Significant Changes to Animal Study Protocols

Purpose: The purpose of this standard is to define significant changes to ASPs, to describe the procedures by which significant changes may be handled, and to communicate these procedures to investigators.

Background: As described in the Public Health Service *Policy on Humane Care and Use of Laboratory Animals* (PHS Policy) (IV.C.1) and the Animal Welfare Regulations (AWRs) [9 CFR 2.31 (d) (1) (i)- (iv)], the IACUC is responsible for reviewing and approving proposed significant changes to Animal Study Protocols (ASPs). Changes must be conducted in accordance with the University's Animal Welfare Assurance and be consistent with the *Guide for the Care and Use of Laboratory Animals* (the Guide), the AWRs, requirements in the PHS Policy, local animal care standards and other guidance documents. Guidance from the Office of Laboratory Animal Welfare (OLAW) describes types of significant changes that may be administratively handled if an IACUC-reviewed and -approved policy is in place to describe the conduct of animal activities consistent with the references above.

Definition(s):

1. A *significant change* to an ASP is one that negatively impacts (or has the potential to negatively impact) animal welfare, substantively alters animal use from that originally approved in the protocol, or impacts personnel safety. (NIH NOT-OD-14-126; Examples are listed below.)
2. An *IACUC-reviewed and -approved policy* for the conduct of animal activities includes IACUC standards, guidance documents, standard operating procedures (SOPs), drug formularies, regulatory or accrediting body oversight documents (e.g., the Guide, AWRs, current policy or position statements) etc., that have been periodically (at least once every three years) reviewed by the IACUC and have been approved as resources to describe acceptable animal use procedures or activities (NIH NOT-OD-14-126). These approved policies will be used when determining administrative processing for proposed significant changes.

Standards: The UMD IACUC will generally review proposed significant changes to ASPs using Designated Member Review (DMR) unless a committee member calls for Full Committee Review (FCR) **or** unless an IACUC-reviewed and -approved policy or guidance document is in place to address the proposed change, and compliance with pre-approved policies/guidance documents is appropriate for the specific situation. In the latter case, the IACUC staff may administratively process the proposed significant change, with or without veterinarian consultation and verification, as described below.

1. Significant changes that **must be approved by either DMR or FCR** include changes:
   a. from nonsurvival to survival surgery;
   b. resulting in greater pain, distress, or degree of invasiveness;
   c. that add new experiments;
   d. in housing and/or use of animals in a location not overseen by the IACUC;

e. in species;
f. in study objectives;
g. in Principal Investigator (PI), and
h. that impact personnel safety.

2. Significant changes that **may be handled administratively** according to UMD IACUC-reviewed and –approved policies subsequent to veterinarian consultation and verification **(VVC)** that the change is consistent with IACUC standards, Department of Laboratory Animal Resources (DLAR) standard operating procedures (SOPs), or other approved resource documents include:

a. **changes in anesthesia, analgesia, tranquilizers and sedatives; other pain-relieving or post-operative measures; or other medications**. Changes must be consistent with the information found in the guidance below and must be consistent with UMD guidelines and SOPs.
   i. Hawk, et al. *Formulary for Laboratory Animals*
   ii. Plumb *Veterinary Drug Handbook*
   iii. Carpenter *Exotic Animal Formulary*
   iv. Peer-reviewed scientific journal articles and/or taxon-specific guides

b. **changes in euthanasia** to any method approved in the most current version of the *AVMA Guidelines for the Euthanasia of Animals*.

c. **increases in animal numbers up to 100%** of the total previously approved animal numbers. This increase may include changes in genotype/strain/stock of animal of the same species provided:
   i. there is no anticipated adverse phenotype/phenotype unknown (newly developed GMOs)
   ii. the GMO has been or does not require review by the IBC (Institutional Biosafety Committee)
   iii. a detailed rationale for the increase is provided. The AV or IACUC Chair will alert the IACUC if the increase is the result of animal mortality or unexpected and/or adverse events.

d. **change in duration, frequency, type or number of procedures** performed on an animal that are not expected to increase pain or distress, impact the approved endpoint criteria, or impact the approved personnel safety considerations. Changes/additions to procedures listed below maybe handled via VVC provided the general procedure (e.g., compound administration, blood collection, injections, etc.) is currently described in the approved protocol. Changes must be consistent with IACUC standards, DLAR SOPs, or reference documents listed in paragraph 2.a. above.
   i. change in substances that are the same class of compounds currently approved in the ASP and which are not expected to increase pain or distress, impact the approved endpoint criteria, or impact the approved personnel safety considerations
   ii. change of compounds to control gene expression, consistent with compounds currently approved in the ASP,

iii. change in injection/administration/procedural frequency consistent with those currently approved in the ASP, and which are not expected to increase pain or distress (changes in food/water restriction must be consistent with IACUC standards**)**
iv. change in genotyping methods
v. change in injection method including:
    - Intradermal (ID)
    - Intravenous (IV)
    - Intramuscular (IM)
    - Subcutaneous (SQ)
    - Intraperitoneal (IP)
    - Intracardiac (IC)
    - Intraorbital (IO)
    - Intranasal (IN)

vi. change in blood collection method including:
    - Lateral Tail Vein or Ventral/Dorsal Artery or Tail Clip
    - Jugular (limited to the rat)
    - Saphenous (medial or lateral approach)
    - Retrorbital Sinus

3. **Amendment Submission:** Amendments requiring DMR or FCR review will be processed as described in corresponding IACUC standards and the PHS Animal Welfare Assurance. Amendments handled via VVC methodology will be processed as described below.

    a. The IACUC authorizes the University Attending Veterinarian (UAV), and DLAR-affiliated clinical/facility veterinarians to assist with VVC and administrative handling of proposed significant changes that meet the criteria outlined above.

    b. Submission of changes to an existing, approved protocol must be submitted via the online protocol submission system (IRBnet) using the amendment form and required attachments, including an updated Animal Study Protocol form (ASP) and updated Personnel Qualifications Forms for all personnel performing any new procedure. A full description of the reason for the change must be provided so that the IACUC office staff may pre-screen the submission to determine whether the requested changes are covered under this policy, as described above (2a-d). Qualifying amendments will be referred to an authorized veterinarian; the veterinarian will verify that the requested changes are: consistent with the IACUC-reviewed and -approved policies, appropriate for the circumstances, and that no IBC concerns are present.

c. The veterinarian, IACUC Chair, and/or any IACUC members may, for any reason, refer the proposed change(s) back to the full committee for review and approval. If the proposed significant changes do NOT meet the parameters in the IACUC-reviewed and -approved policy, the veterinarian or IACUC Chair MUST refer the request back to the

IACUC. If applicable policy or resource documents do not exist, the significant change request must be reviewed by DMR or FCR.

d. VVC handling of changes to protocols must be documented by a veterinarian in the online protocol submission system. Following review and signoff by the veterinarian, the IACUC will issue an approval letter. Changes may not be implemented until the approval letter is issued.

References:

1. Guidance on Significant Changes to Animal Activities: OLAW Special Seminar, August 21, 2014
2. Implementing Guidance on Significant Changes: One Institution's Experience: OLAW Online Seminar, September 8, 2016
3. NOT-OD-14-126: Guidance on Significant Changes to Animal Activities
4. Significant Changes to Animal Activities. https://olaw.nih.gov/guidance/significant changes.htm