review.

6. Designated Review Process and Actions/Recommendations

The Designated Reviewer will review the *Proposal* and any comments by other reviewers, if any. Note that lack of comments by (a) Review Consultant(s) within 7 days may be considered a recommendation for approval. The Designated Reviewer then has the authority to:

a. ***Recommend approval***, if no other revisions are required,
b. ***Require revisions to secure approval***, or

c. ***Request Full Committee Review***. Note that the Designated Reviewer may not "disapprove" or "table" a *Proposal;* any decision other than "recommend approval" or "require revisions to secure approval" must involve a Full Committee Review.

Approval for *Proposals* that involve the use of hazardous substances in living animals is contingent upon safety office/committee review and approval. The IACUC Office and Chair are responsible for ensuring that safety-related contingencies have been met.

7. Full Committee Review

Any committee member may request a Full Committee Review (FCR) of a *Proposal*. In such an instance, a notice, which may include a copy of the *Proposal*, is forwarded to all IACUC members and the assigned reviewers. The Designated Reviewer becomes the Primary Reviewer for the *Proposal*, assisted by the Veterinary and Review Consultants. The Principal Investigator may be asked to participate in Committee discussions related to the proposed research. The IACUC may invite additional consultants to assist in the review of complex issues arising out of its review of proposed activities, although consultants may not vote with the IACUC.

Discussion of the *Proposal* during a convened meeting of the IACUC, in which a quorum (>50%) of the voting membership is present, will be led by the Primary Reviewer and assisted by the Veterinary and Review Consultants. IACUC members with a conflict of interest will not participate in the review process or contribute to the constitution of a quorum. All voting committee members agree that the quorum of members present at a convened meeting may decide by unanimous vote to use DMR subsequent to a FCR when modification is needed to secure approval.

Action on the *Proposal* is based on a majority vote. Possible Full Committee actions/decisions include:

a. ***Approval***, if the *Proposal* is suitable as submitted.

b. ***Revisions required to secure approval***, if contingencies must be met, yet the Committee is comfortable with delegating the review of the response. Such contingencies must be clearly outlined and forwarded to the Principal Investigator by either the Primary Reviewer or Chair, who is then also responsible for ensuring that the contingencies outlined have been met. In accordance with PHS Policy, this reverts the review to Designated Review, and therefore can only occur following a *unanimous* vote for this action (in other words, any dissenting vote requires that the *Proposal* be "tabled"). The IACUC Office will include the revised *Proposal* provided by the PI on the IACUC Activity Report.

c. ***Withhold approval***.

1) Tabled: When issues of concern exist such that the committee requests additional information for Full Committee Review, the *Proposal* is "tabled." All such issues must be clearly outlined and forwarded to the Principal Investigator by either the Primary Reviewer or Chair; the responses by the Principal Investigator are then returned to the next IACUC meeting for deliberation by the Full Committee.

2) Disapproved: When the committee determines that a proposed study protocol is unacceptable according to federal, state, and/or local regulations, or fails to meet University standards,

disapproval may be recommended. The Principal Investigator is notified of disapproval by a letter from the IACUC Chair in which the basis for Committee action is clearly stated.

8. IACUC Chair Review and Action

After Designated or Full Committee Review is completed and other relevant correspondence (*e.g.*, results of various safety committee review) are received by the IACUC Office, the *Proposal* approval letter is prepared for the IACUC Chair. Should the Chair identify additional concerns, they may forward these concerns to the Designated Reviewer for resolution with the Principal Investigator. In the Chair's absence, the Vice-Chair or another scientist member of the IACUC will take final action on a *Proposal*. The Principal Investigator is notified of final *Proposal* action by letter. The date on this letter is considered the *Proposal* initiation date; *Proposal* expiration is three years from this date.

9. Conflict of Interest

The PHS *Policy* and Animal Welfare Act and Regulations state that no IACUC member "may participate in the IACUC review and approval of an activity in which that member has a conflicting interest… except to provide information requested by the IACUC."[1,2] IACUC members and consultants are responsible for disclosing any potential or perceived conflict of interest. A conflict of interest is a situation or relationship that may compromise an IACUC member or consultant's impartial judgment and includes any situation in which an IACUC member or consultant has a significant personal, intellectual or financial interest in the proposed research or clinical investigation. Conflicting interest includes, but is not limited to, the following circumstances where an IACUC member or consultant:

i. Is or will be involved in the design, conduct or reporting of the *Proposal*
ii. Is related to or has a relationship with an individual involved in the design, conduct or reporting of the *Proposal* which would impact his/her ability to objectively review a *Proposal*
iii. Has financial, proprietary, or managerial interest in the research. Examples include receiving salary or other payments for services; equity interest with the sponsor or agent of the sponsor; serving as a supervisor or subordinate to the Principal Investigator
iv. Is involved in a competing research program, access to funding or intellectual information may provide an unfair competitive advantage, or a member's personal biases may interfere with his or her impartial judgment[3]

Any IACUC member or consultant with a conflict of interest must inform the IACUC Chair and IACUC Office and may not participate in the IACUC review. During an IACUC meeting, committee members or consultants should make known any conflict of interests prior to the Committee's discussion of business. IACUC members or consultants with a conflict of interest must recuse themselves and leave the room during deliberations and voting and may not contribute to the *quorum* for conducting official IACUC business. If an investigator believes an IACUC member to have a potential conflict, the investigator may contact the IACUC Chair or IACUC Office to request that member be excluded from the review process.

10. Review Frequency

IACUC *Proposal* approval expires at the end of three years. Four, three, two, and one month(s) prior to *Proposal* expiration, the Principal Investigator is notified by e-mail in order to continue the study, a new *Proposal* must be submitted for *de novo* review and approval. Review is conducted according to the procedures given for new *Proposals*.

11. Appeal Process

The Principal Investigator may appeal an IACUC action. An appeal must be made in writing to the IACUC Chair and/or the Institutional Official. The Institutional Official cannot approve a *Proposal* not approved by the IACUC, but can encourage the IACUC to reconsider its decision. If it is determined that the IACUC will reconsider its action, Full Committee Review of the *Proposal* is required.

References:

1. Public Health Service. Policy on Humane Care and Use of Laboratory Animals (US Department of Health and Human Services, Washington, DC, 1986; amended 2002).
2. Code of Federal Regulations, Title 9, Chapter 1, Subchapter A — Animal Welfare: Part 2 Regulations. §2.31.
3. Office of Laboratory Animal Welfare. Institutional Animal Care and Use Committee Guidebook 2nd ed. 15 (US Department of Health and Human Services, Bethesda, MD, 2002).