The condensed guide to animal welfare regulation for the working research scientist

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The average research biologist has no idea of the enormous weight of regulatory burden poised overhead. Since the US Congress Animal Welfare Act of 1966, the regulatory machinery in the US has steadily grown without much involvement on the part of the regulated enterprise. However, the process is not entirely without reason, there are professional organizations that act as advocates for the scientific community[2] and there is increasing recognition that the process would gain legitimacy by engaging more participation from research scientists.

from WF Raub, Cutting red tape on research, *Iss. Sci. Tech.*, Winter, 75, 1989

Purpose: The use of animals in research imposes substantial legal and ethical responsibilities with which investigators should be familiar.[3] This guide is intended to provide the working scientists at Stony Brook University a condensed tutorial on the structure and operation of the regulatory process. It is meant to provide a relatively painless introduction to animal welfare regulations that the author has gleaned from his own experience as an experimental biologist and as a unfortunate cog in the bureaucratic machinery of animal welfare regulation.

Premise: Research biologists operate under the premise that the humane use of animals in biomedical and basic science research is ethically justified. While this presumption is not universally shared[4], public opinion polls indicate that the majority of the public supports biomedical research using lab animals.[5] However, there is also considerable public antipathy toward subjecting animals to unnecessary pain or discomfort. Certainly, institutionalized cruelty to animals is unacceptable. The use of research animals demands significant responsibility to insure their humane treatment. As stated by the National Association for Biomedical Science (NABR), "biomedical researchers advocate high-quality, humane care of laboratory animals not only for reasons of conscience, but also for reasons of science. Good animal care is good science."

Consider the following scenario: After finishing a day's biomedical lectures to college, graduate and professional students, you return to your office after coordinating all your lab's projects with postdocs, graduate students and technicians to find several people waiting for you. A college student is accusing you and your colleagues of cruelty to animals in your research, a news reporter is wanting comments on how of your latest research discovery in a laboratory animal has biomedical relevance, a lab animal vet is wanting to review details about your animal-use protocols, a federal inspector is demanding to see your laboratory and records, and a university administrator is expecting accountability for your NIH expenditures regarding the

advancement of knowledge and the good of society. Do you need this? No, you need an institutional animal care and use committee - an IACUC.

- You can assure the college student that your IACUC enforces high standards for the care and use of all research animals in all the research projects at the university. Good biological research does not embrace inhumane research methods in animals.
- You can direct the news reporter to the university's public relations office, which has an IACUC FAQ-sheet discussing the importance of animal models in biomedical research and providing internet-based information contacts. Basic biomedical and biological research is the foundation of modern medicine.
- You can refer the veterinarian to your IACUC-approved research protocols. Modern, high-quality veterinary practice is designed into your research methods.
- You can direct the federal inspector to the veterinary records of your research animals and the recent IACUC approval of your lab facilities. You can be certain that your use of laboratory animals is performed within mandated regulations.
- And you can explain to the administrator that the IACUC provides assurance that your research is scientifically meritorious and humane. Moreover, you and the rest of the research community bring highly-regarded prestige to the university and make a substantial financial impact on the local and state economies.

- While regulatory policy gives final authority and ultimate responsibility to the local IACUC for all animal welfare issues, it does not have to operate as a policing agent. It is designed to serve as intermediary between the PIs, the veterinary staff, the university administration, the regulatory agencies and the public.
- The IACUC can shut down your lab for animal-use improprieties, but it can also insulate you from overzealous regulatory creep. At SBU, we try to minimize regulatory burden by promoting simplicity in compliance. By maintaining regulatory compliance from the PIs, we can be effective in serving as advocates for research - for the investigators and the university.
- The IACUC recognizes the PIs' foremost responsibility is to design and complete good scientific investigation. But for the IACUC to serve as an advocate for the individual PI, researchers are expected to exercise diligence in cooperating with the veterinary staff and in complying with regulatory policy.
- On the other hand, as the institutional oversight agent, deliberate and egregious violations by individual researchers can not be tolerated and will not be defended.

Regulatory oversight agencies: Myriad animal welfare regulations and guidelines are promulgated by federal and state agencies (see below), veterinary organizations[6], professional societies[7] and private health organizations.[8] There is a fledgling effort by some of the organizations to "harmonize" and reduce the regulatory burden.

US Dept. Agriculture (USDA); APHIS (Animal and Plant Health Inspection Service)

- enforces provisions of the Animal Welfare Act of 1966, The Improved Standards of Laboratory Animals Act of 1985 and other amendments
- applies to live or dead dogs, cats, nonhuman primates, guinea pigs, hamsters, rabbits or other warm blooded animal used in experimental research or teaching - excluding rats,

mice and birds
- semi-annual, inspection-based enforcement
- professes to "performance standards," but historically tends to be prescriptive in enforcement

Public Health Service (PHS); Office of Laboratory Welfare (OLAW)
- enforces provisions of The Health Research Extension Act of 1985 for appropriate care and use of animals involved in research conducted or supported by the Public Health Service (i.e., National Institutes of Health)
- applies to any live vertebrate animal used in experimental research or training supported by PHS funds
- adheres to the Guide for the Care and Use of Laboratory Animals from the Institute of Laboratory Animal Resources (ILAR) of the National Research Council (NRC)
- five year, assurance-based enforcement negotiated with participating institutions
- uses performance standards established by accreditation from the American Association for Accreditation of Laboratory Animal Care (AAALAC) and/or by the Institutional Animal Care and Use Committee (IACUC)

Food and Drug Administration (FDA)
- enforces the same federal mandates as APHIS and OLAW as they relate to projects yielding data to support new drug and device applications
- applies to all laboratory operations with provisions for animal care, housing, feeding, handling, disease control and treatment, etc.
- uses guidelines set forth in the ILAR Guide for the Care and Use of Laboratory Animals
- enforcement by approval of "Good Laboratory Practices" (GLP) by consultative procedures and review from the FDA Center for Veterinary Medicine

NY Dept. of Agriculture and Markets
- enforces state laws regarding import/export of animals, licensing and health certification of dogs, and animal cruelty

American Association for Accreditation of Laboratory Animal Care (AAALAC)
- has no mandated regulatory authority, but as a professional society of experts in lab animal medicine it's voluntary accreditation attributes a high level of quality care for research animals that exceeds the minimum federal standards
- evaluates the institutional structure for the care and well-being of all vertebrate animals used in research, teaching or testing
- relies on "widely accepted" guidelines, such as those of the ILAR Guide for the Care and Use of Laboratory Animals and supplemental "position statements"
- relies heavily on oversight and tri-annual inspection of the veterinary division of accredited institutions

Intramural responsibilities:

Primary Investigators (PIs):

- Any research or teaching activity that involves the use of animals must be *pre*-approved by the university's IACUC**.**
- PIs must hold a faculty title and must assume primary responsible for the proper and humane use of animals in their research protocols.
- The Animal Welfare Act specifically excludes proscription of experimental design and performance that could interfere with sound research methods. However, PHS policy states that experiments using animal subjects should "be designed . . . with due consideration of their relevance to human or animal health, the advancement of knowledge, or the good of society."
- The new mantra from the regulatory communities is to exercise the 3 "R"s wherever possible: *Replace* animal methods with non-animal methods; *Reduce* the number of animals; *Refine* the experimental procedures to minimize pain and discomfort.

Division of Lab Animal Resources (DLAR):

- The senior veterinary staff are board certified by ACLAM (American College of Laboratory Animal Medicine), the highest level of training in lab animal medicine.
- Essentially all the regulatory agencies hold the university's Chief Veterinarian as ultimately responsible for "adequate veterinary care," which includes:
    - maintenance and accreditation of the institutional lab animal facilities
    - contribution to the establishment of appropriate policies for the veterinary medical care, husbandry, zoonosis, hazard and occupational health
    - oversight of research animal welfare
    - serving as a voting member of the IACUC
- A DLAR advisory committee appointed by the Vice-President for Research serves to advise and oversee the operation of the DLAR.
- The Chief Veterinarian has the authority to terminate or to confiscate distressed lab animals when deemed medically necessary, usually in consultation with the Chair of the IACUC and the PI, if available.
- The veterinary staff (attending veterinarians and veterinary technicians) are charged with:
    - providing advice on humane animal use in light of scientific requirements
    - ensuring appropriate handling, immobilization, sedation, analgesia, anesthesia, and euthanasia
    - overseeing surgery and postsurgical care
    - reviewing protocols and proposals with respect to veterinary care, animal husbandry, and animal welfare
- The lab animal staff provides or assists in the front-line, daily care and maintenance of all the university's research animals.

Office of Research Compliance:

- Coordinates administrative operations of
    - the animal protocol applications and occupational health approvals for investigators
    - the scheduling and recording of minutes for IACUC meetings
    - the regulatory and educational involvement of the Chief Veterinarian
- Provides interpretation and assurances of extramural regulations for the institution

- Mediates communications among the PIs, the IACUC, the DLAR, the university administration and the funding agencies
- Maintains the database of records and the posting of policy regarding animal research compliance

IACUC (Institutional Animal Care and Use Committee):

- Ensures that all animal related research at SBU is scientifically meritorious, humane and conducted in accordance with regulatory controls
- IACUC functions mandated by the Animal Welfare Act and PHS assurance policy include:
    - semi-annual review the entire research program
    - semi-annual inspection of all animal facilities and animal-use areas, including PI laboratories
    - semi-annual report to the administrative officials (University President, Vice-President for Research, Vice-Dean of Medicine)
    - review and investigation of complaints or reports of non-compliance, or concerns for animal welfare
    - make recommendations to the administration regarding any aspect of the research facilities or operation
    - review all proposed activities related to the care and use of animals (i.e., approve, require modification/clarification or withhold approval for animal-use proposals)
    - review any proposed changes in activities related to the care and use of animals
    - take corrective action, suspend animal-use activity and report serious protocol violations to funding agencies and the USDA when necessary
    - ensure the proper training of personnel involved with the care and use of animals
- Complaints, concerns or questions about animal welfare or regulatory compliance should be directed to the IACUC Chair or the veterinary staff.
    - Procedural or medical issues can be handled directly and quickly by consultation with appropriate sources
    - Compliance concerns can come from any source, public or institutional. If the complaint is deemed of valid concern,
        - the PI is usually asked to suspend animal-use activity voluntarily while the issue is under consideration, and to provide a written or in-person explanation to the IACUC along with a time-defined plan of correction. Minor, unintentional violations are usually evaluated by the IACUC without serious repercussions.
        - Intentional or grossly negligent violations can lead to serious consequences for the PI and/or the university, up to immediate suspension of research approval, impounding of animals and referral to the funding agencies and the USDA.

IACUC Membership:

- appointed by, and reporting directly to, the institutional CEO (University President)
- must include at least 3 members, but usually involves 5 or more members (a chairperson, a veterinarian, a scientist, a non-scientist, a non-affiliated public member)

- no more than 3 members from the same department
- includes a representative of the office of Environmental Health and Safety
- includes the *ex officio* representative of the Office of Research Compliance (non-voting)

Research Protocol Review:

- No research animals can be obtained and no animal-related work can proceed, including teaching or field observation activities, without prior IACUC approval.
- Prior to protocol application, PIs may wish to consult the veterinary staff for questions, guidance on animal care issues or for endorsement of lab facilities or procedures.
- The IACUC meets once a month to review submitted protocols, which must be received by the first day of the month.
- Upon review, protocols are either 1) accepted, 2) accepted pending modifications or clarifications, or 3) acceptance is withheld for specified reasons.
    - modifications/clarifications for approval can usually be made quickly by memo
    - denial of acceptance usually occurs due to substantially flawed or incomplete application, and must be resubmitted with an itemized list of corrections
- Approved protocols are valid for 3 years with annual renewal by a brief progress report
- Approved protocols can be amended by memo to the Research Compliance Officer for
    - administrative changes (e.g., add/remove personnel, changes in medical procedures under veterinary advice)
    - minor procedural changes (e.g., change of species, changing number of subjects, minor modification of methods, appending certain "standard" procedures). Requests for minor amendments
        - must describe the change *and* how it differs from current approval.
        - must provide a *scientific* justification for the change.
        - must indicate no change in specific aims, or justify them.
        - must indicate no necessity for changes in monitoring/management of adverse effects, or describe them.
        - More than 3 amendments in an approval period may require new submission of a full application.
    - major procedural changes should be submitted as a new protocol

Expedited reviews: There are no official USDA or PHS provisions for "expedited" reviews. By law, *all* protocols are subject to review by a quorum of the IACUC. However, certain urgent requests can be considered mid-month. For practical reasons, this hastened review mechanism requires at least 5 business days and imposes time demands for some very busy people. It's use is strictly relegated to "emergency" situations. The request

- must *not* contain considerations for major methodological, ethical or procedural issues.
- must have a compelling time-critical justification as assessed by the IACUC Chair.
- must go through a veterinary review for medical propriety, a "designated" review by an IACUC subcommittee and an opportunity for call to full committee review by any committee member. Moreover, all "expedited" considerations are treated

as temporary, subject to full review at the next convened meeting of the IACUC.

Research Proposal:

Like the IACUC operation itself, much of the material in the application for approval to use animals in research or teaching is mandated by law.

- **Scientific merit:** The IACUC does not perform scientific review of research proposals, but it must *assure* adequate scientific merit for the use of animal subjects. Peer review by federal funding agencies is the primary mechanism for rigorous scientific review. For non-federally-funded proposals, the IACUC generally relies on publication history and assurance by departmental Chairpersons for review of scientific merit.
- **Project justification:** PIs are asked to provide a layman's overview of the potential value of the study with respect to human or animal health, the advancement of knowledge, or the good of society. This brief statement should be able to stand as a potential public announcement for the justification for the proposed use of the research animals. Scientific terminology should be avoided. If your grandmother wouldn't understand it, it's not lay language.
- **Alternatives to the use of animals:** While it may seem obvious to the working biologist that the study of biology often requires a biologic subject or tissue, federal law mandates that researchers must state their considerations for why non-animal alternatives are not adequate for the proposed experiments. Because the selection of appropriate animal or tissue models is part of good research design, many scientist find this to be a frivolous demand. However, the animal-use issue is not trivial and, by law, justification must be included in the proposal application. In addition, the scientific reasons for the selection of the specific species proposed must be defended.
- **Consideration of alternatives to painful and distressful procedures:** In another example of congressional micro-management, the Animal Welfare Act specifies that investigators must provide "a written narrative of the consideration of alternatives to painful and distressful procedures." Moreover, congress mandated the creation of a special animal-use library within the National Agricultural Library (AWIC, the Animal Welfare Information Center). Even as it may seem tedious, it is simple enough to use AWIC, MEDLINE or any of several literature search services[9] to satisfy this requirement. You may, in fact, find useful information.
- **Justification of the number of animal subjects:** Due to a mandated obligation to minimize the numbers of research animals used, researchers must justify their requested numbers of subjects in terms of experimental groups, statistical power or other scientific needs. The approved number determines the maximal census of animals that the PI is allowed, thus the SBU application allows for justification of an "optimal" number of subjects which may exceed the absolute minimum.
- **Pain and distress:** Each animal subject must be categorized in terms of the pain and distress expected from the experimental procedures[10]: A. No pain or distress, B. Relieved Pain or Distress, C. Unrelieved Pain or Distress. Category B. requires explicit veterinary oversight. Category C. requires rigorous justification and extensive veterinary oversight.
- **Experimental procedures:** The description of experimental procedures should assume that the IACUC reviewers are scientifically knowledgeable, but not an expert in each specific field of study. It should not include detailed information pertaining to methods

that are not relevant to the research animals. The preferred format is a brief narrative overview of the overall experimental goals and project design, followed by a cookbook description of all experimental procedures related to the care and use of animal subjects. Certain tabular information for veterinary review and AAALAC documentation is also requested.

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End Notes:

1. The author of this guide is himself an over-regulated, working research scientist in the Department of Neurobiology & Behavior, who suffers service as the Chairman of the SBU IACUC. Opinions and comments, inferred or stated, are the author's and do not necessarily reflect those of the IACUC or the university.

2. Some of the more notable scientific societies advocating for researchers include Scientists Center for Animal Welfare, Federation of American Societies for Experimental Biology, American Physiological Society, Society for Neuroscience, National Academy of Sciences, American Psychological Association, Association for Research in Vision and Ophthalmology and others.

3. Moreover, if you are an animal-use researcher who really reads this guide, you will have satisfied one of the mandates to the IACUC from Animal Welfare Act: to "provide for the training of scientists . . . [and] other personnel involved with animal care and treatment . . . as required by the Secretary [of Agriculture of the United States]."

4. e.g., "We have no basic right ... not to be harmed by those natural diseases we are heir to," Tom Regan, The Case for Animal Rights, 1983; "If the death of one rat cured all diseases, it wouldn't make any difference to me," Chris De Rose, Director, Last Chance for Animals

5. ICR Survey Research Group, Associated Press, 1995; Market & Opinion Research International for the Medical Research Council of UK, 1999

6. American Veterinary Medical Association, American College of Laboratory Medicine, American Association For Laboratory Animal Science, Association for the Assessment and Accreditation of Laboratory Animal Care, American Society of Laboratory Animal Practitioners

7. See note 2. for scientific societies; professional teaching societies include the National Association of Biology Teachers, National Science Teachers Association, and others.

8. e.g., American Heart Association, American Cancer Society, Juvenile Diabetes Foundation, incurably ill For Animal Research, Americans for Medical Progress Education Foundation and others.

9. e.g., www.nal.usda.gov/awic; altweb.jhsph.edu, a gateway to various "alternatives to animal testing on the web"; MEDLINE, which now includes major veterinary medical journals and the MESH terms "animal testing alternatives" and "animal welfare"

10. A. No pain or distress (e.g., observational studies, euthanasia for tissue collection, etc.); B. Potential pain or distress relieved by pharmacologic, behavioral or other means (e.g., tranquilization/sedation, general or local anesthesia, post-procedural analgesics, behavioral conditioning to restraint or minor pain/stress, medical treatment of disease states, etc.); C. Unrelieved pain or distress (any procedure that would cause more than momentary or slight pain or distress; e.g., chronic untreated disease states, pain research, etc.)