STANDARD OPERATING PROCEDURE (SOP)

TITLE: Protocol Review and Approval

1. Scope

The IACUC is responsible for assuring that the research, husbandry, teaching and testing programs involving animals at the University of Pittsburgh comply with all applicable regulations and policies and responsibly address concerns regarding animal welfare. To fulfill this responsibility, the IACUC reviews all animal research and testing procedures. **No animal experimentation or use is permitted at the University of Pittsburgh without written approval by the IACUC.** This requires all animal users at the University to complete a protocol application using the Institution's online protocol management system. This system manages the review process from beginning to end, and allows the research team access to the protocol and its state in the review and approval process at all times. The system stores all protocol information in an online database so that the IACUC may accommodate requests for information from the Association for the Assessment and Accreditation of Laboratory Animal Care, International (AAALAC), Office of Laboratory Animal Welfare (OLAW), and the US Department of Agriculture (USDA) and any other regulatory or internal requests.

2. Procedure

A. New Protocol Application Process:

Investigators must submit all new IACUC protocol applications via Animal Research Online (ARO), the IACUC's online protocol management system. A guide for completing online applications can be found Applications are processed in the order that they are received at the IACUC Office. There are no expedited reviews.

The IACUC Chair approves all IACUC reviewers and assigns them to Designated Member Review subcommittees. There are three rodent Subcommittees and one Large Animal Subcommittee. Each Subcommittee contains scientific members with expertise in certain species, nonscientific members, veterinarians, environmental health and safety (EH&S) reviewers, administrative reviewers and other individuals, such as a radiation safety reviewer or environmental enrichment specialist, necessary for the review of any protocol so assigned.

An IACUC Coordinator responsible for guiding the protocol through the review process is assigned to each protocol. The Coordinator reviews all applications for accuracy and completeness. Incomplete applications or applications with administrative errors must be returned to the Investigator for revision before being sent to reviewers. The assigned Coordinator also ensures that all required training for the protocol has been completed by each member of personnel listed on the protocol and will notify the Investigator of any pending requirements.

The IACUC Coordinator assigns each protocol application to one of the subcommittees and five assigned Subcommittee's Designated Member Reviewers (two scientific members, one veterinarian, one administrative reviewer and one EH&S analyst). All changes in assigned Designated Member Review made after the review initiates are approved by the IACUC Chair. Other reviewers are assigned, as necessary. Initial reviews are expected to be completed in two weeks. Reviewers may approve the application, request revisions or ask questions about the application, or refer the protocol to the full IACUC for review.

Once all IACUC Designated Member Reviewers have returned their reviews of the application, the Coordinator sends any questions to the Investigator. The Investigator must answer all questions and revise their application accordingly.

If the investigator does not respond to the reviewers' questions after four weeks, a reminder will be sent. If six weeks passes with no response, the IACUC Office may withdraw the protocol from review.

After the Investigator sends responses (completed review form and rappropriately revised protocol) the Coordinator sends the materials back to the IACUC Designated Member Reviewers for approval. This process will continue until all IACUC reviewers have approved the application, at which time the protocol will be approved by the IACUC Chair or Vice-Chair by electronically signing a letter of approval.

All personnel listed on a protocol must satisfy all IACUC and EH&S mandated training and safety requirements prior to approval.

The entire IACUC receives a weekly listing of new protocols, modification requests and annual renewals submitted to the IACUC Office. The listing provides the name(s) of the Investigator(s), the project title, the funding agency, a project description narrative, the species of experimental animal, and the number of animals to be used in the study. Any IACUC member with an interest in a protocol on the list may request to be assigned as a reviewer and submit a review of the protocol and/or refer it to the full committee for review.

No IACUC member can participate in the IACUC review of a protocol or activity in which that member has a conflicting interest except to provide information requested by the IACUC.

1. Full Committee Review

If a protocol is referred to the full IACUC, a vote of approval at a convened meeting with quorum present is required for the application to be approved, unless the IACUC votes to refer the application back to the original subcommittee. If the full committee has questions, the decision regarding approval will be tabled until the next convened meeting.

Applications may be referred to the full IACUC for any reason by any IACUC member. Typical reasons for referral to the full committee include:

- Applications including death as an endpoint
- Studies including animal pain or distress that is not scientifically justified
- Requests for >12 housing outside of a university-managed facility (such as a laboratory)
- Questions regarding the required harm/benefit analysis
- Requests for an exemption to the *Guide for the Care and Use of Laboratory Animals*

If a protocol is referred to the Full Committee for review, the IACUC may:

- Approve the protocol
- Reject or disapprove the protocol
- Require modifications before approval
- Refer the protocol back to Designated Member Review

The results of the IACUC's deliberations are sent to the Investigator along with any questions or requirements that must be satisfactorily addressed to grant approval of the application by the next scheduled committee meeting.

The Investigator will be notified of the committee's decision following the full committee meeting. If ithe committee decides not to approve the application, the Investigator will be informedof the reason for the action.

2. Committee Decisions

a. Approval

If the IACUC considers that all significant points have been addressed by the Investigator and that all questions that have been raised during review have been satisfactorily addressed. Once a protocol has been approved, the Investigator has permission to conduct the experiments described in the proposal on the number of animals justified.

At the time of approval, the IACUC Office will generate and approval letter and the IACUC Chair will be informed of the results of the review. The IACUC Chair then verifies that the review was conducted in accordance with all regulations and IACUC policies. If the review is deemed appropriate, the IACUC Chair signs the approval letter electronically. The application is not approved until the IACUC chair has issued an approval.

Approval letters are addressed to the Investigator for submission and verification to granting agencies to verify IACUC review and approval. They are available for download any time thereafter. A copy of the approved protocol and Risk Assessment, which delineates the hazards associated with the application and the training/medical surveillance requirements, is always available online to all personnel listed on the protocol.

Once the application is approved by either the subcommittee reviewers or the full committee, the IACUC assigns an eight-digit protocol number to the protocol. The first two digits of the protocol number designate the year of approval, the third and fourth digits designate the month of approval and the last four digits identify the application. For example, 12020033, indicates the application was approved in February of 2012 and assigned number 0033.

IACUC protocol approval is provided for a time period of three years, as specified by PHS Policy IV C 5. This policy requires *de novo* review of the protocol after three years. Protocols that have not significantly changed in the three years since their original submission can be easily resubmitted for review.

b. Disapproval

If an Investigator refuses to modify a proposal in accordance with the full IACUC's directions, or fails to supply information showing that their laboratory has appropriate facilities and staff for the proposed research, the full IACUC may, at a convened meeting with a quorum present, decide not to approve the protocol. The specific reasons for disapproval will be presented to the investigator in writing.

Appeals of a decision not to approve an application may be submitted to the IACUC Chair. Appeals must include additional evidence that was not previously made available or the solicitation of experts able to assist the IACUC in their deliberations.

Disapproved proposals cannot be administratively approved by a higher authority. However, an IACUC approved protocol can be administratively disapproved by the Institution due to financial, facility-related or other considerations.

c. Termination

The IACUC may terminate an approved protocol due to the following reasons:

- Non-compliance issues
- Failure to renew annually
- Failure to complete required training

For non-compliance issues, particularly those that involve animal welfare concerns, protocols may be terminated immediately. For failure to renew annually and failure to complete required training, the Investigator is given a 30 day notice prior to termination. Investigator will be notified of protocol termination by campus mail, phone call and/or email message. The DLAR is notified of all IACUC terminated protocols and will decide the disposition of study animals. Please see the IACUC Policy, *Confiscation and Holding of Animals for Non-Compliance* for further information.

Investigators with protocols that have been terminated due to failure to annually renew must submit an annual renewal application immediately and address any training and/or medical surveillance issues right away. The IACUC Office will not approve annual renewal applications thirty days after termination. If an annual renewal application is not

approved in this time frame, a new protocol application must be submitted, reviewed and approved before research may continue.

d. Withdrawal

The IACUC may withdraw any pending protocol from the review process if the PI does not respond in a timely fashion during the review process. This occurs when questions are sent to the PI and the PI takes longer than 2 months to respond. The IACUC will send notice to the PI that the protocol will be withdrawn from the review process if a response is not forthcoming. The IACUC may also withdraw applications for review if any training requirements are not satisfied in a timely manner.

3. Other Committees

Some protocols may require the approval of other committees within the Research Conduct and Compliance Office (RCCO) before the IACUC will issue a final approval or before animals may be obtained, even if all of the reviewers and/or the full IACUC has approved it. The following conditions always hold:

- If the Investigator identifies a conflict of interest in the protocol, the Conflict of Interest Office must issue its approval before the IACUC protocol will be approved.
- If the application describes the use of human stem cells, the Human Stem Cell Research Oversight Committee (hSCRO) must issue its approval before the IACUC protocol will be approved if stem cells are introduced into the brain or germ-line of a live animal. If stem cells are introduced into areas other than the brain or germ-line of a live animal, the hSCRO must verify that a valid registration has been received, however, the IACUC protocol can be approved prior to hSCRO approval.
- If the application describes the use of genetic engineering, including rDNA use, breeding genetically modified animals, transplanting cells or tissues from genetically modified animals into recipient animals, or introducing genetically modified cells or tissues into animals, approval from the IBC must be secured before animals may be obtained.
- Applications making use of the Regional Biosafety Laboratory must submit an RBL Pre-Project form prior to IACUC Submission. To obtain this form, contact the Center for Vaccine Research, info@cvr.pitt.edu.

B. Protocol Modifications

Both the AWA and PHS Policy require that the IACUC review and approve, prior to initiation, proposed modifications to ongoing activities using animals. Modifications are submitted to the IACUC through the online protocol management system. Modifications to older protocols that have not been approved via the online system are submitted using a Word-based Modificiation Request Form. All requests are reviewed using the same process and have the same requirements. The following modifications cannot be requested using this process:

- Changing the species used
- Adding procedures that do not logically relate to the specific aims of the original protocol
- An unrelated change in the scientific aims of the original protocol application
- Switching from non-survival to survival surgery
- Switching from single to multiple major survival surgeries.

A new protocol application must be submitted to incorporate any of the above changes, because the IACUC is required to review new issues arising related to animal welfare. Any changes to an IACUC protocol that present animal welfare issues not addressed in the original protocol will require the submission of a revised protocol. The revised protocol submission is required to address how all animal welfare issues will be mediated.

Two types of modifications are recognized. An Administrative Modification is an addition or deletion of personnel, protocol title change or addition, a change in the funding source, a change in the animal source or vendor, a request for animal housing or use outside the Institution that meets established IACUC requirements or a request for additional animal strains that do not require additional husbandry or housing considerations beyond those in the approved protocol. Administrative modification requests are reviewed by IACUC Office personnel, and if appropriate changes have been made to the protocol and records, they grant approval usually within two to three business days. Requests for additional personnel require that the new personnel satisfy all IACUC and EH&S mandated training and safety requirements prior to approval.

Other acceptable modifications to an IACUC-approved protocol include: changes in anesthetic or the analgesic agents, changes in euthanasia method(s), changes in any surgical procedures or addition of a surgical procedure, requests for additional animals, changes in nonsurgical procedures involving animals, changes in the animal strain, any changes that will affect the previously approved USDA Pain/Distress Category, requests to use additional test agent(s), and other changes that logically relate to the specific aims of the original protocol application.

The Investigator must clearly explain why the modification is being requested and how it relates to the original specific aims of the previously approved protocol.

Modifications are reviewed using nearly the same process as new protocols. The modification request is assigned by the IACUC Chair or a designee to the species-appropriate Subcommittee and is reviewed by at least four Designated Member Reviewers: one scientific member, one veterinarian, an EH&S analyst and an administrative reviewer. Questions and answers circulate between the reviewers and PI. After all issues have been resolved, and all reviewers have issued an approval, the request is approved and, after review by the IACUC Chair, an approval letter is issued. The approved protocol, with all approved changes integrated, is then available through the online protocol managaement system.

Certain modifications are automatically administratively flagged for full committee review (see A.1.):

- requests for more than 25% of the originally-approved number of animals justified for the study/experiments
- modifications involving death as an endpoint
- requests for new >12 hour housing sites outside of DLAR space all must be approved by the full IACUC.
- Requests for exemptions to the *Guide for the Care and Use of Laboratory Animals.*

3. Annual Renewal

Although PHS Policy grants protocol approval for a three-year period, the AWA requires continuing reviews of activities involving animals at appropriate intervals as determined by the IACUC, but not less than annually. To satisfy this AWA requirement, the University of Pittsburgh's IACUC requires each active protocol to go through an annual renewal process. The IACUC protocol number can be used to determine the month in which the protocol is due for renewal. The IACUC assigns an eight-digit protocol number to the protocol (older protocols have only seven digits, but the principle is the same for both). The first two digits of the protocol number designate the year of approval, the third and fourth digits designate the month of approval, and the last four digits identify the protocol. For example, protocol number 12020033 indicates the protocol was approved in February of 2012 and assigned number 0033. In this example the protocol must go through the Annual Renewal process before the end of February.

The online protocol management system sends Investigators and certain members of their staff reminders to renew their protocols 90, 60, and 30 days before protocols will expire. The Principal Investigator must log in and submit an annual renewal application online. An IACUC Coordinator reviews all applications received for their completeness and accuracy. The IACUC Office will return the renewal application to the Investigator if the application is incomplete or inaccurate. The Investigator is informed of receipt and entry into the review process by e-mail.

Prior to approval of an annual renewal, the entire IACUC receives a weekly listing of annual renewal applications received by the IACUC Office. The listing provides the name(s) of the Investigator(s), the project title, the funding agency, a project description narrative, the species of experimental animal, and the number of animals to be used in the study. Any IACUC member, including the unaffiliated and nonscientific representatives, with interest in an annual renewal on the list, may request a copy and submit a review of the annual renewal and/or call the annual renewal to full committee review.

Following the administrative review of the annual renewal application by the IACUC Coordinator, if no problems are identified the annual renewal is approved by the IACUC Chair or Vice-Chair. No annual renewal application is approved unless all training and medical surveillance requirements have been met. Investigators who do not submit renewal applications will have their IACUC approval terminated. The termination process is as follows:

- The Investigator receives, 90, 60, and 30 days before required renewal notices of the need to renew by e-mail.

- The month of the required renewal, the Investigator will be contacted by the IACUC Office, either by letter or phone call, and made aware of the deadline to renew. The 30-day renewal reminder letter is copied to the Investigator's Department Chair.
- If no response is received by the expiration deadline, the IACUC will terminate the approval of the protocol in a letter to the Investigator, with copies going to the Investigator's Department Chair and the Institutional Official.
- A protocol termination notification will be sent to the DLAR and any animals assigned to the protocol will be confiscated. The DLAR veterinarians will decide the fate of the confiscated animals.