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Course Introduction
Welcome to the "Animal Care and Use" web-based course for VA Research staff. This course is designed primarily for staff who do not work directly with animals but who should have some understanding of the animal care and use program.

This course was funded by the VA Office of Research and Development as part of the "Working with Laboratory Animals" instructional series, and was produced by the VA Employee Education System. It is a shortened version of the course "Working with the IACUC".

Course Goals
Although the principles discussed apply to all animal research, this course includes information that will help you understand how to work with animals specifically in the VA system, and to fill out the standard VA animal form. The course goals are to:

1. Familiarize research staff with the regulations, policies and procedures in place to ensure that animals used in research are treated humanely; and
2. Provide information on important issues that must be addressed when proposing to use animals in a research protocol.
Research in the VA

Let's start with some basic information about VA research. The VA is charged by Congress with conducting research into the diagnosis, cause, treatment and prevention of diseases and conditions that are prevalent within the veteran population. If diseases or conditions involve processes that can only be studied in a living organism, animals become necessary when it is impractical or unethical to use humans. The privilege of using animals for biomedical research is only granted to individuals in the VA committed to the highest level of care for research animals, and the highest level of ethical standards in conducting biomedical research destined to relieve suffering in our veteran population.

The VA Office of Research and Development (called "Headquarters") in Washington, DC manages a research budget of over $300 million yearly, which supports medical, rehabilitative, health services, and cooperative human clinical studies. Research funds are provided to individual VA healthcare facilities called "stations" on a competitive basis.

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VA Institution Animal Care and Use Committees (IACUCs)

By law, an institutional committee must review all aspects of the animal care and use program. This committee is referred to as the Institutional Animal Care and Use Committee, or IACUC.

Because a VA IACUC is technically a subcommittee of the Research and Development Committee, it is also called the "Animal Studies Subcommittee". Regardless of what it is called, it functions just like any other IACUC does outside the VA.

IACUC Basic Functions

The IACUC is responsible for making sure that all federal laws, regulations and policies are followed when investigators perform animal research. The IACUC has many jobs. Some of them include:

- **Reviewing** and approving animal use protocols submitted by investigators.
- **Monitoring** the animal care and use program by conducting thorough reviews of the program and inspections of the animal facilities. The program review and inspection of animal use areas occur twice a year.

Role of the IACUC

VA and other federal regulators regard the IACUC as a critical partner in ensuring compliance with animal welfare laws and guidelines. In effect, the IACUC functions as the self-regulating body for animal research on behalf of the institution. Because the IACUC is such a critically important component of the animal care and use program, evaluating the effectiveness of the IACUC often serves as a barometer of the quality of the entire animal care and use program.
The Privilege of Conducting Animal Research

An effective IACUC protects both the individual investigator and the institution, while inspiring confidence in the general public that animal research is being performed in an ethical manner. Research utilizing animals is a privilege, not a right, and the IACUC must do its part to make sure that animal research is performed according to the highest standards. By assuring that animal research complies with animal welfare laws and guidelines, the IACUC ensures that animals are not subjected to unnecessary pain and distress, and protects both the investigator and the institution.

The entire system is built on trust. However, a single incident of serious noncompliance with animal welfare regulation or guidelines can jeopardize the entire institution's privilege of conducting animal research.

The Animal Component of Research Protocol (ACORP)

To help ensure consistent and quality IACUC reviews across the VA system, a standard animal protocol form is used for projects that will be submitted to VA Headquarters for funding consideration. This standard animal protocol form is known by the acronym "ACORP", which stands for "Animal Component of Research Protocol." At this medical center, the ACORP form is used for all protocols submitted to the IACUC, irrespective of funding source.

The latest version of the ACORP is always available in MS Word format on the "Animal Studies" web page of our Research Service website.

IACUC Approval

Like the extramural NIH granting system, the VA intramural research program now uses a "just in time" (JIT) system of managing applications with animal research. ACORPs are no longer submitted as part of the scientific application.

If VA funding is involved, investigators whose scientific applications have a good chance of being funded are notified that their approved ACORP must be submitted to VA Central Office. Funds will not be released for applications actually chosen for funding until after the submitted ACORP is reviewed and found to be satisfactory. Note that the ACORP must be approved by the local IACUC and R&D Committee before being submitted to VA Central Office. (Other funding agencies generally require a letter verifying IACUC approval.) In either case, investigators must remember that 4 to 6 weeks are required for the approval process once the ACORP has been submitted.

The Research and Development (R&D) Committee

Usually, each station with a research program has a very important committee called the Research and Development Committee, or "R&D Committee" for short. The R&D Committee is composed of scientists and administrators. It has many functions, but it must approve all research projects before they begin. It also acts as the parent oversight committee for committees such as the IACUC and the Research Safety Subcommittee.
The R&D Committee is charged with evaluating the scientific quality and budget of all research proposals submitted at a station. As a practical matter, it is important to understand that receiving IACUC approval for an animal research project is not enough; the overall project must also be submitted to the R&D Committee and receive R&D Committee approval before any work can begin.

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VA Animal Research

In this course, you won't be faced with large amounts of regulatory language, but you must be aware of the basic laws and guidelines that govern animal research in the United States.

VA stations that conduct animal research must comply with all federal laws and guidelines that apply to animal research. VA policies that apply to animal research are described in VHA Handbook 1200.7, "Use of Animals in Research." Released in 2005, it incorporates, by reference, the regulations and guidelines provided by two other federal agencies that have primary responsibility for regulating animal research in the U.S.

The United States Department of Agriculture (USDA)

The first important non-VA agency regulating animal research is the United States Department of Agriculture (USDA). Congress gave the USDA broad authority to regulate animal research when it passed the Animal Welfare Act. The USDA then established the regulations to enforce the Animal Welfare Act. These very detailed enforcement documents are known as the "USDA Animal Welfare Act Regulations", and take precedence over regulatory documents produced by all other agencies.

In addition, the USDA has an Animal Welfare website that clarifies how some of the USDA Animal Welfare Act regulations should be interpreted.
**Scope of USDA Animal Welfare Act Regulations**

As we discussed, the USDA Animal Welfare Act Regulations apply to VA stations using animals for research, teaching, or testing. To what animals do the USDA Animal Welfare Act Regulations apply? Here is the definition of an animal given in the regulations:

"Animal means any live or dead dog, cat, nonhuman primate, guinea pig, hamster, rabbit, or any other warm blooded animal, which is being used, or is intended for use for research, teaching, testing, experimentation, or exhibition purposes, or as a pet. This term excludes: Birds, rats of the genus Rattus and mice of the genus Mus bred for use in research, and horses not used for research purposes and other farm animals, such as, but not limited to livestock or poultry used or intended for use for improving animal nutrition, breeding, management, or production efficiency, or for improving the quality of food or fiber. With respect to a dog, the term means all dogs, including those used for hunting, security, or breeding purposes."

**The Public Health Service (PHS)**

The second important non-VA agency involved in regulating animal use is the Department of Health and Human Services, which is the home of the Public Health Service (PHS). Passed by Congress in 1985, the Health Research Extension Act directed PHS to provide guidelines for animal research. The Office of Laboratory Animal Welfare (OLAW; formerly known as "OPRR", or Office for Protection from Research Risks) is responsible for monitoring institutional compliance with PHS policy and guidelines. OLAW relies primarily on two documents for judging compliance, both of which are very important to animal research.

**The Office of Laboratory Animal Welfare (OLAW) Compliance Documents**

The first, fairly brief one, is the PHS Policy on Humane Care and Use of Laboratory Animals. It incorporates nine U.S. Government Principles For The Utilization And Care Of Vertebrate Animals Used In Testing, Research, and Training that must be considered when institutions receive support from U.S. Government agencies.

The second, lengthier document is the Guide for the Care and Use of Laboratory Animals (usually called the Guide). These two documents together provide important information sometimes collectively called "PHS Policy." Compliance with PHS Policy is a required condition for receiving PHS support for activities involving vertebrate animals.
PHS Agencies

Institutions that accept any PHS agency research funding must agree to follow PHS Policy for animal research. PHS agencies include the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the Food and Drug Administration (FDA). Normally, if an institution does not accept any such funding, it is not subject to PHS guidelines, but VA Policy is that all stations must comply with PHS Policy, even if they do not accept PHS funds.

Application of PHS Policy

PHS Policy covers all vertebrate species used for research, teaching, and testing. This is in contrast to the USDA AWA Regulations and Standards, which are not currently applied to laboratory mice and rats.

The VA uses the PHS definition of an animal for all VA animal research.

The Association for Assessment and Accreditation of Laboratory Animal Care, International (AAALAC)

There is another organization that has played a critical role in ensuring high quality animal care and use in the U.S., but it has no regulatory authority whatsoever. The Association for Assessment and Accreditation of Laboratory Animal Care, International, or "AAALAC", is a non-profit organization that accredits animal facilities. Institutions participate in the AAALAC accreditation program by voluntarily submitting to AAALAC site visits every three years. AAALAC uses the USDA AWA regulations and regulations as well as PHS guidelines, plus other reference documents for evaluations. If an institution meets all applicable standards, then it is awarded AAALAC accreditation, a valuable symbol of institutional commitment to quality care and use of animals.

For most institutions, participation in the AAALAC accreditation program is strictly voluntary. This is not true in the VA system, however. In the VA system participation in the AAALAC accreditation program is mandatory. The cost of the accreditation program for all VA stations is paid by VA Central Office.

IACUC Approval

Whether animals are being used for research or testing, or for teaching, IACUC (as well as R&D Committee) approval must be obtained before any use of animals begins. IACUCs grant approval for animal use based primarily upon written information provided by investigators in standard forms. As covered earlier, the standard VA animal protocol forms are called the "ACORP" in the VA.
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The Veterinary Consult
Consulting with the veterinarian is an important part of filling out the animal forms. The USDA Animal Welfare Act Regulations stipulate that if procedures on animals are proposed that may cause more than momentary or slight pain or distress to animals, consultation with the attending veterinarian or his or her designee must occur in the planning of those procedures.

In the VA system, a consult with a laboratory animal veterinarian is mandatory prior to IACUC review of the ACORP, whether or not proposed procedures will cause more than momentary pain or distress. The consultation can be in the form of an actual meeting or a phone consultation between the principal investigator and the veterinarian, or it can be in the form of a review of the ACORP by the veterinarian before the IACUC meeting so that a revised ACORP can be submitted to the IACUC.

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The Three "R's"
Now is a good time to address the very important concept of alternatives. We've already touched upon it during the discussion of the importance of using the least sentient animal species possible, and during our discussion of justifying animal numbers requested.

Russell and Burch say "Know Your 3 R's!"
- Replacement
- Reduction
- Refinement

The First "R"
The first "R" is replacement. Replacement is simply replacing the use of animals with non-animal techniques. Examples of non-animal techniques that can sometimes replace animals include:

- Computer models.
- Cell culture or tissue culture systems.
- In vitro assays.

The purpose of these concepts is to minimize animal use and pain or distress while still achieving the critical scientific objectives that lead to advances in health and medicine.
Unfortunately, it is not very common for any of the above alternate systems to adequately replace animals in experiments. However, it does happen, and consideration should always be given to non-animal systems.

Practical examples of "replacement" include the use of cell culture techniques to replace animals as incubators for cell lines, the use of immunologic bench assays to replace bioassays involving animals, and the use of computer software to model the pharmacokinetics of drugs in place of animal studies. One might consider the use of less sentient animal species (rats instead of dogs, if possible) to be another example of replacement.

**The Second "R"**

The second "R" is **reduction**. Reduction is simply reducing the number of animals used. Examples of reduction include:

- Limiting group sizes to the minimum needed to obtain statistically significant data.
- Performing multiple experiments simultaneously so that the same control group can be used for all the experiments.
- Sharing tissues with other investigators so that additional animals are not needed.
- Designing experiments so that animals serve as their own controls.
- Using newer instrumentation that improves precision and reduces the number of animals needed per data point.

Reduction is usually more feasible than replacement. However, when considering how to reduce animal use, you must find a balance between causing more pain or distress on fewer animals and causing less pain or distress in more animals. For instance, if an investigator proposes to double the number of invasive surgical procedures on animals so that fewer animals are used, the increased pain and distress experienced by the remaining animals may not be justified by a simple reduction in animal use. This is a difficult area, and the veterinarian and IACUC should be consulted as needed.

**The Third "R"**

The last "R" is **refinement**. As opposed to reducing the number of animals used, refinement refers to changing experiments or procedures to reduce pain or distress in those animals that must be used. Refinements in anesthesia, surgery, analgesia, and many procedures occur frequently.

Examples of refinements include:

- New anesthetics that allow rapid induction and reduced recovery times.
• New analgesics that provide more extended pain relief postoperatively with less frequent administrations.

• New bleeding and injection techniques that cause less tissue damage or distress.

• Improved surgical techniques that minimize trauma and the length of anesthesia.

Investigators should check with the veterinarian and the literature to see if better techniques have evolved that reduce pain or distress on the animals.

**IACUC Legal Requirements**

Now that we have gone through the "3 R's", we have to discuss the legal mandate for considering alternatives. The USDA Animal Welfare Act Regulations require the IACUC to do two things regarding alternatives:

The **first** is to ensure that the principal investigator has considered alternatives if painful or distressing procedures are proposed.

The **second** is to evaluate a written narrative provided by the principal investigator that describes which source or sources were used to determine that alternatives were not available.

**Written Alternatives Narrative**

The bottom line is that the IACUC must evaluate a written account of how investigators determine that alternatives to painful or stressful procedures are not available. A USDA policy states that the following must be part of the written alternatives narrative:

1. The databases searched (Index Medicus, Medline, Current Contents, etc) or other sources used, such as colleagues at scientific meetings, journal articles read, and presentations attended.
2. The date that any database searches were performed.
3. The years of citations covered by database searches.
4. The key words and/or search strategy used when searching a database.
5. A search for reduction and refinement, not just replacement of animals.

There are several websites that contain helpful database search engines for alternatives to the use of animals and several organizations that have active research programs into alternatives to animal use.

**Unnecessary Duplication**

There is another regulatory mandate we have to cover that is similar to the alternatives mandate. The USDA Animal Welfare Act Regulations state that IACUCs must evaluate a written assurance that the proposed animal studies do not **unnecessarily** duplicate previous studies. Note that the critical concept is that **unnecessary** duplication is not allowed. Acceptance of new ideas in science is often dependent upon the ability of other scientists to duplicate published reports. The IACUC can allow duplication of previous work if you can convince them that it is important scientifically to do so.
Websites like "Altweb", provide the ability to do simultaneous searches of multiple medical and research databases in search of alternative approaches to animal research.

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**Occupational Health and Safety**

Because there are allergy, disease, and physical risks associated with animal contact, each VA station must have an occupational health and safety program for personnel who come in contact with animals. Although receiving certain immunizations or medical treatment in the program may be voluntary, PHS Policy requires an institution to offer an occupational health and safety program to employees who "work in animal facilities or have frequent contact with animals."

Offered services usually depend on the type and amount of exposure to animals, and individual risk of contracting zoonotic diseases or developing allergies. Services include rabies immunizations, TB testing, and tetanus immunizations.

**Occupational Health and Safety Plan Enrollment**

The Occupational Health and Safety Plan is administered through the Employee Health Clinic. Each employee who will be involved in using animals or working inside the Veterinary Medical Unit will be required to complete an *Animal Contact Health Questionnaire*. Based on the information provided, the Employee Health Clinic physician will determine services that need to be provided. Although personnel may decline to accept services, they must enroll in the local Occupational Health and Safety Program before they begin work with animals. Some services such as tuberculin testing are required by the institution.

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**Reporting Misuse, Mistreatment, or Non-Compliance**

If you observe misuse or mistreatment of animals, or you see procedures that you don’t think comply with federal regulations or guidelines, report it immediately to the IACUC.

Once an allegation of mistreatment, misuse, or noncompliance is received, the USDA Animal Welfare Regulations and Standards and PHS Policy require the IACUC to review and if warranted, investigate the allegations, whether made by the public or an employee of the institution.
The IACUC recommendations are forwarded to the Medical Center Director, who reviews the report and decides if additional action is needed.

If the IACUC decides that any animal activities need to be stopped to protect either animals or people, they are given clear regulatory authority to do so. In fact, if an IACUC votes to suspend a protocol or animal activity, that decision cannot be overturned by any administrator at the institution.

Any protocol suspension must be reported by the station to the Office of Laboratory Welfare, and to the Chief Veterinary Medical Officer at VA Headquarters.

Other Considerations
Some other considerations:

1. If you see that animals are in danger or in pain, take immediate steps to remove animals from the threat, and notify the animal care staff or veterinarian immediately.

2. If you are not satisfied with the final actions taken by the local IACUC and administration, and remain concerned that animals are being misused, mistreated, or are otherwise not being used properly, contact the Chief Veterinary Medical Officer in VA Headquarters.

The Animal Welfare Act prohibits retaliation against individuals who report improper animal use and more general federal no-FEAR regulations protect personnel against retribution for reporting misconduct.

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Animal Research is Important!

Our veterans and our society need animal research and the accompanying medical advances that have reduced suffering and increased the quality of our lives. By understanding more about animal research, you help your IACUC and the VA assure our veterans and the American public that VA animal research is conducted according to the highest standards.

Iron lungs are a relic due to animal research that resulted in polio vaccines. Our veterans continue to look to researchers for the next medical advances that will cure their diseases, reduce their suffering, and give them good quality lives. Animal research will be necessary for many of these advances. Work with your IACUC to make sure you do your part to inspire confidence in our commitment to high quality VA animal research programs.