IACUC05 TITLE: IACUC Amendment Policy

Prepared by:	Approved by:	Effective date:
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1.0 Purpose:

The IACUC is required to review proposed significant changes to the care and use of animals in ongoing animal activities (i.e., approved animal protocols). This requirement is established in Public Health Service (PHS) Policy IV.B.7 and in the USDA Animal Welfare Regulations 9CFR 2.31(c)(7). The purpose of this policy is to define what constitutes a significant change to an animal protocol versus a minor change to an animal protocol and to outline the IACUC review mechanisms for each type of change.

2.0 Significant Changes:

In general, significant changes are those that will or may negatively impact animal health and/or welfare, impact personnel safety, and/or require substantial changes to the objectives and/or design of an animal protocol.

Significance is determined on a case-by-case basis during pre-review by the IACUC Office and may include consultation with the Attending Veterinarian, Environmental Health & Safety staff, Occupational Health Services staff, and/or IACUC Chair. In cases where consensus cannot be achieved as to whether a change is significant, the matter will be brought to the IACUC for discussion.

a. Significant Changes Reviewed by the IACUC: Guidance from the Office of Laboratory Animal Welfare (OLAW) classifies specific changes as significant and requires that these changes are subjected to IACUC review. These include changes:

i. from nonsurvival to survival surgery
ii. resulting in greater pain, distress, or degree of invasiveness (e.g., addition of a major surgery, change in humane endpoints, other experimental change with related increase in pain/distress categorization, etc.)
iii. in housing and/or use of animals in a location that is not part of the animal program overseen by the IACUC (e.g., use of animals at an animal facility of another institution, use of animals at a location that is not reviewed by the IACUC as part of the semi-annual facility inspection) with the exception of off-site breeding and cryopreservation of approved strains at IACUC-approved vendors
iv. in species
v. in study objectives (e.g., switching from studying disease mechanism to preclinical therapy trials)
vi. in Principal Investigator (PI)

vii. that impact personnel safety (e.g., addition of agents in Class 3 on the Hazardous Chemical Chart, addition of a hazardous or infectious biological agent requiring BCC approval especially when no similar agents are approved)

Protocol changes that fall into one or more of the categories above must be reviewed by the IACUC. To initiate IACUC review, the PI must submit the appropriate form to the IACUC Office through Smartsheet:

- Change in Principal Investigator (PI) – Amendment Form A
  - Change in housing and/or use of animals in a location that is not part of the animal program overseen by the IACUC – Amendment Form C and/or MOU Request Form (contact IACUC Office for guidance) with the exception of off-site breeding and cryopreservation of approved strains at IACUC-approved vendors
- Change in species – Protocol rewrite required, contact IACUC Office for guidance
- All other significant changes – Amendment Form C

Significant changes are reviewed by one of two review mechanisms in accordance with DFCI's Animal Welfare Assurance: Full Committee Review (FCR) or Designated Member Review (DMR). In general, DMR will be the preferred method of review. Approval of a significant change does **not** reset the three-year approval cycle for the animal protocol because the protocol does not undergo a full, *de* novo review.

Approved significant changes are recorded in IACUC Online (the animal protocol database) as addenda to the original, IACUC-approved animal protocol within one business day of IACUC approval.

b. Significant Changes Reviewed by Veterinary Verification and Consultation (VVC): Guidance from OLAW classifies specific changes as eligible for administrative handling according to IACUC-reviewed and –approved policies and with veterinary verification and consultation (VVC). At DFCI, the following changes are eligible for VVC:

i. change in anesthesia or analgesia within the scope of SOP T005
ii. changes to experimental substances, including a change in test compound, dose, or route of administration, as long as the change does not result in a change in study objectives or greater pain, distress, or degree of invasiveness and except…
   a. addition of a non-pharmaceutical grade drug, or a change from a pharmaceutical grade to a non-pharmaceutical grade drug requires additional justification and cannot be handled by VVC
   b. for addition of or changes to the approved route or dose of a test compound, the investigator must submit a reference to show that the compound is efficacious at the route and or dose (e.g., at or below MTD) and is not expected to cause adverse effects – if a reference does not exist, the change cannot be handled by VVC
iii. change in euthanasia to any method approved in the AVMA Guidelines for the Euthanasia of Animals (including a method that is acceptable with conditions as long as the conditions are met) or within the scope of SOP T016 (mice) or SOP T017 (rats)
iv. change(s) in duration, frequency, type, or number of procedures performed on an animal within the limits of Guideline G012 and within any limits set in the IACUC-approved SOP for the procedure(s)

v. change in dose of radiation and/or number of fractions in a fractionated dose where the type of radiation is approved on the protocol and the change is within the scope of Guideline G014

vi. changes in strains used, except…
   a. when negative effects are involved (e.g., a new or more adverse phenotype), in which case DMR is required
   b. when the only change is a change in vendor for an approved strain, in which case the vendor change can be processed administratively

vii. off-site breeding, cryopreservation, and rederivation of approved strains at IACUC-approved vendors.

Eligible changes **cannot** be handled by VVC if any of the following apply:

- The change involves any of the criteria for DMR/FCR in section 2.a
- The change involves pain/distress Category E animal work, even if the protocol is approved for Category E work
- The change involves addition of a new procedure
- The change involves addition of a new experimental design not previously approved by the IACUC
- The change involves addition of a pilot study, even if similar to a previously approved experimental design
- The change involves adverse effects (for addition of new experimental agents) or adverse phenotypes (for addition of new strains) where there is significant impact on health and welfare (e.g., pain and/or distress, endpoints, monitoring)
- The change involves a greater than 20% increase in animal numbers (see section 2.c.iii)

VVC is coordinated by email through the IACUC Office. To initiate VVC, the PI can…

- complete Amendment Form C and submit the form to the IACUC Office through Smartsheet
  - **Most amendments to make significant changes should be submitted on Amendment Form C**
  - This option is particularly appropriate for amendments that involve any of the changes in section 2,a of this policy and/or include any new animal work, multiple changes, complicated changes, increases in animal numbers, or changes in experimental design

- email a written description of the amendment to the Attending Veterinarian for review
  - **This option is for targeted, time-sensitive changes to approved animal work with no change in animal numbers or experimental design**
  - When an amendment submitted this way is verified by VVC, the IACUC Office will attempt to quickly confirm PI approval for the change (unless amendment submitted by PI)
  - Examples include:
    - changes in approved anesthetics or analgesics (e.g., replacing one anesthetic with another)
    - adding anesthetics or analgesics for approved procedures within the scope of SOP T005
    - changes to approved experimental substances (e.g., drugs, cell lines), such as changes in route to an equally or less invasive route or in dose where the new dose is not expected to cause adverse

effects or in volume or frequency within what is described in guideline G012
    - replacing one approved strain with another similar strain that does not exhibit a new adverse phenotype
    - other changes on a case-by-case basis – these should be submitted to the IACUC Office for pre-review to confirm that Form C is not required

Amendments eligible for VVC are reviewed by the Attending Veterinarian using the following references:

- *Formulary for Laboratory Animals*, 3rd Edition Compiled by: C. Terrance Hawk, Steven L. Leary and Timothy H. Morris
- JoVE | Peer Reviewed Scientific Video Journal - Methods and Protocols
- Reference articles on ARF Admin drive
- *The Mouse in Biomedical Research*, Vol I-IV Edited by: James G. Fox, et al
- *The Laboratory Rat* Edited by: Mark A. Suckow, Steven H. Weisbroth and Craig L. Franklin
- DFCI library of SOPs, policies and guidelines

The AV has the authority to request an Amendment Form C (if one was not submitted) and to escalate a change submitted for VVC to the IACUC for FCR or DMR for any reason.

Significant changes verified by VVC do **not** reset the three-year approval cycle for the animal protocol because the protocol does not undergo a full, *de* novo review. During VVC, the AV is not performing Designated Member Review.

Changes verified by VVC are recorded in IACUC Online (the animal protocol database) as addenda to the original, IACUC-approved animal protocol within one business day of VVC completion.

Note that significant changes submitted by the Attending Veterinarian are not eligible for VVC and are routed to the IACUC for review.

c. Significant Changes Handled Administratively: Guidance from OLAW permits one significant change to be handled administratively without IACUC or veterinary consultation: An increase in previously approved animal numbers. However, OLAW requires that clear limits are set on when such an increase can be handled administratively.

To implement an increase in animal numbers, the PI must submit Amendment Form C to the IACUC Office through Smartsheet. These amendments are handled as follows:

i. Increases in previously approved animal numbers **up to 10%** of the approved three-year animal total may be handled administratively by the IACUC Office when the increase only involves animal work previously approved by the IACUC **and** does not involve animal health or welfare concerns (e.g., increase required due to unexpected death resulting from poor technique) **and** does not involve Pain/Distress Category E work.

   Examples of increases in animal numbers that can be handled administratively by the IACUC Office include, but are not necessarily limited to, adding exact repeats of experiments approved by the IACUC to validate results and corrections in animal number calculations for experiments approved by the IACUC.

ii. Increases in previously approved animal numbers **up to 20%** of the approved three-year animal total may be handled by VVC when the increase is to accommodate a repeat of animal work previously approved by the IACUC and where the increase involves other changes eligible for handling by VVC (e.g., a repeat of an approved experiment with addition or substitution of an experimental agent or strain)

iii. Increases in previously approved animal numbers **greater than 20%** of the approved three-year animal total must be reviewed by DMR or FCR. The same applies for changes in animal numbers up to 10% when the increase involves other changes that cannot be handled by VVC. In either of these scenarios, an updated rationale for the number of animals used on the protocol will be required as part of completing Amendment Form C.

This policy applies to increases in approved mouse, rat, and zebrafish numbers. Increases in animal numbers are recorded in IACUC Online (the animal protocol database) as addenda to the original, IACUC-approved animal protocol within one business day of administrative review, VVC, or DMR/FCR.

3.0 Minor Changes:

The following changes may be handled administratively by the IACUC Office without IACUC review or veterinary consultation:

i. **[With PI approval and ARF training staff review]** Changes in personnel other than the PI, such as addition or removal of administrators, grant managers, and lab personnel
ii. **[With PI approval and congruency review, when applicable]** Changes in funding, such as addition or removal of federal and private funding sources
iii. **[With PI approval and ARF review]** Changes in off-hours access to the animal facility
iv. **[With PI approval]** Changes in lab location(s) used for animal work (e.g., euthanasia for tissue collection)
v. Other minor protocol updates or corrections where **none** of the criteria in section 2 apply, such as:
    a. **[With PI approval]** Changing from sterile to sterile plus housing or vice versa
    b. **[With PI approval]** Correction of nomenclature for approved strains
    c. Change in vendor for an approved strain where both vendors are on the ARF's approved vendor list and there are no other changes to the protocol
    d. Correction of typographical errors
    e. Correction of grammar
    f. Updates to contact information

In addition, use of fewer animals than approved does **not** require IACUC review or approval, veterinary review, or administrative review by the IACUC Office. Researchers do **not** need to report to the IACUC Office or IACUC when using fewer animals than approved.
Minor changes are coordinated by email through the IACUC Office. To initiate review, the PI must submit the following to the IACUC Office through Smartsheet as appropriate for the type of change:

- Changes in personnel other than the PI: Amendment Form B
- Changes in funding, lab location, off-hours access, and other minor changes: Amendment Form D (Smartsheet web form)

All minor changes are reviewed by the IACUC Office. IACUC Office staff may consult with ARF staff and/or IACUC members in the review of any minor change to an animal protocol. Lastly, IACUC Office staff are required to escalate changes to VVC or to the IACUC for FCR or DMR when any criteria in sections 2.a or 2.b apply.
Minor changes are recorded in IACUC Online (the animal protocol database) as addenda to the original, IACUC-approved animal protocol within one business day of administrative confirmation that all necessary information has been provided.

4.0 References:

- Public Health Service Policy for the Humane Care and Use of Laboratory Animals. Bethesda, MD: Office of Laboratory Animal Welfare, 2002. (http://grants.nih.gov/grants/olaw/references/PHSPolicyLabAnimals.pdf)
- United States Department of Agriculture Animal Welfare Act and Animal Welfare Regulations. 9 CFR 2.31. 1985. (https://www.aphis.usda.gov/animal_welfare/downloads/Animal%20Care%20Blue%20Book%20-%202013%20-%20FINAL.pdf)
- NIH Notice NOT-OD-14-126, “Guidance on Significant Changes to Animal Activities” (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-126.html)