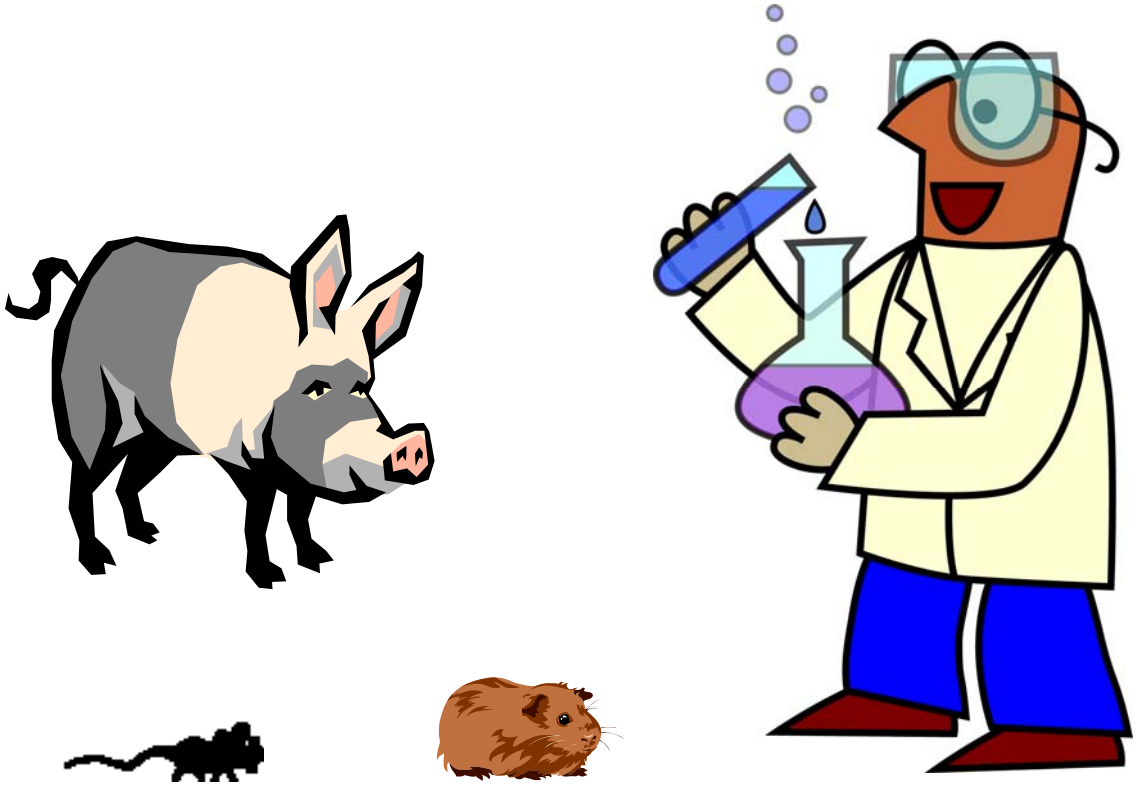
How to Write an Application Involving Research Animals



And What is Required After You Have Obtained IACUC Approval.

For use by Investigators covered by the Lifespan Animal Welfare Committee (IACUC)

Adopted from the National Institute of Allergy and Infectious Diseases' "All About Grants" Series

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Requirement for Using Research Animals

If you are a principal investigator planning to use live, vertebrate animals for research, research training, or biological testing, you must adhere to requirements in the Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals and the Animal Welfare Act and Regulations.

If you are applying for funding from an outside source, you may or may not be required to obtain institutional animal care and use committee (IACUC) approval at the time of application submission. Some sponsors require IACUC approval before the application is reviewed. NIH has instituted just–in–time review for animal applications. If your application to NIH receives a fundable priority score, you should have your animal use protocol reviewed and approved by the IACUC as soon as possible.

To receive a grant award, you need IACUC approval.

Research Planning is a Team Effort

Planning and teamwork are key to preparing a successful application. An animal subject's application requires a lot of work, so start early, leave time for unanticipated issues, and involve experts in your project from the beginning.

Ask senior IACUC members to validate your ideas and methods. Consult with the Central Research Facilities (CRF) Manager and the attending veterinarian about available facilities, equipment, personnel, and products. For example, the veterinarian may know of a new analgesic that introduces fewer variables into the research. If this is your first animal use application, then you are also required to meet with the IACUC Chair to review your responsibilities as a principal investigator.

These early consultations protect you and your institution. Since NIH allows just-in-time IACUC approval of animal use protocols, a PI can move a research project all the way through NIH initial peer review before an IACUC has a chance to see it. If your IACUC has last minute problems with your protocol, e.g., you have no biosafety level four facilities to inject mice with Ebola virus; you might not receive funding you otherwise could have received.

Consider Alternatives to Using Animals

When planning your research, consider whether you can achieve your scientific objectives while reducing or refining the use of animals by minimizing their pain or distress, or even better, not using them at all.

USDA regulations require that investigators search the scientific literature for alternatives, but if this isn't done until the IACUC approval stage, most researchers will have already determined what animals they are going to use and how.

Considering alternatives during the planning stage gives you enough time to incorporate methods that benefit the animals and the science. It also shows peer

reviewers that you are thorough and reduces your chances of a bar to award because of animal welfare concerns.

Limit animal use and discomfort

- Limit animal involvement by using the minimum number required to obtain valid results.
- Use non-animal methods, such as mathematical models, computer simulation, or *in vitro* biological systems.
- Avoid or minimize animal discomfort, distress, and pain as is consistent with sound scientific practices.
- Use appropriate sedation, analgesia, or anesthesia when your procedures will cause more than momentary pain or distress. Do not perform surgical or other painful procedures on non-anesthetized animals.

Resources

- National Library of Medicine
  - Bibliography: Alternatives to the Use of Live Vertebrates in Biomedical Research and Testing
  - Index Medicus
  - Medline Plus
  - PubMed
- National Agricultural Library
  - Agricola

Personnel Qualifications and Training

The IACUC must ensure that staff working with animals are qualified and train investigators on policies and means to minimize animal pain and distress.

All personnel must complete Central Research Facility (CRF) Orientation and must be approved by the attending veterinarian to perform any procedure on live animals.

Occupational Health and Safety

Each investigator must have an occupational health and safety program for all personnel who work with animals. The program will depend on the research activities, hazards, and animal species involved. Minimally, the program should include the following.

- Pre-placement medical evaluation by the appropriate personnel health facility
- Identification of hazards and safeguards against risks.
- Appropriate testing and vaccinations.
- Staff training on hazards, safeguards, and roles and responsibilities.
- Provisions for documenting personnel training in the safe handling and disposal of biohazards used in the protocol(s)
- Policies and facilities that promote cleanliness and safety.

- Provisions for documenting and treating job-related injuries and illnesses.

For guidelines on establishing and maintaining an effective safety program, check out *Occupational Health and Safety in the Care and Use of Research Animals*, published by the National Research Council.

Working With The IACUC

The IACUC is an oversight body appointed by the institutional official. The Office of Laboratory Animal Welfare relies on the IACUC to enforce PHS policy and your institution's animal policies. IACUCs do the following.

- Review and approve animal use protocols, including changes* to previously approved protocols.
- Monitor your animal care and use program, including a semi-annual inspection of animal facilities.
- Instruct individuals on institutional animal policies and procedures, e.g., what is expected, which protocol forms to use, and where to get animals, how to report concerns.
- Evaluate compliance with institutional policies.
- Report annually and notify OLAW of suspensions and instances of serious noncompliance with policy.

Within Lifespan, policies for research animals are a combination of institutional and USDA and PHS requirements.

* Implementing a significant change without IACUC prior approval is a serious violation of PHS policy.

Resources

- Guidelines for Submission of Proposed Changes to Animal Care and Use Protocols

How the IACUC Is Structured

The Lifespan IACUC has at least five members, including people with the following backgrounds.

- A veterinarian with experience in laboratory animal science and medicine, who has direct or delegated authority and responsibility for activities involving animals at the institution.
- A practicing scientist experienced in research with animals.
- A person whose primary concerns are in a nonscientific area, e.g., an ethicist, lawyer, or member of the clergy.
- A person not affiliated with the institution who represents community interests and who is not a laboratory animal user.

Other IACUC members are usually faculty members and fellow researchers who are familiar with the issues you are facing and can serve as resources to help you prepare the best possible application.

Write Your Protocol

Coordinate writing your application and protocol. Be sure to write your protocol early enough for the IACUC. It is extremely important that the information in the animal care and use plan (ACUP) submitted to the IACUC is consistent with the information in your grant application and/or research plan.

Before writing your protocol, consult with the attending veterinarian on the latest technologies and procedures that could improve your approach. Also send the veterinarian a draft of your protocol to resolve any issues at least two weeks before it goes to the IACUC. A standard animal protocol includes the following information.

- **Description of project.** Help IACUC members understand your animal procedures by avoiding technical language only people in your field will understand. Use visual aids, such as flow charts and bullets, to illustrate your points or break up text.
- **Justification for using animals.** Describe why an animal model is necessary. If you're studying a human health problem, state its cause, existing therapies, and the potential contribution of your experiments to further its understanding. Use lay language, explaining all medical terms and defining acronyms the first time you use them.
- **Justification for species.** Tell IACUC members why you chose one species over others. You should generally use the most appropriate and least sentient species capable of providing the data you need. The following is a typical hierarchy of sentient animal species.
    1. Non-human primates, such as monkeys, marmosets, and baboons.
    2. Large animals, such as cats, dogs, and pigs.
    3. Rabbits.
    4. Rodents, such as hamsters, rats, and mice.
    5. Non-mammalian vertebrates, such as poultry, reptiles, and fish.

Your rationale for using a species may be size, availability; the existence of previous work or laboratory data that validates the use of a certain animal model; or the availability of reagents.

- **Justification for number of animals.** Request the amount of animals you need and explain why. Use the minimum number needed to yield statistically significant results.
- **Consideration of alternatives.** Convince IACUC members that you have adequately explored alternative methods. Use techniques to minimize pain and distress. These are known as "refinements" to your protocol. List databases you searched and when, citations derived, and the keywords or search strategy. List other sources, such as journal articles, presentations, and colleagues.
- **Description of animal procedures.** Include non-surgical methods, such as injections and sample collections; surgical methods, such as suturing and anesthesia; and other measures, such as pre-anesthetic fasting, drugs, and care during recovery.

- **Assurance that qualified staff will perform work.** Name all personnel who will be working on your study, along with their animal research experience and familiarity with your proposed procedures. If you or someone on your staff does not have the necessary experience, list experts at your institution who can provide training. The IACUC will have to verify that this training took place before animal work can begin.
- **Endpoint criteria.** Choose endpoints that achieve the aims of the study and avoid unnecessary pain and distress. Include the criteria you will use to decide when to intervene or end animal use in the study, e.g., pain that cannot be controlled with analgesics, tumor size, and stage of disease. Interventions include euthanasia, treatment, or discontinuance of procedure.

Complete the Animal Care and Use Protocol (ACUP)

The Animal Care and Use Protocol (ACUP) is posted in the forms and templates library in IRBNet. You must answer all questions in the basic application and attach all appendices as applicable.

Complete the Core Form

All applications must include an Animal Care and Use Protocol Part 1 (Core Form). This form describes who will be responsible for the project, the type of research that will be done and how it will be funded. If you indicate that the application is part of an external grant or contract application, then you will not be able to begin the work until the project is funded. If you wish to begin the project using unrestricted departmental funds, then you must provide the appropriate departmental cost center. Your Department Chair and administrator must sign the application to indicate that the project is scientifically valid, that the staff is qualified to perform the work, and that it is an appropriate use of departmental resources.

Include the Grant Application or a Research Plan

The IACUC does not serve as peer review for grant applications; however, it is responsible for ensuring the use of animals is justified and the validity of the science. You must provide copies of the grant application to the IACUC. The IACUC will compare the grant proposal with the ACUP to ensure consistency. If the project has not been submitted for external funding, then investigators are required to include a research plan.

All information for the research plan should be typed. Organize the plan to answer these questions: (A) What do you intend to do? (B) Why is the work important? (C) What has already been done? (D) How are you going to do the work?

Submit Your Application

The Office of Research Administration must enforce application due dates to ensure adequate time for thorough IACUC review. Your application must be received by the due date unless there are major extenuating circumstances and prior permission for an extension of the due date.

Most applications are due to the IACUC on the first Monday of each month. However, holiday schedules are implemented during some months. Remember, veterinary pre-review is required at least two weeks before the IACUC submission deadline. Consult the deadlines as posted on the Research Administration website.

Review of Your Protocol at the IACUC Meeting

After your application is received and found to be complete, it will be processed for review by the IACUC. At least two members, including a veterinarian will serve as primary reviewers. You are required to attend the IACUC meeting to present your application and answer any questions that may arise. All members will have access to your application and may also ask questions in addition to the assigned primary reviewers.

Read Your IACUC Correspondence Carefully

Minutes from the IACUC meeting will be sent to you within one week after the meeting. Be sure to read each bullet of the minutes carefully. You will be asked to provide any additional information or corrections as requested by the IACUC.

Sometimes the IACUC requires extensive changes that must be reviewed by the convened IACUC at the next meeting, or by designated reviewers.

Final approval will not be granted until all IACUC issues have been resolved. You cannot begin any animal work until you have received an approval letter from the IACUC.

The terms and conditions of your approval are detailed in your approval letter. Projects are approved for no greater than one year. You will be required to submit a progress report before IACUC approval expires.

IACUCs Monitor Your Progress

During the life of your project, there are several reporting requirements.

Monitor your work closely. As PI, you are accountable for <u>all</u> activities involving animals during the project.

Your approved animal use protocol is a contract between you and the IACUC, stipulating that your project will follow all institutional polices and procedures. You must obtain IACUC approval *before* you make any changes to the research, including the following.

- Study objectives.
- Non-survival to survival surgery.
- Species or number of animals.
- Invasiveness of a procedure.
- Use of anesthetics or analgesics.
- Methods of euthanasia.
- Change in PI.

Progress Reports must be submitted to secure approval for continuation prior to expiration of IACUC approval. No work can be done after IACUC approval expires

You will also need to get a new IACUC approval every three years. Institutional officials and IACUCs do not have authority to extend an IACUC approval beyond its expiration date. Conducting research in the absence of a valid IACUC approval constitutes noncompliance with PHS policy and it is reportable to OLAW.

Semiannual Reviews and Inspections

As part of its semiannual program review and facility inspection, the IACUC will conduct routine assessments of institutional animal activities.

This review covers institutional policies and responsibilities, IACUC membership and functions, and IACUC record keeping and reporting procedures. It also looks at the adequacy and appropriateness of veterinary care, staff training, and occupational health and safety programs.

A facility review is a physical inspection of buildings, areas, and vehicles (including satellite facilities housing animals for more than 12 hours) used for confinement, transport, maintenance, breeding, or experiments, including surgery.

Your lab may be inspected as part of a facility review, or your IACUC may randomly visit to verify that you are following your protocol.

IACUCs report the results of their program evaluation and facility inspection to the institutional official for animal welfare. These reports describe any deficiencies found and include plans and schedules for correcting each one.

Institutional officials submit semiannual IACUC reports to OLAW only if requested or if the institution is submitting a new or renewal animal welfare assurance. Lifespan is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) and must submit copies of the semi-annual reports to AA

Avoid Suspension of Animal Activities

The IACUC can suspend your project if it finds serious or continuing noncompliance with PHS policy or the institution's assurance or deviations from the approved protocol or the *Guide for the Care and Use of Laboratory Animals*.

The IACUC will convey its reasons for a suspension to the institutional official for animal welfare, who will take corrective measures and report the situation to OLAW.

OLAW can withdraw approval of your institution's assurance, though this is extremely rare. Should this happen, your institution would become ineligible for funding activities involving animals, and PHS or the sponsor/grant agency may seek to recover its monies.

OLAW can also place restrictions on an institution's assurance until compliance problems are fully resolved. OLAW always emphasizes corrective rather than punitive

actions and will only restrict or withdraw approval of an assurance if an institution's efforts to correct its problems are unsuccessful.

Keep Your Records Accessible

You must keep your project records, animal procedure descriptions and post-operative survival records available at all times.

You must keep your project records accessible for three years after the grant ends. If an issue arises, your sponsor must be able to verify the records, which must include all data and fiscal information.

Under PHS policy your institution is required to maintain the following records for a minimum of three years:

- Assurance approved by the Office of Laboratory Animal Welfare.
- Minutes of IACUC meetings.
- Records of IACUC activities and deliberations.
- Minority IACUC views.
- Documentation of protocols reviewed by the IACUC, and proposed significant changes to protocols (this documentation must be maintained for an additional three years after completion of animal activities).
- IACUC semiannual program evaluations and facility inspections, including deficiencies identified and plans for correction.
- Accrediting body determinations.

In Conclusion

We hope these pages have helped you. If you have questions that weren't answered here, please contact the IACUC Manager (401) 444-5843 or the IACUC Coordinator (401) 444-2093 for help.