Research Community Comments on New Guide are Critical

Everyone at NABR member institutions is encouraged to comment on the National Institutes of Health’s (NIH) proposed adoption and implementation of the new Guide for the Care and Use of Laboratory Animals (Guide). Whatever your role in research and animal care, whether working with laboratory animal models in industry or academia, the Guide is a primary reference document that affects overall program management and your daily operations. The way in which the recent revisions (Eighth Edition, 2011) are incorporated into the assurance process for U. S. Public Health Service-funded institutions also stands to influence how the new Guide will be utilized by AAALAC International for facility accreditation purposes in the future. Given the significance of the Guide to all laboratory animal care and use programs, NABR members should take very seriously the current opportunity for public comment. NIH has extended the comment deadline until May 24, 2011 as reported previously in the NABR Update. An online form has been provided for submitting comments. The Guide is available to download and may be viewed or purchased from the National Academies Press.

NABR’s most recent webinar on April 12, “The New Guide: How Will It Impact Your Institution,” attracted more than 500 registrants, our largest webinar attendance to date. Therefore, we know there are many questions about the Guide changes. On behalf of our membership and with its assistance, NABR has drafted comments that express general concerns about the 2011 Guide and the consequences of accepting it as currently written. At this time, NABR cannot recommend adoption of the new Guide in its entirety for several critical reasons:

- The 2011 version contains numerous provisions that will, in effect, function as legally binding regulations, rather than guidelines for the care and use of research animals.
- There is insufficient scientific evidence for several key revisions reflected in the new Guide.
- Implementing and adhering to the new Guide provisions will have a major economic impact on PHS-assured institutions.

Research Community Comments on New Guide are Critical (cont.)

Some have suggested a phase-in approach could be a potential solution to the problem. While a phase-in would likely have less immediate financial impact, the economic commitment of hundreds of millions of dollars in initial capital investment with hundreds of millions more in annual recurring costs remains the same. Since scientific evidence is lacking for some new requirements in the 2011 Guide, NABR believes strongly that the concerns listed above must be addressed before it is adopted and implemented. So that the new Guide’s full effects on the animal research community will be understood before an implementation plan is decided, NABR is recommending the NIH re-issue a request for public comment that gives an opportunity to provide meaningful comments on the substance of the Guide. Please see NABR’s draft comment letter to NIH dated May 11 for further details about our concerns based on what has been learned thus far from members. If it will benefit your institution to have additional time to carefully evaluate the 2011 Guide in relation to your research and animal care programs, at this juncture please support the NABR recommendation in your individual comments or those from your institution. Also please feel free to use any information included in NABR comments and, if applicable, add illustrations that reflect your situation or concerns. Nevertheless, remember there is no way to predict NIH’s next steps or final decision regarding an additional comment period; therefore, this may be our only opportunity to provide input. Should you have additional questions or need more information, please contact us by phone at 202/857-0540 or email info@nabr.org.

Thank you for taking advantage of this opportunity to express your views about the Guide, a reference document of great importance to the entire research community.
HUMANE ENDPOINTS FOR RESEARCH ANIMALS

Animal pain, distress, or suffering is generally not necessary for animal experiments. In fact, animals in pain, suffering or in distress can significantly complicate research data outcomes and may confuse the findings of an otherwise well designed study while wasting the time and resources of the researcher. Careful consideration of clear study endpoints, after which animals will be provided with analgesia, removed from the study, or euthanized will maximize the reliability of outcome data while assuring humane attention to creatures which can feel pain and can suffer. Employing humane endpoints in the design and performance of animal research activities is, for many reasons, the right thing to do!

According to federal regulations (USDA 9th CFR; PHS Policy; various federal laws), the Institutional Animal Care & Use Committee (IACUC) must consider whether the animals enrolled in a specific study are provided with appropriate analgesia, are assigned reasonable humane endpoints, and are protected from unnecessary pain or distress. In fulfilling its federal mandate, the IACUC will review all uses of animals which may involve procedures that cause clinical symptoms or morbidity in animals; more specifically, the IACUC must determine whether the researcher has sufficiently considered the impact of the study upon the animal being used in the study. For example, the IACUC will evaluate:

• The expected and possible adverse effects the research animals may experience in the study (e.g. pain, distress, illness, etc.);
• The most likely time course / progression of adverse effects (e.g. is tumor metastasis likely? Does infection often following this procedure?);
• The earliest or most predictive indicators of present or impending adverse effects (e.g. Is anemia likely 15 days after treatment? Does pneumonia generally occur after 20 days of this therapy?);
• The researcher proposed endpoints (e.g. what will occur of an animal reaches a specified painful condition); or
• Any argument that scientific requirements justify modification of the humane endpoints.

The effective use of study endpoints requires properly qualified individuals perform both general and study-specific observations of the research animals at appropriate time points. However, such performance requires a clear understanding of normal behavior in the animal and a reasonable expectation of the progression of disease or an increasingly infirmed condition of the animal.

Optimally, live animal studies are terminated when animals begin to exhibit clinical signs of disease; especially if this endpoint is compatible with meeting the research objectives. Termination of animal studies prior to causing the animal significant pain or distress is necessary both for minimizing unnecessary pain and distress in the research subject, and because such performance is the ethical and appropriate thing to do. Termination of the animal’s participation in the study upon observation of animal pain or distress is preferable to death.

Except in the very few cases where the IACUC has approved a ‘death as an endpoint’ study, no animal should be allowed to ‘die naturally.’ In research where there is a high likelihood of animals dying is the disease is allowed to proceed unmitigated, there will routinely be a point where the data obtained from the animal begins to decline in quality – a point research data is no longer useful. The researcher should determine what level of animal condition is likely to cause less reliable inferences, and at that point, euthanasia must be considered.

Moribund: Of all terms describing animal condition, moribundancy is one of the most difficult to accurately define. The moribund condition is defined as a clinically irreversible condition leading inevitably to death. As a general rule, proposals where moribundancy is a potential outcome for the animal subject should consider the following:

• Criteria that establish when the endpoint has been reached: There are several examples that might be considered as an outline for selection of clear end point criteria:

  • Body Condition (BC) Scoring for determining moribundancy:
    BC1: Emaciated
    Skeletal structure prominent
    Ribs prominent
    Little to no fat covering
    Vertebrae distinctly segments

  NOTE: BC 1 would be classified as moribund and would require euthanasia!
**AALAS LEARNING LIBRARY AVAILABLE TO DUKE RESEARCHERS**

The Duke animal program has an institutional license for the AALAS Learning Library, which can provide essential training for technicians, managers, and investigators working with animals in a research or education setting. The Learning Library emphasizes appropriate handling, care, and use of animals, and meets all federal and local IACUC requirements for qualified training; and its FREE to members of the Duke animal care and use community! The AALAS Learning Library organizes courses in libraries according to topic area or source of the material.

**The Animal Care and Use Library** has courses on certification, regulatory mandates, bioethics, bio-methodologies, biosafety, and management.

While use of the Learning Library is free to the Duke animal care & use community, you MUST have a USERNAME and PASSWORD. Contact Bill Wade at the Office of Animal Welfare Assurance to obtain the necessary information. You can reach me at 919.668.6724 or my email at w.wade@duke.edu.

If you have thoughts on particular topics that are needed by your laboratory members, please let me know.

Bill

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**OESO HAS SEVERAL GUIDELINES FOR SOP DEVELOPMENT OF HAZARDOUS AGENT USE IN ANIMAL PROTOCOLS**

OESO Biosafety Division has a great web site which assists researchers with specific SOP development! For example:

- Guide for Developing an SOP for the use of Biohazards in Animals
- Guide for Developing SOP for the use of Hazardous Drugs
- SOP for the use of Toxic Chemicals in Animals
- Guidelines for the Safe Handling of Animals Exposed to LPS in Research
- Radiation Safety Animal Care and Use Protocol Wizard

You can reach this site and use these links by going to the OESO Biosafety site at:

http://www.safety.duke.edu/BioSafety/Animals.htm

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**Disposing of Expired Controlled Substances:**

The DLAR pharmacy now operates under a DEA distributors license. This means that controlled substances purchased from DLAR must be disposed of by the registrant (PI) via a reverse distributor or if a small quantity by means as described below. They cannot be returned to DLAR for disposal.

For CS not purchased through DLAR, there are a few options:

A. Inject expired CS into a deceased (not alive) research animal. Dispose of the carcass in the standard manner.

B. Mix the expired CS with ‘kitty litter’ and toss the ‘wet litter’ in the trash can.

C. Toss the expired CS in an incinerator.

**For options A, B, or C, an observer must sign the log sheet documenting the disposal. Keep the log sheet for 3 years past the disposal date, after which time, shred the page.**

D. Dispose of the CS through ‘hazardous chemicals’ disposition.

**The one way you SHOULD NOT dispose of CS agent is injecting it into the lab sink drain!**

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**UPCOMING DATES & DEADLINES**

- May 19, 2011 Amendment Meeting
- May 23, 2011 Amendment Deadline
- June 2, 2011 Amendment Meeting
- June 7, 2011 New Protocol Deadline
- June 16, 2011 Amendment Deadline
- June 16, 2001 Amendment Meeting
- June 23, 2011 New Protocol Meeting
BC2: Under conditioned:
- Skeletal structure observable
- Ribs observed but soft appearing
- Minimal fat
- Vertebrae evident; pelvis palpable

BC 3: Well conditioned:
- Skeletal structure not seen
- Ribs not seen
- Smooth rounded appearance
- Vertebrae / pelvis palpable with slight pressure

BC 4: Over conditioned
- Rounded body shape
- No skeletal structure observed
- Vertebrae / pelvis palpable with firm pressure

BC 5: Obese
- Bulky body shape

General Appearance Assessment for determining moribundancy: Moribund (requiring euthanasia) could be classified as have 5 or more of the following signs:
- Loss of skin turgor (dehydrated)
- Ruffled, unkempt fur
- Dull eyes,
- Dry cracked nose or mouth
- Rapid abdominal respiration
- Zero to minimal urine over a 24 hour cycle
- No feces within 24 hours
- No locomotion or painful locomotion
- Body weight less that 60% of normal
- Measurable clinical signs, depending on severity and duration, that may independently constitute an endpoint, or might be included in the assessment criteria. These include, but are not limited to:
  - Sudden unexpected weight loss (tumor studies may see weight gain)
  - Diarrhea, especially if debilitating
  - Progressive dermatitis, especially if pruritic
  - Rough hair coat, hunched posture, lethargy or persistent recumbency.
  - Coughing, labored breathing, nasal discharge.
  - Jaundice and/or anemia
  - Neurological signs
  - Bleeding from any orifice
  - Self-induced trauma (often an indicator of pain)
  - Unprovoked behavior of biting or vocalizations
  - Strong adverse response to external stimuli
  - Any condition interfering with eating or drinking (e.g. difficulty with ambulation)
  - Excessive or prolonged hyperthermia or hypothermia.

Additional signs for neoplasia studies: These signs may constitute an endpoint include, but are not limited to:
- Mice with tumors 2000 mm³ in size (which is roughly 10% baseline body weight) or greater, or rats with tumors 5000 mm³ in size or greater.
  - Tumors may be measured using the following formula: $TV = \frac{(Width)^2 \times Length}{2}$.
  - Tumors that are ulcerated. If an exemption is provided for this condition, then the affected animals are required to be single housed (may require protocol amendment and / or alternate environmental enrichment or medical treatment).
  - Tumors where the animals chew on the lesion or pay undue attention to the ulcer.
  - Tumors that interfere with “normal” animal functions (e.g. eat, drink, or ambulate).

A plan for monitoring the animals both before and after the period where the above signs may be observed: Daily monitoring is the baseline for all animal care and use. Daily monitoring also includes assessment on weekends and holidays. During periods when signs of disease or progression of disease are likely, the frequency of assessment must be increased. The plan for monitoring must be included in the animal protocol proposal.

Identification of personnel responsible for evaluation of humane endpoints: The IACUC will want to know who will serve as the responsible individual to assure humane endpoints are maintained as approved by the IACUC. Checklists, spreadsheets, or score sheets may be helpful to ensuring the required observations are performed as approved; interpreted as required; and documented as necessary.

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Dysfunctional Germ Family

YOU MAKE ME SICK!