

NCI ACUC Policy for Significant Changes (Modifications) to Animal Study Proposals

I. Introduction:

This policy is in place to comply with the NIH Animal Research Advisory Committee (ARAC) [Guideline Regarding Significant Changes to Animal Study Proposals](http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-126.html) which was revised to address the OLAW Revised Guidance on Significant Changes to Animal Activities:
<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-126.html>

II. Significant changes: Categories 1, 2.1 and 2.2 are classified as significant changes

Category 1: Mandatory non-administrative review process

These changes require consideration by **Full Committee Review** (FCR) or an expedited **Designated Member Review** process (DMR):

- Changes from non-survival to survival surgery
- Changes resulting in greater pain, distress or degree of invasiveness. This will be indicated by an increase in pain category and accompanied by a literature search for potential alternatives to the new painful or distressful procedures.
- Changes in housing and or use of animals in a location that is not currently part of the animal program overseen by the ACUC
- Changes in study objectives
- Changes in Principal Investigator (PI)
- Changes that could impact personnel safety. (i.e. Addition of a hazardous agent that would alter the existing safety recommendations associated with a protocol.)
- Increase in animal numbers greater than **50% (up to 500 animals) for USDA unregulated species (e.g. mice and rats bred for research purposes) or 5% for USDA regulated species (e.g. NHPs and Dogs)**
- Change in genotype/strain/stock of animal with adverse phenotype or that requires DOHS review or registration.

Procedure:

- **Submission:**
 - All modifications are submitted to the ACUC using iRIS. A detailed description of the submission process can be found in the iRIS instruction manual.
 - Once a modification is submitted through iRIS, the ACUC office staff will review the item to determine if it is a Significant or Minor change using the guidelines detailed in this document.
- **Pre-Review:**
 - If an item is considered a significant change, it will be sent to at least one Veterinarian and a DOHS representative for pre-review. The pre-reviewers will be given one week to respond with any comments. Note: Pre-review comments are suggestions not mandatory changes.
 - At the discretion of the ACUC office, the item may be sent to additional reviewers for comment (i.e. Division of Radiation Safety, Animal Facility Management, or an ACUC member with expertise with a specific procedure, ect.)
 - Pre-Reviewers will provide comments to the ACUC office by the deadline. The ACUC office will compile the pre-review comments into a single outcome letter that is sent through iRIS to the Principal Investigator and Study Contact(s).
 - Investigators are given one week to resubmit the modification.
- **ACUC Review:**

- Significant modifications are assigned to a primary reviewer for presentation at the ACUC meeting. Primary Reviewers are given one week to review the modification and provide a recommendation at the convened meeting to:
 - Approve the modification as written.
 - Approve pending minor clarifications.
 - Tabled pending Designated Member Review (DMR). The designated members are the chair or vice chair (whomever is presiding at the associated meeting) and the DOHS representative.
 - Tabled pending Full Committee Review.
 - Disapprove.
- Post-Approval:
 - Once the necessary signatures have been collected, the modification is approved in the iRIS system and two e-mails are sent to the Principal Investigator, the Study Contact(s), and the associated facility staff.
 - E-mail #1 - Alerts the contacts that the modification is approved and provides a copy of the finalized item.
 - E-mail #2 - Provides the official outcome letter with the approval date.

Category 2.1: Conditional Administrative Review Process (Veterinary Verification and Consultation)

These changes may be approved by the NCI Attending Veterinarian or alternate [*designate by name or title*] in consultation with the principal investigator when the changes are within the scope of the following:

- Changes in **anesthesia, analgesia, sedation** when consistent with ***Ketamine combinations for rodent anesthesia; Postoperative Analgesic and Care Recommendations for mice.***
- Changes in **method of euthanasia** which are not expected to increase pain or distress or impact the approved personnel safety considerations and when consistent with the following:
 - [Guidelines for the Euthanasia of Rodent Fetuses and Neonates](#)
 - [Guidelines for Euthanasia of Rodents Using Carbon Dioxide](#)
 - [Guidelines for Use of Zebrafish in the NIH Intramural Research Program](#)
 - Other methods of euthanasia that are approved or approved with conditions by the [AVMA Guidelines for the Euthanasia of Animals: 2013 Edition](#)
 - Other methods of euthanasia that are listed in the [Methods of Euthanasia \(NCI Bethesda ACUC Guideline\)](#)
- Changes 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.
- Changes in **substances** that are **different types of compounds** (i.e. imaging contrast agents) than those currently approved in the ASP but which are not expected to change the objectives of the study, increase pain or distress, impact the approved endpoint criteria, or impact the approved personnel safety considerations.
- 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. The following procedures are allowed:

- Blood sampling method, volume, & frequency consistent with ARAC guidelines http://oacu.od.nih.gov/ARAC/documents/Rodent_Bleeding.pdf and/or **Blood Collection Guidelines for Macaques**
 - Food/water control consistent with ARAC guidelines http://oacu.od.nih.gov/ARAC/documents/Diet_Control.pdf
 - Genotyping method consistent with ARAC [Guidelines for the Genotyping of Mice and Rats](#)
 - Opposite side jugular catheterization provided the methods are consistent with the originally approved protocol
 - Replacement of osmotic minipumps, provided the methods are consistent with the originally approved protocol
 - Biopsy number provided the methods are consistent with the originally approved protocol
- Increase of $\leq 50\%$ (up to 500 animals) of previously approved animal numbers for USDA unregulated species (mice and rats bred for research) or 5% for USDA regulated species (NHPs and dogs). A rationale for the increase should be provided and the designee needs to alert the ACUC if the increase is due to animal deaths, unexpected or anticipated events, etc. The proposed increase of animals should be consistent with the originally approved protocol and not result in a change to the study objectives.
 - Change in genotype/strain/stock of animal with no anticipated adverse phenotype and that does not require DOHS review or registration
 - Addition of personnel who will perform surgical procedures.
 - Change in genotype/strain/stock of animal with no anticipated adverse phenotype and that does not require DOHS review or registration

Procedure:

- Submission:
 - All modifications are submitted to the ACUC using iRIS. A detailed description of the submission process can be found in the iRIS instruction manual.
 - Once a modification is submitted through iRIS, the ACUC office staff will review the item to determine if it is a Significant or Minor change using the guidelines detailed in this document.
- Processing:
 - The ACUC office will route the modification to the Attending Veterinarian or alternate for review and digital signature.
 - The Attending Veterinarian or alternate will review the modification, provide any comments that must be addressed prior to approval, and sign-off
 - If no comments are provided - the modification is approved.
 - If comments are provided:
 - The ACUC office will send the comments to the Principal Investigator and Study Contact(s) through iRIS.
 - Once the revised modification has been received, the modification will be resent to the Attending Veterinarian or alternate to review and sign.
- Post-Approval:
 - Once the necessary signatures have been collected, the modification is approved in the iRIS system and two e-mails are sent to the Principal Investigator, the Study Contact(s), and the associated facility staff.
 - E-mail #1 - Alerts the contacts that the modification is approved and provides a copy of the finalized item.

- E-mail #2 - Provides the official outcome letter with the approval date.
- The modification is listed in the minutes with a brief description, approval date, and the name and role of the reviewer.

III. Minor Changes (Modifications):

Category 3: Unconditional Administrative Process (ACUC Designee)

These changes may be approved by the ACUC Coordinator

- Correction of typographical errors
- Correction of grammar
- Contact information updates
- Change in personnel other than the PI
- Change in room location or other area currently overseen by the ACUC

Procedure:

- The ACUC designee can make these changes without further ACUC notification; however our ACUCs have traditionally provided the ACUC with a list of minor changes for their information.
- Submission:
 - All modifications are submitted to the ACUC using iRIS. A detailed description of the submission process can be found in the iRIS instruction manual.
 - Once a modification is submitted through iRIS, the ACUC office staff will review the item to determine if it is a Significant or Minor change using the guidelines detailed in this document.
- Processing:
 - The ACUC office will route the modification to the ACUC Coordinator for review and digital signature.
 - The ACUC Coordinator will review the modification to ensure that the training requirements for new personnel have been completed, provide any comments that must be addressed prior to approval, and sign-off
 - If no comments are provided - the modification is approved.
 - If comments are provided:
 - The ACUC office will send the comments to the Principal Investigator and Study Contact(s) through iRIS.
 - Once the revised modification has been received, the modification will be resent to the ACUC Coordinator to review and sign.
- Post-Approval:
 - Once the necessary signatures have been collected, the modification is approved in the iRIS system and two e-mails are sent to the Principal Investigator, the Study Contact(s), and the associated facility staff.
 - E-mail #1 - Alerts the contacts that the modification is approved and provides a copy of the finalized item.
 - E-mail #2 - Provides the official outcome letter with the approval date.
 - The modification is listed in the minutes with a brief description, approval date, and the name and role of the reviewer.
- Training Requirements for New Personnel
 - Investigators with no live animal contact:
 - Must complete either the OACU Initial Principal Investigator Course or Initial Animal Users Course at least once. Once the initial course is completed, an

- investigator must complete the OACU Refresher course or retake one of the initial courses every 3 years.
- Investigators with live animal contact:
 - Must complete either the OACU Initial Principal Investigator Course or Initial Animal Users Course at least once. Once the initial course is completed, an investigator must complete the OACU Refresher course or retake one of the initial courses every 3 years.
 - Must enroll in the Animal Exposure Program (AEP) either through Occupational Medical Services (OMS) or a comparable program through a contracting company (i.e. Leidos, Sobran, Charles River, ect.)