Responsible Conduct in Research Training

Animal Research and the IACUC
Session Overview

- Overview U.S. regulatory framework for animal research
- *A Day in the Life of a BRC Veterinarian*
- Breakout discussions of scenarios
- Panel discussion / Q&A
Legal Framework for Use of Animals in Research

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Ethical Principles Embedded in Regulations

Non-maleficence and Beneficence
Non-maleficence and Beneficence

Non-maleficence
• The duty to do no harm or to minimize harm in pursuing a greater good*

Beneficence
• The duty to do and to maximize good*

Yet we understand that we do not afford all of the same considerations to animal subjects as we do human subjects.

*L. A. Demmer (2005)
Non-maleficence and Beneficence

Non-maleficence

• Cause no harm (pain, distress, discomfort) that is not necessitated by scientifically valuable research.

Beneficence

• Promote welfare of animals to the extent it will not interfere with the research goals.

“Unless the contrary is established, investigators should consider that procedures that cause pain or distress in human beings may cause pain or distress in other animals.”
Non-maleficence and Beneficence

**Non-maleficence**
- 3 Rs
  - *Replace* animals with non-animal systems
  - *Reduce* the number of animals used
  - *Refine* methodologies
- Do not withhold basic needs

**Beneficence**
- Relieve pain/distress/discomfort
  - Anesthetics, analgesics
  - Nursing care
  - Humane endpoints
- Optimize basic care
- Provide medical care
- Provide for behavioral needs
Harm-Benefit Analysis

Key information for IACUC:

“Explain why this research is significant to the general public including the importance to human or animal health, the advancement of knowledge, or the good of society.”
Regulatory Standards
Important!

Enforcement of the animal welfare laws and regulations in the United States relies heavily upon self-policing at the institutional level.
<table>
<thead>
<tr>
<th>Agency</th>
<th>Method of Oversight</th>
<th>Species Covered</th>
<th>Enforcement Authority</th>
</tr>
</thead>
<tbody>
<tr>
<td>USDA/APHIS</td>
<td>Annual &amp; special inspections, annual report of animal use</td>
<td>Warm blooded animals excluding birds, rats &amp; mice bred for research, ag species used in ag research</td>
<td>Fines, law suits, animal confiscation, notification of funding agencies</td>
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<tr>
<td>NIH/OLAW</td>
<td><strong>Assurance statement</strong>, self reports, site visits (mostly “for cause”)</td>
<td>All vertebrates</td>
<td>Withhold PHS funds</td>
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</tbody>
</table>
Required Organizational Components for Internal Oversight

- Institutional Official
- Institutional/Attending Veterinarian
- Institutional Animal Care and Use Committee (IACUC)
Institutional Official

- IO must ensure institutional obligations are met; must be able to commit on behalf of institution
- Establish and provide resources for program
Attending Veterinarian

- Must have direct or delegated program authority and responsibility for activities involving animals at the institution.
- Must ensure “adequate veterinary care”
- Oversee the adequacy of other aspects of animal care and use
- Member of the IACUC
IACUC

• At least 5 members, including:
  • At least 1 practicing scientist
  • At least 1 non-scientist
  • At least 1 public/non-affiliated representative
  • Attending Veterinarian
IACUC Responsibility & Authority

- Responsible to the IO
- Semiannual review of animal care and use program
- Semiannual inspection of animal housing and use areas
- Prepare reports
- Review and investigate animal welfare concerns
- Make recommendations to IO
- Review/approve activities involving animals
- Be authorized to suspend activities
Explicit AUA Content Requirements

- Identification of and rationale for the species and approximate number of animals used
- Complete description of the proposed use of animals
- Description of procedures to limit discomfort and injury to animals to that which is unavoidable
- Euthanasia method
Some Required Considerations for Approval

- Consideration of the use of 3 Rs
- Unnecessary duplication of experiments
- Nonstandard housing and husbandry requirements
- Impact of the proposed procedures on the animals’ well-being
- Appropriate sedation, analgesia, and anesthesia
- Appropriateness of humane endpoints
- Adequacy of training and experience of personnel
Researcher Responsibilities

- Secure and maintain IACUC approval for all animal activities conducted
- Ensure personnel are familiar with approved procedures
- Ensure personnel working with animals have appropriate qualifications and training
- Report non-compliance
- Report adverse events
Reporting Concerns

Safeguarding animal welfare is the responsibility of every individual associated with the program.

Program must have methods for reporting and investigating animal welfare concerns.

Need to include a mechanism for anonymity, compliance with applicable whistleblower policies, nondiscrimination against the concerned/reporting party, and protection from reprisals.
Main Points to Remember

- Animal discomfort, pain, and distress must be minimized to that which is unavoidable in scientifically valuable research and teaching.
- The IACUC must evaluate and oversee the program to ensure compliance and has the authority to suspend activities that are not in compliance.
- The Attending Veterinarian must provide adequate veterinary care and has authority for activities involving animals.
- Anyone may report concerns about the use of animals without fear of reprisal.
A DAY IN THE LIFE OF A BRC VETERINARIAN

BY KEN ALLEN, DVM, DACLAM
ASSISTANCE WITH PROTOCOL DEVELOPMENT/SUBMISSION

- Study involves use of chinchillas
  - PHS and USDA regulations
- Otitis media study
- Animals will receive bacterial inoculation
  - Intranasal or transbullar
  - Pain/distress
- Use of analgesics isn’t included since it is noted that nonsteroidal anti-inflammatory or opiate drugs may affect the experimental outcome
- Deviation from standard housing of this species
  - Dust baths not allowed

- What should I tell the investigator?
  - Use of analgesics is required for procedures known to, or likely to, cause pain unless approved by the IACUC
    - Scientific justification
  - Approval by the IACUC is required for a deviation from standard housing
    - Scientific justification
AUA AMENDMENT REVIEW

• ZEBRAFISH
  • Goal of the studies is to understanding the genes and signaling pathways that function during normal development and during disease processes.
  • Multiple surgical procedures added
  • No analgesics given postoperatively
  • Literature is not conclusive if fish experience pain
  • Few studies are published regarding analgesic use in fish

• How should I deal with this?
  • Unless the contrary is established, investigators should consider that procedures that cause pain or distress in human beings may cause pain or distress in other animals
HEALTH CASE

- Mouse
  - Inoculated with human tumors previously
  - A superficial tumor is >2 cm in diameter and ulcerated
  - Endpoint in the AUA
    - > 2 cm diameter or ulceration
  - The experimental endpoint is in 7 days
  - Investigator wants to keep the animal alive for 7 days to meet the experimental endpoint

- How should I respond?
  - I have to default to what is written in the AUA
  - I explain to the investigator that she must follow what is written in the AUA regarding endpoints
  - I suggest amending the AUA in the future if she wants more flexibility
    - IACUC will likely require a scientific justification
HEALTH CASE

• Rat
  • Involved in a hypertension study
  • Respiratory distress
  • Increased rate and depth with open-mouth breathing
  • Laboratory staff and investigator cannot be reached by phone

• How should I respond?
  • Follow protocol endpoints
  • Federal regulations give the veterinarian authority to intervene and administer treatment, including euthanasia, as appropriate
WHAT ARE THE PARTS OF THE AUA I REFERENCE WHEN MAKING DECISIONS ON ANIMAL WELFARE?

• Section K, 1.0. Do these animals have any inherent behavioral or physical phenotypic abnormality that may dictate the need for special care or result in clinical signs of illness?

• Section K, 2.0. Are any induced characteristics, clinical signs† or lesions expected in the animals used on this AUA as a result of a test agent or procedure?

• Section K, 5.0. Animals will be euthanized when their clinical condition meets or exceeds the following:
  • ENDPOINTS
ENDPOINTS IN THE AUA

- **General**
  - Severe emaciation/loss of body condition characterized by extremely prominent skeletal structure with little or no flesh cover and distinctly segmented vertebrae.
  - Respiratory distress characterized by major increase in respiratory effort/rate and/or open-mouth breathing.
  - Severe neurologic signs such as seizure activity lasting more than 10 minutes continuously and/or severe ataxia i.e. loss of control of body movements
  - Severe morbidity characterized by marked depression of activity, reluctance to move upon prodding, piloerection i.e. rough hair coat, and hunched physical posture.
  - Moribundity characterized by a comatose state or minimal response to tactile stimulation.
ENDPOINTS IN THE AUA

• Rodent and Rabbit Surgical Models
  - Dehiscence of a surgical incision with exposure of a body cavity or of a previously implanted device such as a telemetry unit, vascular catheter, etc. This does not include the portion of a catheter that is purposefully exteriorized for infusion, blood pressure monitoring, etc.

• Rodent Tumor Models
  - A visible tumor more than 2 cm diameter in a mouse or more than 4 cm diameter in a rat.
  - An ulcerated tumor.
  - A tumor interfering with ambulation or the animal's ability to eat or drink normally.
Breakout Discussions