Regulatory requirements for adequate veterinary care to research animals

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Abstract: Provision of adequate veterinary care is a required component of animal care and use programs in the US. Veterinary care may be provided by many program participants other than veterinarians. Understanding the legal basis and conditions of a program of veterinary care will help program participants such as researchers and technicians to meet the requirements advanced in the laws and policies. Here I offer a discussion of the US regulatory requirements for the provision of veterinary care to research animals as a training primer for non-medically trained research personnel, technicians, and administrators.

The *Guide for the Care and Use of Laboratory Animals* (Guide) and the Animal Welfare Act require the provision of adequate veterinary care to animals used in research. [1,2] The term "veterinary care" implies a responsibility of the attending veterinarian (AV), but the provision of veterinary care is a collaborative effort. Many participants in animal care and use programs provide veterinary care, including the AV, clinical veterinarians, animal health technicians, and husbandry technicians. Researchers and research technicians who do surgical or nonsurgical procedures on animals under approved protocols are also providing veterinary care and institutions must assure their compliance with the regulations regarding provision of that care.

The animal welfare laws and policies indicate that the IACUC with the expertise of the AV should establish standards for the provision of veterinary care. Those standards should be built on the requirements detailed in the laws and policies, but also should be based on the "accepted standard of veterinary care". The goal of this manuscript is to provide a foundation for non-medically trained researchers and technicians about what the provision of adequate veterinary care operationally means. In this manuscript, we summarize what constitutes an adequate program of veterinary care, what "standard of care" means, and how programs of veterinary care are implemented. Finally we discuss what researchers and animal care staff should understand and accomplish in the program of veterinary care relative to today's regulatory framework. The provision of quality veterinary care translates into better science.

The Legal Basis and Program Design

The animal welfare laws and policies outline the need for a program of veterinary care. The program establishes standards and requirements, usually in standard operating

procedures (SOPs) that are reviewed, approved, and implemented by the Institutional Animal Care and Use Committee (IACUC). As a medically trained professional, the AV is responsible for establishing the standards and providing oversight of veterinary care, regardless of who is actually providing the hands-on care for the animals. The legal basis for the program is summarized below.

Animal Welfare Act. The Animal Welfare Act provides much of the legal foundation for the program of veterinary care and covers regulated species.[2] Regulated species are those covered under the Animal Welfare Act definition of animal. This definition is currently "any live or dead dog, cat, nonhuman primate, guinea pig, hamster, rabbit, or any other warmblooded animal, which is being used, or is intended for use for research, teaching, testing, experimentation, or exhibition purposes, or as a pet." The definition specifically excludes rats of the genus *Rattus* and mice of genus *Mus*, specifically rats and mice bred for research. Farm animals used for basic science research are covered by the act, but those used for food and fiber research are not covered. Birds are also excluded.

Under the regulations advanced by the United States Department of Agriculture (USDA), research facilities must register with the USDA (2.30.a) and acknowledge receipt of the regulations (2.30.b). The IACUC must review and approve all animal activities, otherwise known as the "program for animal care and use" (2.31.c.1). An animal activity is anything done with or to an animal, including husbandry, veterinary care or research. The research facility must provide sufficient facilities, personnel, equipment and resources to comply with the regulations (2.33.b.1). The research facility must employ a veterinarian (2.33) either full time or part time and, if part time, the program of veterinary care must be in writing (2.33.a.1). The veterinarian must have access to all animals and have the authority to provide care (2.33). The veterinarian must be a member of the IACUC (2.33.a.3).

The Animal Welfare Act regulations further state that the program must enable the prevention, diagnosis and treatment of disease (2.34.b.2), daily observation of the animals (2.34.b.3), and direct line of communication to the veterinarian (2.34.b.3). The animal care program must provide to investigators and other personnel guidance on handling, immobilization, anesthesia, analgesia, tranquilization, and euthanasia (2.34.b.4).

The IACUC has many responsibilities in the program of veterinary care. The IACUC must review all proposed animal activities, including research procedures, husbandry, sanitation, etc. For research activities, there are several items that the IACUC specifically evaluates. The IACUC reviews procedures to determine that pain and distress are minimized (2.31.d.1.i) and that painful procedures are done with "appropriate" anesthetics, analgesics or sedatives (2.31.d.iv). Personnel conducting

procedures must be trained (2.31.d.viii). Medical care must be available to the animals as required (2.31.d.vii). Euthanasia methods must meet defined criteria (2.31.d.xi). In addition to these aspects relating to direct animal manipulation, the IACUC must also review the animal use proposal for other regulatory issues such as, but not limited to animal numbers requested and consideration of alternatives to procedures that cause pain or distress.

Training of animal care and use personnel is an integral part of the provision of adequate veterinary care (2.32a). Further, training and qualifications must be reviewed by IACUC at "sufficient frequency to fulfill the research facility's responsibilities" (2.32b). This means qualifications must be repeatedly or progressively reviewed. Training must include humane methods of experimentation, proper handling methods, proper pre- and post-procedural care, aseptic surgical methods, and proper use of anesthetics, sedatives, and analgesics (2.32b).

The Animal Welfare Act regulations and its supporting policy statements have much to say about painful procedures, surgery, pre-operative care, and post-operative care. Planning for painful procedures must involve a veterinarian (2.31.d.iv). Painful procedures must involve the use of anesthetics, analgesics or sedatives unless withholding such can be scientifically justified (2.31.d.iv). Survival surgery must be done aseptically (2.31.d.ix) with "appropriate" pre-operative and post-operative care, according to "established veterinary medical and nursing practices" (2.31.3.ix). There are qualified limitations on the number of surgical procedures an animal may undergo (2.31.d.x). Animals in chronic pain should be humanely euthanized at the end of the procedure unless there is a scientific justification for not doing so (2.31.d.v).

Finally, the USDA has a Policy Manual that clarifies certain aspects of the regulations. USDA Policy 3[3] mandates that drugs must be in date and should be pharmaceutical grade (if available), survival surgery must be done aseptically, and that pre- and post-operative care must be detailed in the proposal reviewed by IACUC. Health records should be maintained and those records must be available to all personnel involved in the care and use of the animals (centrally available records). Finally, euthanasia should conform to the *AVMA Guidelines on Euthansia*.[4]

Public Health Service Policy. The *Public Health Service Policy for the Humane Care and Use of Laboratory Animals* (PHS Policy) also mandates the development of a program of animal care and use that covers all animals used in federally funded research.[5] This program is detailed in a negotiated document required by the National Institutes of Health (NIH), Office of Laboratory Animal Welfare. This NIH Animal Welfare Assurance Statement (NIH Assurance) details how institutions receiving federal research dollars will comply with the *Guide for the Care and Use of Laboratory Animals*.[1] Chapter 4 of this Guide is dedicated to the program of veterinary care.

Since the NIH Assurance is required for institutions to receive federal research dollars and the PHS Policy requires compliance with the Guide, these standards are for all intents a mandate with legal foundation in the Health Research Extension Act of 1985.[6] The Health Research Extension Act of 1985 empowers the Director of NIH to establish guidelines for the proper care of animals to be used in research and the proper treatment of animals while used in research. The PHS Policy establishes these guidelines and uses the Guide as performance criteria for the program. In contrast to the Animal Welfare Act, the Guide covers all vertebrate animals produced for or used in research. Taken together, the Animal Welfare Act and the Guide cover virtually all animals used in biomedical research.

The program of veterinary care covers all aspects of animal health, including acquisition, preventative medicine, daily surveillance for disease or debility, provision of medical care, research related disability, animal restraint, pre- and post-operative care, surgery standards, pain and distress management, anesthesia and analgesia, and euthanasia. The Guide advances performance based standards that define what the veterinary care should accomplish without being prescriptive. The "accepted standard of care" principle is implied throughout Chapter 4 of the Guide. In this sense, the anesthesia, analgesia, surgery, medical records, and euthanasia standards are all similar to the Animal Welfare Act regulations and these two standards are very consistent with one another.

The Guide has many sections relevant to researcher activities in chapter 4 and other chapters. In Chapter 1, the Guide provides performance standards for IACUC review of animal use proposals. The animal use proposal is the primary interface of the researcher with the institutional compliance program. The review criteria relative to veterinary care define what the researcher needs to be concerned with in the proposal.[1] The proposal should include "a clear and sequential" description of all procedures done to the animals, details of nonstandard husbandry, the impact of all procedures on the animals' well-being. Details should also include appropriate sedation, analgesia, and anesthesia, assessment of the level of pain or distress, surgical procedures, pre- and post-procedural care, humane and scientific endpoints, criteria for intervention, euthanasia methods, and training and experience of personnel on the project. Nonstandard husbandry includes atypical housing and food or fluid restriction or alteration. The IACUC is required to review the use of non-pharmaceutical grade drugs prior to their use since non-pharmaceutical formulations may or may not be fully efficacious.[3] The IACUC is also charged with monitoring animal use after approval of the proposal.

The concepts of humane and scientific endpoints are important aspects of animal use that the researcher should advance clearly in the IACUC proposal. This is emphasized

now in the Guide and this constitutes a component of veterinary care directed at management of pain and distress.

Humane endpoints are those that define objective clinical signs resulting from experimental or surgical debility. The criteria advanced should be related to the procedure done and should prompt consideration of removal from study or euthanasia to prevent unnecessary pain or distress. The use of general or unqualified criteria is difficult to interpret by animal care personnel who evaluate the health status animals daily. More objective criteria such as percent weight loss over a defined unit of time or specific endpoint tumor dimensions are more readily interpretable. Humane endpoints should be considered for each proposed procedure since the types of debilitation produced may differ from one procedure to the next. A plan for unexpected outcomes should also be developed, such as those for odd phenotypes resulting from gene manipulations.

Scientific endpoints are research readout measurements that indicate that an experimental paradigm has answered the primary research question (whether or not the null hypothesis can be rejected). Ideally, scientific endpoints should precede humane endpoints. This suggests that if at all possible, the experiment should end with a reasonable answer before pain or distress is an issue.

What is "Standard of Care"?

The regulations and policies use several key terms that are important. These include terms such as "appropriate", "proper", and "established veterinary medical and nursing practices". These terms and performance based standards refer to the concept of "generally accepted standard of care" that is well known in medical and veterinary practice. "Standard of care" is defined as: "the level at which the average, prudent provider in a given community would practice. It is how similarly qualified practitioners would have managed the patient's care under the same or similar circumstances."[7] This is essentially the standard accepted as appropriate by the community of veterinary practitioners and also, in this case, laboratory animal specialists. Several statements in the regulations and USDA Policy 3 imply that the USDA uses this standard in its assessment of veterinary care. The position statement on "Adequate Veterinary Care" advanced by the American College of Laboratory Animal Medicine also provides considerable guidance on the accepted standard of care.[8]

Implementation of Veterinary Care Programs

The regulations and policies indicate that veterinary care programs are "institutional". This means the standards apply to all personnel involved in the program of animal care and use. Standards are usually defined in operating procedures (SOPs) or policies. IACUC should approve all standards and review them periodically. Most animal care

programs publish the standards either in a handbook or website since this information should be available to all program participants, including research staff. Training in the standards is an absolute requirement of all regulations and policies. Finally, the program must be monitored for compliance with those published standards and approved IACUC protocols.

Practical Application for Researchers

The essence of practical application for the research investigator is that he or she should propose carefully what is to be done in the research and then to do the work *exactly* as approved by the IACUC. The IACUC protocol is where research procedures and the veterinary care associated with them are detailed. Protocols should be written with clarity for regulatory targets that IACUC is required to review.[9] Altering the research methods without IACUC approval is a protocol violation for both the Animal Welfare Act and the PHS Policy. Protocols can be amended to reflect needed alterations in the course of the research and this approval must be obtained before the changes are implemented. This is a requirement of the laws and policies. It is also important that research records accurately reflect what was done to the animals. Investigators should recognize that in many public university circumstances, protocols and research records are considered "public" (subject to sunshine laws).

The concept of "established veterinary medical and nursing practices" has many tenets. Personnel should be trained for their role and activities with records of training. Anesthesia should be appropriate for the procedure, correctly applied, and well monitored. For survival surgical procedures, use of aseptic technique is required. Post-operative care should be provided. IACUC approved humane and scientific endpoints should be honored as closely as possible to avoid unnecessary pain and distress.

Research and Procedural Records. Good science requires good records and good records are required to write research publications. However, veterinary care programs also require good animal health records. USDA Policy 3 indicates that "Health records are needed to convey necessary information to all people involved in an animal's care. Every facility should have a system of health records sufficiently comprehensive to demonstrate the delivery of adequate health care. "[3] There are some implications in this USDA policy statement that should be clarified. "Convey necessary information to all people…" means that the health records should be readily available and interpretable by all program participants and regulators that need to see them. "Comprehensive…" means that the records should be sufficiently detailed to document that proper care was provided. While centralized records are not clearly indicated, it is often a distressing challenge for researchers and program administrators to collate dispersed records in

the stress of a regulatory site visit. Regulatory site visits go much more smoothly when these records are readily available.

What information should be in animal health records? "Standard of care" applies for this question, as well. However, the *Animal Care Inspection Guide* of the USDA also provides substantial information about what should be in an animal health record.[10] Table 1 provides a listing of information that should be easily found in the records. In a one line statement, health records should include anything that reflects or affects the health, status, and care of the animal. Comprehensive health records include medical care records, surgical care records, and research care records, preferably in one place, progressive, and well organized.

Table 1 Animal Health Records
All research and medical procedures
Date of Procedure
Name of Procedure
Operator(s)
Start Time/End Time
Anesthesia Used (if required) with Dose and Route
Post-Procedural Monitoring Points/Events
All Medical or Surgical Treatments
All Drugs or Chemicals Administered with Date, Dose and Route
All Diagnostics (labs, imaging, etc.)
Euthanasia
Post Mortem Findings (gross and histology as required)

Interfacing to Regulators

There are few events in research life that are as stressful as regulatory site visits going badly. However, if programs of veterinary care and use are well maintained and all participants know what is required, these site visits need not be troublesome. Researchers should understand what some of the more common violations are in order to prevent or eliminate them. Some common regulatory violations in veterinary care are listed in Table 2.[11] These deficiencies are based on an older publication and on the author's personal experience in inspections. Understanding these violations should provide good information on what not to do in the research laboratory.

Table 2 Common Researcher Violations
Out of date Drugs
Drugs required in the protocol but not readily available for use (e.g., analgesics)
Drugs not approved in the protocol are present (unapproved alteration)
No or inadequate procedural records

Records not readily available to all people involved in animal care
No post-operative care provided (or documented)
Humane endpoints not defined or followed, resulting in pain or distress
Personnel training for procedures not documented
Procedures done are not consistent with the approved protocol (unapproved alteration)
Animals not correctly classified for pain/distress or missing justifications for pain/distress

More critical is to anticipate what may be requested on a site visit and have that information ready, easily accessible, complete, and current. Table 3 reflects items that are commonly inspected and/or requested or records that are requested from researchers as part of a regulatory site visit. The implications from the information above are that drugs present in the laboratory should be in date and reflect those approved in the protocol. Records of activities should be present and reflect IACUC approved procedures. Post-operative care should be provided as approved and reflected in those records. Recorded data should indicate the scientific or humane endpoints were followed. Regulators will likely appreciate organized records where required information is easily found. This condition reduces their workload and fosters a much more polite interaction. Researchers should also recognize that regulators are permitted to photograph animals, housing areas, and laboratories and they are permitted to photocopy all records. Prudent investigators should be able to produce any information within 15-30 minutes of a request.

Table 3 Common Requests in Regulatory Site Visits
Inspection of animals and assessment of health status
Visits to investigator laboratories where animals are used
Review of drugs and equipment maintained in the research laboratory
Requests for approved standard operating procedures that affect veterinary care
Requests for specific approved protocols and amendments
Requests for comprehensive animal health records
Requests for investigator research records that involve provision veterinary care

Conclusions

The overall goal for this training primer is to educate researchers, administrators, and animal care personnel about what is required of them in the provision of adequate veterinary care. While the attending veterinarian must oversee this activity, researchers and technicians often provide significant components of this care. Understanding what is required in such programs advances compliance, improves the health, care, and well-being of our animal subjects, and critically, may keep animal care and use programs out of trouble. The off-shoot of excellent veterinary care is good science.

Competing Financial Interests

The author declares no competing financial interests.

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