

Welcome to the Fall 2016 of the IACUC Connection, a quarterly newsletter designed to help researchers with questions regarding animal research at UConn Health. This issue is going to review the USDA and PHS requirements of the 3R's and the Search for Alternatives to Painful Procedures. UConn Health is required to ensure that animal use conforms to a multitude of state and federal regulations that include compliance with the Animal Welfare Act in accordance with the Animal Welfare Regulations (9 CFR, 2013), the Public Health Service Policy on Humane Care and Use of Laboratory Animals (2015), and the recommendations promulgated by the *Guide for the Care and Use of Laboratory Animals*.

The 3R's: Replacement, Reduction, and Refinement- An Overview

The concept of Replacement, Reduction, and Refinement was first introduced in 1959 by two British researchers, W. Russell and R. Burch. In their landmark book The Principles of Humane Experimental Technique, they were the first to argue that, far from being a hindrance to animal research, humane treatment and care of laboratory animals resulted in healthier animals and better research results. Their work eventually resulted in new animal research legislation in Great Britain in the 1970's and, by 1985, in the United States. Both Public Health Service (PHS) Policy and the USDA (via the Animal Welfare Act) require that the 3R's be addressed in every research protocol involving animal use.

Replacement- The act of replacing the animals in a research project with non-animal techniques or lower organisms. This can include species that are phylogenetically lower than the proposed animal, bacteria or fungi, cell culture, or computer simulations. Replacement can also be absolute or relative; that is, completely replacing your animals with an alternative or replacing part of your animals. What is ultimately chosen as a replacement methodology depends upon the goals of the research project; there are no "standard replacements" available to researchers. One way to determine if there are replacement options for your research is to perform a good literature search **prior** to writing your research protocol.

Reduction- The act of minimizing the number of animals involved in a research project. Though the concept may be theoretically simple, it is sometimes hard to actually apply. Having a sound experimental design is vital in determining the appropriate number of research animals any protocol needs. It is also wise to perform a power analysis to ensure that your results will be statistically valid.

Refinement- Typically understood to mean ensuring that the procedures being performed on the laboratory animals are designed to induce the least amount of pain and/or distress to those animals. Therefore, most researchers consider the appropriate uses of anesthetics and/or analgesics to be the total picture of replacement, but this is not accurate. Careful, and possibly updated, design of your experiment that takes into account all the possible causes of pain and/or distress is a refinement technique. Using enrichment strategies that are appropriate for the species you are using is a refinement of the protocol. There are others as well. **Please note** that if you are using a USDA-regulated species, the law requires you to consult with a veterinarian during the **planning** stages of your experimental design if you are going to perform procedures that have the potential to cause pain and/or distress to the animal.

Search for Alternatives to Painful and/or Distressful Procedures

Despite an effort to educate investigators, there are very few aspects of the animal care and use protocol that are as misunderstood as the “Search for Alternatives” requirement. Researchers should be aware that this search for alternatives is a USDA, PHS, **and** institutional requirement and is not a **search for alternatives to painful and/or distressful procedures that are contained in the protocol**. It is not a search for an alternative to animal use or a search for duplication of research (though those may comprise part of the Search for Alternatives strategy). One protocol quite possibly can require more than one search as **each** potentially painful and/or distressful procedure performed on the laboratory animal **must** be addressed. Review of the Search for Alternatives information on the IACUC website (<http://research.uchc.edu/animal/iacuc/alternatives/>) is recommended for all researchers.

How to get started with the search- When planning your experimental design, perform a literature search to “see what’s out there.” This will help you satisfy the 3R requirements as well as possibly exposing you to new techniques that are being performed by other researchers in the field. The next step is to list all of the potentially painful and/or distressful procedures the experimental design employs (“D” and “E”). This may include surgical procedures, other non-surgical invasive procedures, and other obvious painful techniques. But the requirement also includes distressful procedures that can include food/fluid restriction, prolonged restraint, and multiple injections and/or blood collections from the animals. Remember, if the procedure has the potential to cause more than momentary pain or distress to humans, it has the potential to cause more than momentary pain or distress to the research animals. This also includes terminal procedures performed under general anesthesia.

Once you have a list of your painful procedures, then you are ready to perform the Search for Alternatives. This does **not** have to be a literature search (though the USDA maintains that a literature search remains the best way to fulfill the Search for Alternatives requirement).

Literature search- If you decide to perform a literature search to meet the Search for Alternatives requirement, you must first decide on your **search strategy**. Improper strategies are the most common reason this search requirement is not met. You must pick your key words carefully and link them appropriately. For more detailed information on how to do this, ask the IACUC Office for a copy of “Meeting the Search for Alternatives Requirement.” The search information that must be detailed in your protocol includes: search strategy used, the date you performed the search, the years searched, and the databases searched (must have at least two). Recommended databases include BIOSIS and AGRICOLA, as well as the standard MEDLINE. If the search yields a *bona fide* alternative, and you decide not to use it, you must state the reason(s). Similarly, if there are no alternatives to your potentially painful and/or distressful procedures, you need to state that in your protocol as well.

Workshops/Meetings- There are occasions where a literature search is not the most appropriate way to determine if there are alternatives (e.g., highly innovative research). One way to satisfy the Search for Alternatives requirement is to reference information presented at scientific workshops or meetings. If you choose to do this, you must detail in your protocol the following information: meeting or workshop attended, who presented the information and his/her credentials, and the date the meeting or workshop was held.

Experts- Another way to meet the requirement is discussion with experts in the field. If information is provided from a reference book, for example, you must detail the name of the book, the author and his/her credentials, and publication date. If you converse with the expert, you must provide the name, his/her credentials, and the date of your conversation.

Frequently Asked Questions

My protocol is a surgical procedure that has no alternatives. What should I do in this case?

In this case, the best thing to do is to ensure that anesthetics/analgesics are most appropriate via a literature search or, possibly, a reference book. Discussion with the veterinarian is also a good idea and **mandatory if you are using a regulated species**. You must ensure that post-operative care for pain management is accomplished and adequate. You need to state that there are no alternatives. For example, if you are performing a craniotomy in order to implant electrodes, you need to state that there is no other way to implant electrodes into the brain without performing a craniotomy. Your supplemental

information would need to indicate that there is ***no other way to get the data you need other than by implanting the electrodes.***

Where does this information go in the protocol?

All of this information goes in Section 4 – Animal Use – of the IACUC protocol in Topaz.

Is this a new regulatory requirement?

This may seem to be a new regulatory requirement, but it has been the law since December, 1985 when the Farm Bill was passed for USDA regulated species. Our PHS assurance statement makes it a requirement at this institution, for all species. In the past, the requirement was presented as a Search for Alternatives to animal use or duplication of research efforts. Though these two topics must be addressed in research protocols, this doesn't represent the full search requirements as written in the Animal Welfare Act.

How will my search be evaluated?

The IACUC will review the search to see if it is appropriate and that all potentially painful and/or distressful procedures being performed are addressed. In literature searches, some things will raise a red flag, such as: only one database searched, terms included would provide information on duplication of research or non-animal use only, the term "alternative" used alone, keywords not relevant to the protocol's painful procedures, keywords and concepts linked incorrectly, and inadequate time period searched (e.g., <5 years). In the other methods, the IACUC will evaluate the credentials of the authors and/or experts, the applicability of the workshop/meeting information on the submitted protocol, and the references provided from a standard reference book.

Upcoming Training, October 2016 – December 2016

New Animal Users Initial Basic Core Training

Monday, October 17	9:00 am – 12:30 pm	Low Learning Center
Monday, November 14	9:00 am – 12:30 pm	Low Learning Center
Monday, December 19	9:00 am – 12:30 pm	Low Learning Center

PLEASE NOTE: Individuals who wish to attend training must complete a registration form and submit it to the IACUC office. Forms and instructions are located at <http://iacuc.uchc.edu/training/initialtraining.html>.

PLEASE NOTE: All individuals working at UCH starting 9/1/13 or later must complete animal training documentation. The document can be found on the web at http://iacuc.uchc.edu/documents/protocols/training_records_form.docx. We will be copying this information, or asking that they be sent to the IACUC office, when we perform semi-annual inspections in June and December.

New Institutional, State, or Federal Regulations

Institutional

None

State

None

Federal

None

Important Reminders to Principal Investigators

⦿ When an individual leaves your laboratory, and is no longer an active animal user, you **must** contact the Animal Care Committee Office (ooacc@uchc.edu) with this information.

⦿ Remember, your animal care and use protocol cannot be used once it is expired; this is a violation of PHS Policy and the Animal Welfare Act.

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Next Issue: Facility Security

Have ideas for future IACUC Newsletter topics? Email pohl@uchc.edu