Reviewing the Protocol

REVIEW OF ANIMAL PROTOCOLS

Criteria for Review of Protocols

A. Experiments involving live, vertebrate animals and the procurement of tissues from live animals for teaching or research must be performed by, or under the immediate supervision of a qualified scientist with training and/or experience in animal care and use.

B. Teaching or research studies utilizing non-human animals as subjects are required to have a reasonable expectation of contributing significant knowledge that will be beneficial to the future health and welfare of human and non-human animals.

C. If pain or distress are necessary elements of the experimental study, these must be minimized in both intensity and duration. In particular, alternative methodologies must be sought in lieu of procedures that require continuation of severe pain and distress until the death of the subject.

D. Procedures producing pain and distress are tolerated only if it can be demonstrated that pain and distress are the primary direct objects of research explicitly designed to produce beneficial knowledge.

1. Such procedures must be restricted and used only when, on the basis of expert opinion, it is anticipated that their utilization will undoubtedly contribute knowledge or benefit to man or animals.

2. Such procedures must be carefully supervised by the Principal Investigator or other qualified senior scientists.

3. The procedures are not tolerated when pain and distress are avoidable as determined by the IACUC.

4. The fewest number of subjects should be employed for the shortest period such that significant data is obtainable.

E. Post experimental care of animals must be such as to minimize discomfort and the consequences of any disability resulting from the experiment, in accordance with acceptable practices in veterinary medicine.

F. If it is necessary to euthanize an experimental animal, this must be accomplished in a humane manner, i.e., in such a way as to ensure immediate death in accordance with the American Veterinary Medical Association (AVMA's) Euthanasia Guidelines.

G. There should be justification for the selection of the species, especially those endangered or threatened with extinction.

Protocol Review Background Information

If pain and distress are necessary concomitants of the study, these must be minimized in both intensity and duration. Alternative methodologies must be sought in lieu of procedures that require more than momentary pain or distress in the animals. In general, an acceptable concomitant is to employ the fewest number of subjects for the shortest period. The three R's (Reduction, Refinement and Replacement) must be addressed in every protocol.

The IACUC has established Guidelines for Harm-benefit Analysis at UWM. The IACUC conducts harm/benefit analysis on all protocols that fall into category "D"or "E". This is accomplished by having a discussion during protocol review with the PI as to how the benefits of the study outweigh the potential harm to the animals. The reviewers must agree that the study is worthwhile to approve the protocol.

The IACUC reviews the PI's justification for animal use including types of animals used and animal numbers. Literature searches are mandatory.

All investigators are encouraged to discuss the protocol with the veterinarian. Protocols are submitted to the veterinarian who performs an initial review.

The IACUC is responsible for continuous monitoring of protocols after approval.

Review Process

A protocol is prepared by the Principal Investigator and submitted to the Animal Care Program in the Department of University Safety and Assurances. Animal Protocol Review Forms are available in I-Manager.

For certain funded projects, the experimental section in grant applications that involves animal use is reviewed by the Veterinarian to ensure that the description in the grant is congruent with the animal use described in the protocol at the time of award. There is a Pre-Award Animal Care Certification Procedure set up by the Office of Sponsored Program. The grant is filed with the approved protocol.

Original protocols are assigned a protocol number and the entire protocol is sent electronically to all IACUC members by the Animal Care Program personnel. The IACUC members then have five days to request either a full committee review of the protocol or designated member review by the working group, a subset of the Committee. If full committee review is requested, the protocol is reviewed at the next scheduled meeting of the IACUC (quorum required) or a special meeting is called. The investigator is invited to the review session. Under full IACUC (FCR) review, the committee either approves or requires modifications to the protocol to secure approval or withholds approval of the protocol. The investigator is notified of the review and encouraged to attend but is not present for the vote. The investigator receives written notification of IACUC decisions. If the IACUC requires modifications to the protocol the investigator is notified. If the IACUC decides to withhold approval of a protocol, it sends written notification including a statement of the reasons for the decision and gives the investigator an opportunity to respond in person or in writing. If the IACUC requires modifications to secure approval, it will determine if the full committee should review these or if a designated reviewer can be appointed to do so. The committee has a policy that a quorum of members present at a convened meeting may decide by unanimous vote to use designated member review (DMR) after full committee review (FCR) when modification is needed to secure protocol approval. However, any member of the IACUC may, at any time, request to see the revised protocol and /or request FCR of the protocol.

If FCR is not requested, the IACUC proceeds with a DMR by appointed reviewers at the next monthly IACUC work session. At least four members of the IACUC comprise each monthly working group session of designated reviewers. The IACUC Chair and Veterinarian determine the constitution of the work groups to ensure that there is appropriate expertise for the review in all the groups. The investigator is invited to the review session to discuss the protocol but is not present for the final decision. At a work session the designated reviewers review and either approve or require modifications in

the protocols to secure approval, or they request full committee review of a protocol. If the work group of designated reviewers requires modifications to the protocol, the investigator is notified. The DMR group will decide if the revisions will be reviewed administratively, by one member of the group, or by the entire DMR working group.

The Chair may also allow a designated member review (DMR) by appointing one or more qualified reviewers to review the protocol if time constraints prevent the review from occurring at the next work group review session. These reviewer(s) may only approve, require modifications to approve or request full committee review of those research projects. If the designated reviewer(s) require modifications to the protocol the investigator is notified. The modifications are circulated to the designated reviewer(s) for their final approval when received from the investigator.

If the animal work is being done at another Institution with an NIH Assurance in collaboration with one of UWM's investigators, the IACUC may opt for a deferred review to that IACUC. The UWM IACUC must receive a copy of the approval letter from the other institution as well as a copy of the protocol. An MOU outlining each institution's responsibilities must be established and/or the responsibilities must be outlined in the sub-award. The local investigator is sent annual renewal notices for this project and must provide review and approval information from the other Institution. The UWM IACUC notifies the other institution's IACUC that they are deferring the review to them. The investigator is informed that the UWM IACUC must be notified of any changes in the status of the protocol or any relevant findings on the other institution's facility tours as they apply to the protocol.

Protocol approval remains in effect for three years with continual reviews conducted on at least an annual basis. Annual renewal notices are automatically sent to investigators prior to the first and second anniversary dates of the original approval date. The IACUC is notified of the review at the time the renewal notices are sent out so they have the opportunity to participate in the review and receive the annual renewal and protocol. Otherwise, the attending Veterinarian and the Vice-Chair of the IACUC review annual renewals. To renew a protocol on the third anniversary date of the original approval date the principal investigator must resubmit on the current protocol form. The protocol then goes through the IACUC review process for original protocols.

If a protocol involves the use of recombinant DNA material or bio-hazardous materials, a separate Biosafety Registration Form must be submitted to the UWM Institutional Biosafety Committee. An IACUC protocol cannot be approved until the IBC has approved the Biosafety Registration Form. If the protocol involves hazardous chemicals, a HazChem SOP must also be approved.

The IACUC has the authority to suspend any activity involving animals if it determines that the activity is not being conducted in accordance with provisions of the Animal Welfare Act, the NIH Guide for the Care and Use of Laboratory Animals, and the UWM Animal Care Training Manual (Links to an external site.). The Veterinarian and or Chair may terminate an experiment if the activity is deemed egregious enough, until a quorum of the IACUC can meet to discuss the issue.

No IACUC member may participate in the review or approval of a protocol in which the member has a conflict of interest (e.g., is personally involved in the project) except, to provide information requested by the IACUC; nor may a member who has a conflict of interest contribute to the constitution of a quorum. IACUC members, who wish to review protocols while traveling, must inform ACP of their absence and leave forwarding information.

Through the ACP, the IACUC notifies an investigator in writing, of its decision to approve or withhold approval of the animal protocol or of modifications required to secure IACUC approval. Approved protocols are maintained electronically in I-Manager

All animal purchases for ARC facilities are approved by the Veterinarian or Lab Manager to ensure adequate space to house the animals, and to ensure that quantities ordered do not exceed those approved by the IACUC.

If the IACUC decides to withhold approval of a protocol, it shall include in its written notification a statement of the reasons for its decision. If the IACUC suspends an activity involving animals, the Chair of the IACUC will take appropriate action and ACP personnel will report that action with a full explanation to the Institutional Official, AAALAC, USDA, PHS, and the sponsoring agency, as appropriate.

Animal Care and Use protocols that have been approved by the IACUC may be subject to further appropriate review and approval by officials of the institution. However, these officials may not approve sections of the protocol related to the care and use of animals if they have not been approved by the IACUC.

Appealing a Decision in the Review Process

An investigator may appeal to the IACUC at any stage of the review process. The Institutional Official oversees appeals by researchers, but final decisions are made by the IACUC.

Frequency of Committee Review

Working groups of designated reviewers of the IACUC meet 10 times a year. The entire IACUC meets five times a year unless a specific meeting is called for at another time. Meeting dates and the deadlines for submissions are posted on the Animal Care Program/IACUC website.

Protocol Modifications

All modifications to protocols are submitted through I-manager. The IACUC has established Guidelines for Major versus Minor Protocol Modifications at UWM. Minor protocol modifications are reviewed by the Chair of the IACUC or his/her designee. Minor modifications include changes in title or funding agency with the animal protocol being the same, and changes in personnel other than the Principal Investigator or an increase in animal population of less than 10 %.

Major modifications are treated the same as a new protocol submission. If a full review by the entire Committee is not requested, the significant protocol modifications are reviewed at the next monthly IACUC work group of designated reviewers. If there are time constraints the Chair may designate one or more IACUC members to review the protocol prior to the monthly session. Major modifications include but are not limited to the following: changes in the objectives of the study, proposals to switch from non-survival to survival surgery, changes in the degree of invasiveness of a procedure or discomfort to an animal, or a change of PI. Some modifications can be reviewed by Veterinary Verification and Consultation (VVC). This is a process by which changes that have been pre-approved by the IACUC can be reviewed and approved administratively by the veterinarian. Please reference the IACUC Guidelines on our website to see what modifications qualify for VVC.

Humane Endpoints

The IACUC agrees that the humane endpoint of a study occurs when the pain or distress in an experimental animal is prevented, terminated, or relieved. The IACUC has established “Guidelines on Humane Endpoints for Animals Used in Teaching or Research”. Once a humane endpoint is reached the animal should be immediately euthanized or treated as described in the approved protocol. The Guidelines list

criterion for euthanasia, discuss moribund conditions, death as an endpoint, and review endpoints used in behavioral studies.

The IACUC ensures that endpoints based on the particular protocol are in place so that unnecessary pain or distress does not occur. The IACUC reviews all protocols, and the PI must describe their monitoring procedures and their determination of when animals will be euthanized. The PI's justification must be both humane and scientifically sound. The IACUC either approves or requires modifications to a protocol, as recommended by the Veterinarian, if the monitoring and euthanasia description is not adequately addressed. The IACUC can also mandate a pilot study be performed in order to reduce the potential for unnecessary pain and distress to large numbers of animals during the beginning stages of a proposed protocol.

Adverse Events and Unexpected Outcomes

The IACUC has established "Guidelines for Prompt Reporting of Adverse Events or Unexpected Outcomes" that provide examples of unexpected outcomes that must be reported. There is a question in the protocol form that asks the investigators to describe any adverse events that they think may occur and how they will react to them. The PI must certify in the protocol form that they will complete the "IACUC Adverse Event or Unexpected Outcome Report for UWM" if necessary, according to the established Guidelines. Information that is asked in the form includes: date of event, location, outcome, description of event, how the event was managed, and corrective actions taken by the PI and/or lab. This form is then submitted to the IACUC for review.

The Animal Care Program SharePoint site for aquatic animal users has specific forms for reporting aquatic animal incidents that are sent directly to the Veterinarian.

In the event of an animal health emergency, the Veterinarian has the authority to euthanize or implement treatment of an animal without PI approval. ARC staff, PIs and research staff can also euthanize and treat animals per veterinary protocols in an emergency situation, under the direction of the Veterinarian.

The IACUC has the authority to suspend any activity involving animals if it determines that the activity is not being conducted in accordance with provisions of the Animal Welfare Act, the NIH Guide for the Care and Use of Laboratory Animals and any other pertinent regulations.

Physical Restraint

The PI must describe in the protocol how conscious animals will be restrained for purposes other than performing routine clinical or experimental procedures such as blood sampling, injections, etc. They must describe the prolonged restraint, justify (with references) why the longer restraint is necessary, and provide criteria for observation and release. To minimize distress or pain associated with restraint, the period of restraint should be no longer than required to achieve the aims of the project. They must also describe how animals are acclimated to the restraint procedure.

Multiple Major Survival Surgeries

The IACUC will determine whether surgery is major or minor. Major surgeries include those that expose a body cavity or produce substantial impairment of physical or physiological function. The IACUC requires scientific justification for multiple major survival surgeries on a single animal and follows the guidelines for multiple survival surgeries in the "Guide." The IACUC ensures that appropriate surgical techniques are followed, and that the surgeon(s) are appropriately trained. The Veterinarian and the IACUC review the use of anesthetics and analgesics and surgical procedures. The IACUC will review these protocols with particular emphasis on rationale and purpose; number of animals required; training and experience of personnel involved, as well as post procedural care and monitoring.

Protocols involving multiple major survival surgeries are reviewed by the full committee if requested or by the DMR method. A scientific justification must be provided for multiple major survival surgeries. The welfare of the animal is considered to ensure that the procedures are necessary and performed appropriately.

Dietary Manipulations and Food/Fluid Restrictions

Investigators are required to describe any dietary manipulations or special feeding requirements for their animals in their protocols. The IACUC has established "Guidelines on Food or Fluid Restriction for UWM". Scientific justification is required when: 1) neonates are fasted beyond 3 hours, 2) any animal is fasted beyond 24 hours, or 3) fluids are withheld for more than 12 hours. If animals are provided less than ad lib food or drinking water for experimental reasons, investigators must provide details, including amount/day, monitoring, and criteria used to determine well-being of animals and a scientific justification.

Use of Non-Pharmaceutical-Grade Drugs and Other Substances

The IACUC has established "Guidelines on the Use of Non-Pharmaceutical Grade Drugs and Other Substances at UWM". Scientific justification must be given for any PI request to use a non-pharmaceutical grade substance. Use is approved when there is no pharmaceutical grade option available, or if the PI has scientific justification (with references) and has provided a detailed description of how the drug will be prepared, used and stored. The PI must also include a monitoring plan for the detection of adverse results related to the use of non-pharmaceutical grade drugs, and any adverse effects must be reported to the ARC and the IAUC. The IACUC can mandate a pilot study if deemed necessary.

Field Investigations

Field studies that require animal handling are reviewed by the same standards used for all animal studies on the regular protocol form. If the field study is an observation only study, the investigator uses a special protocol form for observation only that is reviewed by the Veterinarian and the IACUC Chair to determine if it is exempt from further review. This is determined based upon the potential risks to the animals or their habitat.

Animal Transfers

The IACUC Protocol form includes an area for investigators to indicate options for their animals at the conclusion of their study. Options include donation to the ARC for the serology program, donation to a PI with an approved protocol for research or training purposes, or adoption.

Post approval monitoring (PAM)

The IACUC has a PAM program whereby at least once each semester an IACUC member or members meet with a PI and their staff to review their procedures. A different PI is chosen for each review based upon the complexity of the studies.

For more information, please refer to the CITI course "Working with the IACUC (Links to an external site.)"