

## Animal User Training Handbook

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## I. ANIMAL CARE AND USE PROGRAM OVERVIEW

### 1. Overview

Proper care, use, and humane treatment of animals used in research, testing, and education require scientific and professional judgment based on knowledge of the needs of the animals and the special requirements of the research, testing, and educational programs.

The University of Connecticut Health Center is required to ensure that animal use conforms to a multitude of state and federal regulations which include compliance with the Animal Welfare Act (AWA) in accordance with the Animal Welfare Regulations (9 CFR, 1985, 2013), the Public Health Service (PHS) 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* (2011).

Responsibility for directing the program lies with the Director of the Comparative Medicine (CCM). The institution is responsible for maintaining records of the activities of the Institutional Animal Care and Use Committee (IACUC) and for conducting an occupational health and safety program as well as a training program. Overall responsibility for the animal care program and the IACUC lies with the institutional official (IO).

### 2. Brief History of Animal Use and Literature Review

The use of animals in the life sciences dates back to ancient Greece and the earliest medical experiments. To learn about swallowing, ancient physicians would cut open the throat of a living pig. To study the beating heart, they cut into its chest.

For centuries, physicians, and researchers used animals to enhance their knowledge about how the various organs and systems of the body functioned, as well as to hone their surgical skills. As this knowledge grew, new scientific disciplines were born. First, physiology and pharmacology and, much later bacteriology and immunology, evolved as animal experimentation became more widespread.

As long as animals have been used in experiments, people have expressed concerns about such research. Questions about the morality, necessity, and scientific validity of animal experiments have been in the public consciousness since those ancient physicians first began to study bodily functions.

The rise of modern biomedical science in the nineteenth century saw an increase in both the numbers of animals used in experiments and in the number of complaints about vivisection. Although opinion varied among scientists and the public about the degree of suffering experienced by animals, most scientists were united in the belief that animal experiments were necessary to expand their knowledge.

If you look in the literature, you see that, from the mid-1800s on, there is a steady increase in animal use in medical education. Harvard University and Johns Hopkins School of Medicine were early advocates of animal use. The use of rats and mice as research animals dramatically increased in the early 1900s with the Wistar Institute in Philadelphia and Jackson Labs being leaders in the use of these rodents.

The UK was the first country to establish any laws regarding animal welfare with the British Cruelty to Animals Act of 1876. However, the United States had some of the first organizations formed with the primary function of opposition to animal use in research and testing. These organizations included the Pennsylvania Society for the Prevention of Cruelty to Animals (1867), American Antivivisection Society (1883), and the California Antivivisection Society (1908).

The stage was set for the use of animals in research and testing in 1949 with the Nuremberg Military Tribunal's decision in the case of the United States v Karl Brandt *et al*. This decision includes what is now called the Nuremberg Code, a ten point statement delimiting permissible medical experimentation on human subjects. Point 3 of this Code states that a human experiment should be designed and based on the results of animal experimentation and knowledge of the natural history of the disease or other problem under study. Also, the anticipated results must justify the performance of the experiment.

The animal protection movement has broadened its scope and support base considerably during the post-World War II period. There was a large economic boom in the US and a resultant large increase in scientific research. There was also a huge increase in the NIH budget which helped to increase scientific research. Animal rights activists were not the only individuals to be involved in discussions of the use of animals in research — the scientists were now getting involved in what they perceived as their right to, and the necessity of, animal research. In 1950, the Animal Care Panel was founded by Drs. Nathan Brewer, Elihu Bond, Robert Flynn, Bennett Cohen, and Albert Schroeder who were all veterinarians and truly pioneers in laboratory animal medicine. Their mission was to ensure the humane treatment of animals used in research and testing. In 1951, they published their *Proceedings of the Animal Care Panel* — a document which was utilized by the US legislature as it wrote both the Animal Welfare Act and PHS Policy approximately 15 years later. In 1957, British researchers W. Russell and R. Burch published their book *The Principles of Humane Experimental Technique*. It was in this publication that the authors advocated the “three Rs” of Replacement, Reduction, and Refinement. These concepts are now considered standard concepts in reviewing applications of animal research having been incorporated into US law in 1985.

In 1952, the Institute of Laboratory Animal Resources (ILAR) was founded. The Animal Facilities Certification Committee (Board) was formed which, in 1965, would change its name to the American Association for the Accreditation of Laboratory Animal Care (AAALAC). AAALAC is now known as the Association for the Assessment and Accreditation for Laboratory Animal Care – International. In 1962, an NIH grant was used to generate a publication to promote standards in laboratory animal care with *Guide for Laboratory Animal Facilities and Care*, the first edition of what is now the 8<sup>th</sup> edition (2011) of the *Guide for the Care and Use of Laboratory Animals* (the *Guide*). In 1967, the Animal Care Panel formed in 1950 had changed its name to the American Association for Laboratory Animal Science (AALAS).

Not to be outdone by the scientists, the US government started to regulate animal research. The Laboratory Animal Welfare Act was first passed in 1966 which changed to the Animal Welfare Act (AWA) in 1970. 1971 saw the development of the NIH Policy which required institutions using NIH funds to have an NIH assurance and suggested accreditation through AAALAC, required annual inspections, and demanded compliance with the AWA and the *Guide*. The Public Health Service (PHS) Policy was first passed in 1973 included animals for research, testing, education, and demonstration. 1985 saw the passing of the PHS Act (Health Research Extension Act of 1985) which further regulated laboratory animal care.

The public was not to be outdone, either. The 1962 publication of *Silent Spring* by Rachel Carson brought animal welfare to society as a whole, not just the activists, scientists, or government agencies. 1966 saw an article in LIFE magazine entitled “Concentration Camps for Dogs” which fired up animal activists and the general public. Greenpeace was founded in 1969. With the publication of Peter Singer’s 1975 treatise, *Animal Liberation*, animal welfare issues continued to be a hot topic. When society became aware of what became known as “The Silver Spring Monkeys” case and the University of Pennsylvania Head Injury Studies (both of which used non-human primates and had some deplorable animal care problems), the debate regarding animal use sky-rocketed and continues to this day. Some of the “animal welfare” organizations have challenged, and continue to challenge, whether human beings have the right to “use”

animals for any purpose. Others question the morality, necessity, and validity of animal tests, just as their counterparts did centuries ago.

It has been due, in large part, to the tension between researchers who view laboratory animals as essential to their work and individuals who oppose animal tests that the modern alternatives movement has evolved. In the 1980's and 1990's, humane animal care philosophy has enabled researchers and animal welfare advocates to come together with a common goal: to find scientifically valid alternatives to animal tests.

In March, 1997 NASA promulgated the document "NASA Principles for the Ethical Care and Use of Animals". It was intended to guide careful and considered discussion of the ethical challenges that arise in the course of animal research under NASA's auspices, but is helpful to animal use in general. Briefly stated, the document states that a strong allegiance to the principles of bioethics is vital to responsible research practices and that vertebrate animals warrant moral concern. The use of animals in research involves responsibility — not only for the stewardship of the animals, but to the scientific community and society as well. The three basic principles of the document include:

1. Respect for life— this principle requires that animals used in research should be of an appropriate species and health status and should involve the minimum number required to obtain valid scientific results. It also recognizes that the use of different species may raise different ethical concerns.
2. Societal Benefit— This principle entails that where animals are used, the assessment of the overall ethical value of such use should include consideration of the full range of potential societal good, the populations affected, and the burdens that are expected to be borne by the subjects of the research.
3. Non-maleficence— this principle entails that the minimization of distress, pain, and suffering is a moral imperative. Unless the contrary is established, investigators should consider that procedures that cause pain or distress in humans may cause pain or distress in other sentient animals.

Humane care and use of laboratory animals is a topic which is world-wide. The 2013 Canadian Council on Animal Care polled Canadian citizens about the use of animals in research. 54% of those polled stated that the welfare of the animal is important in determining what is an acceptable or unacceptable use of animals. 30% stated that the benefits of using animals to advance science or human and animal health outweighs animal welfare issues.

Similar polls have been performed in the US and UK with similar results. It is reasonable to assume that the issue of humane animal care will continue to be in the public consciousness for the foreseeable future. It would be reasonable to conclude that humane laboratory animal care and use is assured only by a close working relationship between society, governmental agencies, scientists who use laboratory animals, and the institutions (through their IACUCs) which perform animal experimentation.

### **3. Protocol Review**

Adequate review of your protocol depends on the Institutional Animal Care and Use Committee (IACUC) receiving a thorough, well-written document that conforms to USDA and PHS policies as well as recommendations set forth by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC) and the *Guide*.

There are many federal agencies which govern protocol requirements: the PHS Policy (Health Research Extension Act of 1985 with revisions in 1986, 2002, and 2015); NRC Guide on OHS (1977), Animal Welfare

Act (9 CFR) and USDA animal care policies (19997-2015). In addition, AAALAC requires institutions to follow all recommendations in the *Guide* to maintain accreditation with that organization.

Animal research in the United States is considered by many experts to be more highly regulated than human research.

The UCH uses Topaz for its animal use protocols. The form used in this system has been devised to conform to key information required by AAALAC, PHS, and the USDA and last updated in January 2013. The mandated information includes: selection and justification of species; living conditions of the animals; justification for the use of animals; applications of the principles of replacement, reduction, and refinement; ethical cost-benefit relationship; treatment of pain and discomfort; post-procedure monitoring; restraint; euthanasia; qualification of research personnel; and occupational health and safety.

There are differing requirements of how long a protocol is “valid”; PHS policy and USDA policy are similar yet different in this regard. PHS Policy requires the IACUC to perform a **complete re-review** of the project **at least** once every three years. USDA requires the IACUC to conduct continuing review **no less** often than annually. In order to satisfy both requirements, the IACUC uses the following criteria for review: A protocol is valid for approximately 3 years providing that a yearly review form is submitted after years one and two. If a protocol will be continuing after 3 years, a new protocol must be written and submitted.

#### Protocol Review Methods

There are only two protocol review methods (for initial review, modifications, and continuing review) which fulfill PHS and USDA requirements: Designated Member Review (DMR) and Full Committee Review (FCR). We use both protocol review methods at UConn Health. In FCR, a primary, veterinary, safety, and regulatory reviewer is assigned for each protocol by the IACUC Administrator. At a convened meeting of a quorum of the IACUC, each protocol is presented by the primary reviewer and then the protocol is discussed by all IACUC members to approve, modify, or disapprove the protocol by a simple majority vote. In DMR, a primary, veterinary, safety, and regulatory reviewer is assigned to each protocol to represent the full committee. Every member of the IACUC is notified of the review for an opportunity for review and call for a FCR if any member wants it. If no one calls for an FCR, then it is up to the dedicated reviewers to review the document, request changes, and approve the protocol. DMR cannot disapprove protocols- only a full committee review may do that.

#### Approval Criteria for a protocol review

##### Selection and Justification of Species

- The animal model selected should be the most appropriate species for the project based upon anatomical, physiological, or other characteristics in consideration of the scientific objectives and the need to obtain valid results.

##### Living Conditions of Animals

- The living conditions of animals must be appropriate for their species and contribute to their health and comfort. Any deviation from standards set forth by the *Guide* and the USDA regulations must be scientifically justified and approved by the IACUC.

##### Justification for the Use of Animals

- Procedures involving animals should be designed and performed with due consideration given to their relevance to human or animal health, the advancement of knowledge, or the good of society.

- Protocols involving animals should have a sound research design and the animals selected should yield valid results.
- Projects involving animals must not unnecessarily duplicate previous experiments. While duplication is often a scientific necessity, it should be justified.

#### Application of the Principles of Replacement, Reduction, and Refinement

- Replacement: When an objective(s) can be achieved using reasonably available non-animal models or *in vitro* models, the alternative should be used, thus avoiding the need for live animals.
- Reduction: The number of animals to be used should be minimized to the greatest extent possible consistent with sound scientific and statistical standards.
- Refinement: Procedures should be used that have the least amount of potential pain, discomfort, distress, or morbidity (PDDM) in consideration of any limitations imposed by the objectives of the project. PDDM should be minimized through pharmacological and other means.
- The investigator must provide a written narrative describing the methods and sources used to determine that alternatives to painful/distressful procedures were not available. The written narrative must include: databases searched (must be greater than one), or other sources consulted (i.e., named expert), the date of the search, the years covered by the search, and the key words and/or search strategy. All three Rs must be addressed.

#### Ethical Cost-Benefit Relationship

- The ethical cost of the research must be outweighed or balanced by the potential value of research to human or animal health, the advancement of knowledge, or the good of society.

#### Treatment of Pain and Discomfort

- Unless the contrary is established, investigators should consider that procedures that cause pain or distress in human beings may cause pain or distress in animals.
- Procedures that may cause more than momentary or slight pain or distress to the animals will be performed with state of the art sedation, analgesic, or anesthesia unless withholding is justified for scientific reasons.
- Pain alleviating agents should be administered as part of a continuum when appropriate in accordance with established veterinary practices. Where pain is concerned, the animal should always be given the benefit of the doubt.

#### Post-Procedure Monitoring

- All animals must be monitored at appropriate intervals which are dictated by the species, the nature of the intervention(s), the degree of potential post procedure pain, discomfort, or distress, the likely duration, and the possible complications.
- During monitoring, animal should be evaluated for the presence of pain, discomfort, or distress. In assessing animal welfare, the monitor should use criteria based upon the normal behavioral pattern of the species. Simple observation by a skilled monitor can reveal a great deal of information.
- All monitoring must have written documentation.

## Restraint

- Mechanical restraint must be justified. It is unacceptable to use mechanical restraint procedures on conscious animals if non-mechanical forms of restraint can be used.
- The restraint device must provide the animal with the opportunity to assume its normal postural adjustments. The animal should be conditioned to the device, the duration of restraint must be minimized, and the animal observed at appropriate intervals.

## Euthanasia

- The method of euthanasia should be based upon the species, size of the animal, the scientific objectives of the experiment, and its ability to quickly and painlessly produce a loss of consciousness and death. Euthanasia must comply with current AVMA guidelines.

## Qualification of Research Personnel

- Personnel who perform procedures involving live animals must be knowledgeable about the biology of the species under study and must be fully qualified by training and experience to carry out their assigned surgical and non-surgical procedures and responsibilities related to the care of the animals. Any individual who lacks the prerequisite qualifications must be trained before they interact with the animals.

## Occupational Health and Safety

- The IACUC must be satisfied there is an effective occupational health and safety program which ensures that the risks associated with the experimental use of animals are reduced to acceptable levels and that personnel are appropriately trained.

## 4. The Three Rs: Replacement, Reduction, and Refinement

The growth of medical and veterinary research and of the pharmaceutical and biotechnology industries has brought about a vast increase in the numbers of non-human animals employed as the subjects of experiment. We owe to animal experimentation many, if not most, of the benefits of modern medicine and countless advances in fundamental scientific knowledge. With the increase of the use of animals, it has been recognized that the most humane treatment of experimental animals, far from being an obstacle, is actually a prerequisite for successful animal experiments.

The treatment of experimental animals may be broadly divided into two categories: their treatment when not actually under experiment (husbandry) and their treatment in the course of the experiments themselves. We look toward providing humane treatment in both categories.

**Replacement** is the substitution for conscious living higher animals of insentient material. **Reduction** is a decrease in numbers of animals used to obtain information of a given amount and precision. **Refinement** is any decrease in the incidence or severity of inhumane procedures applied to those animals which still have to be used.

There is clearly overlap between these categories; however, despite the overlap, this threefold division is useful as a means of bringing some order to the subject of humane use of laboratory animals.

“Replacement technique” is a term commonly used to describe any scientific method employing non-sentient material which may replace methods which use conscious living vertebrates. This would include higher plants, microorganisms, and metazoan endoparasites.



Replacement techniques may be relative and absolute. In relative replacement, animals are still required. In absolute replacement, animals are not required at all. Absolute replacement may be seen as the ideal, but having relative replacement combined with reduction is seen as a viable alternative.

Reduction is desirable in any procedure, however directly humane, which employs large numbers of animals. Reduction is of great importance and, of all modes of progress on the three Rs, it is the one most obviously, immediately, and universally advantageous in terms of efficiency. One general way in which great reduction may occur is by the right choice of strategies in the planning and performance of whole lines of research. Many investigators settle early in their research career on some strategy that appears to suit them and are liable never to change from that strategy.

In a research project by Hume (1957), he showed that every time any particle of statistical method is properly used, fewer animals are employed than would otherwise have been necessary. Failure to make some of the planned observations is a common mistake in many experimental procedures.

Refinement choices change as our knowledge of science increases. We have much more effective pain relieving alternatives today than we did even 10 years ago. Refinement techniques include the basic experimental design being used in the protocol- using those techniques which have been shown to give the best results- the choice between procedures for a given objective. The research design should avoid elaborate and roundabout methods. Careful formulation of research questions is another refinement technique: it is a useful guiding principle in experimentation to ask the question and then draw up, at least mentally, a list of procedures by which it could be answered.

The choice of species is among the most important variables in the determination of procedures. The species you choose for your experimentation should be the species which best matches the requirements of the investigation. It is preferable to use lower vertebrates when given a choice of species.

### *Methods to Reduce Animal Numbers*

#### 1. Statistics and Power Analysis

The term **Reduction Alternatives** describes methods for obtaining comparable levels of scientific procedures or for obtaining more information from a given number of animals. Proper statistical design is essential. There is evidence that poor experimental design and inappropriate statistical analysis has led to the inefficient use of animals. This may be due to a low level of statistical expertise in the investigators so that they are unaware of the potential value of obtaining statistical advice. Alternatively, they may be unable to do so because of a lack of qualified biometricians with experience in their field of interest.

Statistical significance and biological significance are not the same; however, statistical and biological significance can be linked through the use of statistical power analysis. The statistical power of a test is the probability of getting a statistically significant result, given that the null hypothesis is false. Power is proportional to the sample size, significance criterion, and effect size, and is inversely proportional to the variance in the population. Effect size is a measure of biological significance: it is the difference between the results predicted by the null hypothesis and the actual state of the population being tested. Power analysis can be used to determine whether the experiment has a good chance of producing a statistically significant result if a biologically significant difference exists in the population or, in other words, determining if the experiment has a high power given a biologically significant effect size. What constitutes "high power" is best left to the researcher, but conventions of 0.8 and 0.95 have been suggested in the literature.

It is beyond the scope of this general introduction to teach statistics to the researchers, but there are methods that are out there that are available. Consultation with a biostatistician can yield benefits to the PI and the experimental animals. For a good general article on selecting appropriate numbers of animals for research, as well as web sites for statistical education, please refer to the following IACUC website: <http://research.uhc.edu/animal/iacuc/reduction/>.

## 2. Pilot Studies

Pilot studies are a good way to reduce the number of animal used; the IACUC may even require a pilot study when reviewing a protocol. Pilot studies can be used to estimate variability and evaluate procedures and effects.

## 3. Appropriate Use of Endpoints

The precision of an experiment depends mainly on the sample size and error variance. Careful attention must be given to the type of endpoint used. Qualitative endpoints (e.g., dead/alive) often involve severe pain and distress and generally provide less information than quantitative measurements. More information can generally be found using quantitative endpoints and can, in some instances, lead to a reduction in the number of animals used during an experiment.

## 4. Sharing Animals

In some instances, it is possible to share research animals. For instance, animals euthanized by one investigator can provide tissue for use by another investigator. There are instances in which this should never be attempted (e.g., animals have been exposed to biological hazards or recombinant DNA), but it is a method to reduce animal numbers that should be explored by researchers.

## 5. Use Quality Animals and Veterinary Care

When PIs use the correct choice of an animal model- one that uses healthy, genetically similar animals- it generally decreases variability and, hence, animal numbers. You can minimize the loss of animals by providing good post-operative care, avoiding unintended breeding, and planning ahead so that the appropriate number of animals needed for the studies are ordered and/or bred.

## 6. Computer Simulations

Though not always possible, there are cases in which there are computer simulations available which can mimic functions of physiology. These are typically most helpful in the case of training protocols.

## 7. Use of Cell Culture

When possible, consider the use of cell cultures rather than animals. For example, there are *in vitro* systems which use cell culture to generate monoclonal antibodies rather than using laboratory animals.

## 8. Auto Controls

It would be helpful, whenever possible, to design experiments in which animals serve as their own control. For example, if a procedure were to be performed on a limb, instead of doing the procedure on both limbs of an animal- and having separate control animals- do a unilateral procedure with the control being the opposite limb. Though this is not always possible, it is a well-established method for reducing animal numbers.

## 9. New Instrumentation and Techniques

Using new instrumentation or innovative techniques that can improve precision can reduce the number of animals needed for a study. This has the added benefit of also being a refinement technique for the protocol.

## 5. Evaluating Pain and Distress in Laboratory Animals

Government agencies and the *Guide* state that, unless determined to be otherwise, anything that would be considered painful or distressful to humans should be considered to be painful or distressful in animals. The USDA, under the AWA, states that for any procedures which are determined to cause pain / distress in laboratory animals, a veterinarian must be consulted in the planning stages of the procedure(s).

Acute pain and/or distress in animals is generally rapid in onset and more intense than chronic pain. The following are signs that may be exhibited by an animal in acute pain and/or distress:

- Guarding: animal protects painful area by moving away or biting the handler
- Vocalization: animal may vocalize on movement or on palpation of painful area
- Self-mutilation: animal may repeatedly lick, bite, scratch, or shake the painful area
- Restlessness: pacing, constant shifting of weight, repeated standing up or lying down
- Abnormal ambulation: reluctance or difficulty in moving or rising from a lying to a standing position
- Abnormal postures: hunched posture, head hanging down, stiff-legged, tucked abdomen

Chronic pain/distress may be more intermittent or less intense than acute pain/distress and is often more difficult to assess. The following are signs that may be exhibited by an animal in chronic pain/distress:

- Clinically evident body weight loss and/or dehydration
- Change in temperament or behavior towards handler
- Lack of self-grooming, as evidenced by ruffled or soiled hair coat
- Reluctance to move or ambulate

### Criteria for establishing endpoints:

The following parameters should be considered when establishing humane endpoints:

1. Body weight of animals as compared to age-matched, untreated cohorts or to a defined baseline
2. General physical appearance of the animal
3. Behavior of the animal
4. Response of the animal to external stimuli
5. Measurable clinical signs (e.g., body temperature, blood cell counts)
6. Ability of an animal to gain access to food and water and normal eating/drinking habits
7. Ability of an animal to ambulate

The following are endpoints that would require notification of the Attending Veterinarian and initiation of treatment, removal of animals from study, and/or euthanasia of animals:

1. Rapid body weight loss (>10% in 48 hours or >20% over course of experiment)
2. Debilitating diarrhea (>48 hours in duration)
3. Self-induced trauma
4. Bleeding from any orifice

5. Neurological signs incompatible with maintenance of normal life functions (e.g., inability to eat, drink, or ambulate)
6. Excessive or prolonged (greater than 24 hours) hyper- or hypothermia
7. Respiratory difficulties (e.g., labored breathing, nasal discharge, coughing)
8. Ambulatory difficulties: any animal unable to ambulate or maintain a normal body position
9. Jaundice or anemia
10. Change in behavior (e.g., lethargy, hunched posture)
11. Inability to gain access to food or water and eat/drink normally
12. Non-responsive to external stimuli
13. Moribund condition

Any animal found moribund should be euthanized immediately or the Attending Veterinarian should be notified for consultation on immediate medical intervention plans. For group-housed animals, consideration should be given to moving animals to individual cages when their condition deteriorates to the point that injury from other animals is likely.

### *Monitoring*

Any animal experiencing adverse clinical signs should be monitored a minimum of twice each day. Monitoring and clinical care should be provided and documented similarly on weekends and holidays. Written records of all monitoring and treatments must be maintained in order to assure adequate care is being provided. Checklists/score sheets may be helpful in ensuring appropriate observations are made, consistently interpreted, and properly documented. Personnel should be identified who are responsible for the evaluation, record keeping, and notification of the investigator and/or Attending Veterinarian. The plan for the parameters to be monitored, the frequency of monitoring, the qualified personnel who will perform evaluations, and the criteria for euthanasia must be described in the approved animal care and use protocol.

The *Guide* and the federal Animal Welfare Act require that the criteria and process for timely intervention and removal of animals from study be specified in animal care and use protocols. In addition, the methods used to eliminate or ameliorate pain or distress in animals on study must be described in the protocol(s) that are reviewed and approved by the IACUC.

Appropriate endpoints must be chosen based on consideration of the scientific requirements of the study, the expected and possible adverse effects animals may experience, the expected time course and progression of adverse effects, and the earliest predictive indicators of adverse effects.

It is essential that properly qualified personnel monitor the animals at appropriate intervals to ensure adequate observation and care of the animals. Optimally, studies should be terminated when animals begin to exhibit adverse clinical signs **IF** this endpoint is compatible with meeting research objectives, since such endpoints minimize pain or distress. It is preferable to use the earliest endpoints compatible with the scientific requirements of studies; however, if the study requires moribundity or mortality as an endpoint, this must be specifically described and approved in the animal care and use protocol approved by the IACUC.

## 6. Death as an Endpoint

The use of death as an endpoint has been regarded as essential in some investigations, but rapid developments are being made in this field, and it is an area where both investigators and the IACUC should make particular efforts to keep abreast of the current literature. The usual reason for selecting death as an endpoint is the difficulty of reliably differentiating animals that will die from those which will recover, despite them showing severe clinical signs of illness or toxicity. When clinical signs include subjectively distressing changes such as convulsions or severe dyspnea, then there is particular pressure to euthanize an animal rather than allow further deterioration of its condition.

Several constructive suggestions have been put forward to reduce the need for death as an endpoint in studies. In some circumstances, simple clinical indices such as the development of profound hypothermia can be used to reliably predict death. The use of death as an endpoint must be scientifically justified and approved by the IACUC during protocol review. In these circumstances, the IACUC must carefully assess whether criteria can be developed during the progress of the project under consideration. In many instances, failure to develop criteria may be due to insufficiently frequent observation of the animals, or critical events may occur at times of the day when personnel are not usually available, thereby precluding detailed observation. Animal care and use protocols that propose the use of moribundity or death as an endpoint must include the following information:

1. The scientific rationale for death or moribundity as an endpoint
2. Considerations of alternative endpoints
3. Why pain/distress relieving medications and/or treatments cannot be utilized
4. Number of animals to be used and why this is the minimum number of animals required
5. Plan that details the parameters to be monitored, the timetable and frequency of monitoring, and the personnel responsible for making recorded observations
6. Whether animals will be euthanized when moribund and, if not, what information is to be gained in the interval between moribundity and death.

There seems no doubt that progress in refining endpoints has only occurred as a result of investigators carefully evaluating their own particular models. It may be that even after careful assessment, no progress is made and animals must be allowed to die if the aims of the study are not to be compromised. **Under no circumstances** may the use of death as an endpoint be applied simply because it is an unambiguous and easy criterion to apply.

## 7. Personnel Qualifications and Training

Qualified and well-trained personnel assures humane care and use of laboratory animals, supports good science, supports efficient management of the animal care and use program, fosters high self-esteem among employees, and assures legal and regulatory compliance.

UConn Health is ultimately responsible for assuring that personnel are adequately trained. The IACUC has delegated responsibility from the Institutional Official (IO) to assess the effectiveness of training. Employees and their supervisors (including the principal investigator) are also accountable.

It is federally mandated that anyone who is responsible for laboratory animal care, treatment or use is adequately trained: including scientists, research technicians, students, animal care staff, and IACUC members. It is optional for peripheral individuals to be trained (e.g., vendors, contractors, maintenance personnel).

Again, PHS policy and USDA policy differ on their minimum training requirements. USDA regulations: people must be trained in humane methods of animal care and use, methods that limit animal use or minimize animal distress, use of pain-relieving agents, and how to report deficiencies. PHS policy regulations: people must be trained in humane methods of animal care and use, methods that minimize the number of animals required, and methods that minimize animal distress.

The *Guide* states that the institution should provide formal or on-the-job training for animal care and use personnel and suitable orientation, background materials, access to appropriate resources, and specific training to assist IACUC members.

Training should include: Information on applicable laws, regulations, and policies; ethical and scientific issues; alternatives to animal use, responsibilities of the institution, IACUC, and research and veterinary staff; information regarding pain and distress, information regarding the use of anesthetics, analgesics, tranquilizers, and neuromuscular blocking agents; survival surgery and post-surgical care; and euthanasia.

## 8. Occupational Health and Safety

It is UConn Health's responsibility for providing an adequate occupational health and safety program (OHSP) in which **all animal users must be enrolled**. The OHSP is responsible for assessing risks associated with animal contact (e.g., zoonoses, chemical, microbiological, and physical hazards), communicate those risks to personnel, provide training to help protect personnel (e.g., with respect to personal hygiene, protective equipment, and competent care and use methods), and implement procedures to monitor personnel. At the Health Center, this program is administered primarily by Employee Health Services (EHS) with some input from the Research Safety Office. It is the responsibility of the IACUC to review and assess the effectiveness of the OHSP as part of the semi-annual program review.

Enrollment in the occupational health surveillance program is simple; go to the OHS page of the IACUC website (<http://research.UCH.edu/animal/iacuc/ohshome/surveillance/>). The first thing they should do is to perform a risk analysis in the context of their work with animals. The risk assessment is at (<http://research.UCH.edu/animal/iacuc/ohshome/risk-assessment/>) and is categorized by species. Once a person is aware of this preliminary assessment of hazards working with particular species, they should then fill out a Mandatory Annual Certificate of Enrollment (MACE) for which is located on the web.

The foundation of a good occupational health and safety program is one that addresses employee risks of illness and injury associated with the care and use of research animals. Program design requires an understanding of the tasks of at-risk employees; those employees' diversity in experience, education, and language proficiency; characteristics of the work environment; and the institutional mission. The work environment and mission are of paramount importance because they determine the nature of the hazards presented by the animal research activities. Areas of importance are:

- Knowing the hazard(s)
- Avoiding and controlling exposures
- Training and education
- Rules and guidelines
- Consistency
- Recordkeeping and monitoring
- Commitment and coordination

An important overall concept which is important in terms of running and effectively operating a program depends on interaction among distinct functional parts of an institution. These functional parts include:

- Animal care and use
- Research
- Environmental health and safety
- Occupational health
- Administration and management

There are various areas within an effective occupational health and safety program which should be addressed by the institution. These areas include knowing the physical, chemical, and protocol-related hazards, allergens, zoonoses, and occupational health care services. Principal elements of an occupational health and safety program include:

- Administrative procedures
- Facility design and operation
- Exposure control
- Education and training
- Occupational health
- Equipment performance
- Information management
- Emergency procedures
- Program evaluation

The goal of an occupational health and safety program is to prevent occupational injury and illness. The program must be consistent with federal, state, and local regulations, but the principal focus of the program should be on the control of hazards and the reduction of risks, as opposed to merely satisfying regulations. The strategies that promote health and safety in the care and use of research animals are similar to those applied generally in a research laboratory. The use of animals in research is an extension of other experimentation that occurs in the laboratory. Research animals and the procedures and techniques that attend their use can present unique problems and challenges, many of which increase the hazards of experimentation. Those problems and challenges must be considered in the management of occupational health and safety programs.

#### Knowing the hazards

Determining the level of protection that is needed in any given situation depends on understanding the hazard in question. Defining and quantifying a hazard is sometimes referred to as risk assessment. The assessment, insofar as possible, should be based on scientific information. In the case of infectious agents, dose-response relationships, virulence, communicability, prevalence, routes of exposure, shedding patterns, stability, and availability of prophylaxis and therapy are important considerations. For chemical agents, one has to know about toxic doses, stability, form (liquid, gas, or solid), type of toxicity (irritation, corrosion, carcinogenicity, narcosis, lethality, etc.), severity of reaction, mode of action, and metabolic products. The main sources of information for risk assessment are the scientific literature and professionals and consultants with unpublished field experience.

#### Avoiding and Controlling Exposures

It is common sense that it is better to avoid a hazard than to deal with the consequences of exposure to it. Measures related to the principle include training, work practices, containment equipment, personal

protective equipment, control of access to hazardous areas, and use of purpose-bred animals. Safety measures should be implemented in advance rather than after a problem emerges. Although reducing risk to employees is the primary goal of an occupational health and safety program, it should be recognized that it is impossible to totally eliminate risk.

### Training and Education

Once a hazard is known, this knowledge must be communicated to animal care and use employees most directly involved and other employees (such as janitorial and maintenance workers) who might be at risk of exposure. Employee training begins with orientation immediately after hiring. Standard operating procedures should include methods for performing duties safely. New employees should be carefully instructed in those procedures by an experienced co-worker before assuming duties independently. Laboratory procedures can be reinforced with signs and posters. Periodic meetings to encourage safe work practices are advisable, and safety newsletters and electronic bulletin boards sometimes can be beneficial in keeping employees updated on changes. An institution has a crucial role in ensuring that its employees remain both well-informed of relevant health and safety information and proficient in the use of safe practices.

### Rules and Guidelines

Rules are necessary to ensure safety in the workplace. Rules governing the training of personnel, adherence to work procedures, use of disinfectants and decontaminants, access, waste disposal, use and maintenance of equipment and safety devices, emergency procedures, reporting of accidents and exposures, and personnel behavior (smoking, eating, and hand-washing) should be rigidly enforced. Rules are “musts” whereas guidelines are recommendations and suggestions that allow for some judgment.

### Consistency

Consistency is essential to the success of an occupational health and safety program, including consistency in rules, enforcement, and application to all workers. Lack of consistency can undermine a program. However, too-rigid safety rules, at times considered unreasonable by employees, can undermine the credibility of a program.

### Recordkeeping and Monitoring

Developing and maintaining records is essential in an occupational health and safety program. It might start with a medical history of each employee to discover any facts that would bear on the general susceptibility of the employee to injury or illness. Reports of accidents, exposures, and work-related illnesses are absolutely necessary and sometimes required by law. Other forms of recordkeeping can provide useful information for monitoring safety programs and identifying deficiencies.

### Commitment and Coordination

Commitment to safety must be a feature of an organization from top to bottom. Even the best safety program will fail if employees ignore the rules. The hierarchy of management must be committed if a safe attitude is to be instilled in workers. Animal facilities are rarely autonomous organizations; coordination is required among administrators, research scientists, veterinarians, technicians, and maintenance workers. Every person's role should be clearly defined because safety programs can fail if responsibilities are diffuse and not well understood.



## II. REGULATIONS

### 1. Overview

As stated previously, there are two federal agencies governing the use of laboratory animals, the United States Department of Agriculture (USDA) and the Public Health Service (PHS):

- **Animal Welfare Act**- specifically governs the use of animals under the jurisdiction of the USDA and includes all warm-blooded vertebrate animals other than mice of the genus *Mus* and rats of the genus *Rattus* bred for research purposes and birds.
- **Health Research Extension Act of 1985**- specifically governs the use of all vertebrate animals in agencies utilizing PHS funds.
- **PHS Policy on the Humane Care and Use of Laboratory Animals**- is the policy stated to require institutions to establish and maintain proper measures to ensure the appropriate care and use of all animals involved in research, research training, and biological testing activities (hereinafter referred to as activities) conducted or supported by the PHS.
- **US Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training**- principles used to implement the Health Research Extension Act of 1985.

These two federal agencies vary in their requirements to animal care and use programs. UCH has made a concerted effort to ensure that the policies and procedures used comply with both agencies, as we use both USDA covered species and PHS funding.

In addition, PHS policy states that animal care facilities should use the standards and recommendations set forth in the *Guide*. The American Association for the Accreditation of Laboratory Animal Care (AAALAC) also require the use of the *Guide* in laboratory animal care programs and facilities.

The following pages contain some of the regulations which must be adhered to.

### 2. Animal Welfare Act

The Animal Welfare Act (AWA) was first introduced in 1966 partly as a response to animal welfare groups. It has been amended at various points: the 1986 amendment introduced the requirements for exercise for dogs, requirements for the psychological well-being of non-human primates; requirements for pain alleviation, and justification requirements for multiple survival surgery. We are currently in the 2013 version of the AWA.

Regulatory authority under the AWA is vested in the secretary of the U.S. Department of Agriculture (USDA) and implemented by the USDA's Animal and Plant Health Inspection Service (APHIS). Rules and regulations pertaining to implementation are published in the Code of Federal Regulations, Title 9 (Animals and Animal Products), Chapter 1, Subchapter A (Animal Welfare).

The following is a summary only. For full text go to: [www.nal.usda.gov/awic/legislat/usdaleg1.htm](http://www.nal.usda.gov/awic/legislat/usdaleg1.htm)

For more than a quarter of this century, the U.S. Department of Agriculture (USDA) has enforced the Animal Welfare Act (AWA) to protect certain animals from inhumane treatment and neglect. Congress passed the AWA in 1966 and strengthened the law through amendments in 1970, 1976, 1985, 1990, and 2005, and 2013. The USDA's Animal and Plant Health Inspection Service (APHIS) administers the AWA, its standards, and its regulations.

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### The Law

The AWA requires that minimum standards of care and treatment be provided for certain animals bred for commercial sale, used in research, transported commercially, or exhibited to the public. Individuals who operate facilities in these categories must provide their animals with adequate care and treatment in the areas of housing, handling, sanitation, nutrition, water, veterinary care, and protection from extreme weather and temperatures. Although Federal requirements establish acceptable standards, they are not ideal. Regulated businesses are encouraged to exceed the specified minimum standards.

### Exemptions

The AWA regulates the care and treatment of warm-blooded animals, except those, such as farm animals, used for food, fiber, or other agricultural purposes.

Currently, cold-blooded animals, such as snakes and alligators, are exempt from coverage under the Act. Retail pet shops are not covered under the Act unless the shop sells exotic or zoo animals or sells animals to regulated businesses. Animal shelters and pounds are regulated if they sell dogs or cats to dealers. Pets owned by private citizens are not regulated.

### Pet Protection

To help prevent trade in lost or stolen animals, regulated businesses are required to keep accurate records of acquisition and disposition and a description of the animals that come into their possession. Animal dealers also must hold the animals that they acquire for a period of 5 to 10 days to verify their origin and allow pet owners an opportunity to locate a missing pet.

### Animal Fighting

The AWA prohibits staged dogfights, bear or raccoon baiting, and similar animal fighting ventures.

### Licensing and Registration

The AWA also requires that all individuals or businesses dealing with animals covered under the law must be licensed or registered with APHIS.

### Research Facilities

In addition to providing the required standards of veterinary care and animal husbandry, regulated research facilities must provide dogs with the opportunity for exercise and promote the psychological well-being of primates used in laboratories. Researchers must also give regulated animals anesthesia or pain-relieving medication to minimize the pain or distress caused by research if the experiment allows. The AWA also forbids the unnecessary duplication of a specific experiment using regulated animals.

Research facilities must establish an institutional animal care and use committee to oversee the use of animals in experiments. This committee is responsible for ensuring that the facility remains in compliance

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with the AWA and for providing documentation of all areas of compliance to APHIS. The committee must be composed of at least three members, including one veterinarian and one person who is not affiliated with the facility in any way.

The AWA also does not permit APHIS to interfere with research procedures or experimentation. Regulated research facilities include hospitals, colleges and universities, diagnostic laboratories, and many private firms in the pharmaceutical and biotechnology industries.

## AWA Enforcement

APHIS ensures that all regulated commercial animal breeders, dealers, brokers, transportation companies, exhibitors, and research facilities are licensed or registered. APHIS also searches for unlicensed or unregistered facilities.

Before APHIS will issue a license, the applicant must be in compliance with all standards and regulations under the AWA. To ensure that all licensed and registered facilities continue to comply with the Act, APHIS inspectors make unannounced inspections at least once annually.

If an inspection reveals deficiencies in meeting the AWA standards and regulations, the inspector instructs the facility to correct the problems within a given timeframe. If deficiencies remain uncorrected at the unannounced follow-up inspection, APHIS documents the facility's deficiencies and considers possible legal action.

APHIS also conducts reviews and investigates alleged violations. Some cases are resolved with Official Notices of Warning or agency stipulation letters, which set civil penalties for the infractions. Civil penalties include cease-and-desist orders, fines, and license suspensions or revocations. If APHIS officials determine that an alleged AWA violation warrants additional action, APHIS submits all evidence to the USDA for further legal review.

## Cooperation

In addition to conducting regular inspections, APHIS will perform inspections in response to public input about the conditions of regulated facilities. Concerned individuals also are encouraged to inform APHIS about facilities that should be licensed or registered.

Many State and local governments have passed additional animal welfare legislation. The public is encouraged to work with Federal, State, and local officials as well as local humane organizations to help eliminate inhumane treatment of animals.

### **3. Health Research Extension Act of 1985**

The Health Research Extension Act of 1985, Public Law 99-158, "Animals In Research" (November 20, 1985) provides the statutory mandate for the PHS Policy. In 1986, the HREA incorporated the *U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research and Training* (see section 5). The Principles were incorporated into the PHS Policy in 1986 and continue to provide a framework for conducting research in accordance with the Policy.

### **4. Public Health Service Policy on Humane Care and Use of Laboratory Animals**

The first PHS Policy on Humane Care and Use of Laboratory Animals was passed in 1979. It required that assurances are to be held in institutions before funding is received from PHS. PHS Policy covers all live vertebrates. Like the Animal Welfare Act, it has been amended on various occasions, most recently in 2015. The 1985 Policy included the Health Research Extension Act (see section 3), required a more detailed PHS assurance, mandated that the IO is ultimately responsible for all animal research, required a CEO to appoint IACUC members, set forth minimum requirements of an IACUC, and finally required protocol review. The 2002 version of PHS Policy reflects the August 7, 2002 PHS Policy amendment permitting institutions with PHS Animal Welfare Assurances to submit verification of Institutional Animal Care and Use Committee (IACUC) approval for competing applications or proposals subsequent to peer review but prior to award (67 FR 51289).

### **5. U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training**

The *U.S. Government Principles* were promulgated in 1985 by the Interagency Research Animal Committee and adopted by U.S. Government agencies that either develop requirements for or sponsor procedures involving the use of vertebrate animals. The following is a copy of these Principles:

The development of knowledge necessary for the improvement of the health and well-being of humans as well as other animals requires in vivo experimentation with a wide variety of animal species. Whenever U.S. Government agencies develop requirements for testing, research, or training procedures involving the use of vertebrate animals, the following principles shall be considered; and whenever these agencies actually perform or sponsor such procedures, the responsible Institutional Official shall ensure that these principles are adhered to:

I. The transportation, care, and use of animals should be in accordance with the Animal Welfare Act (7 U.S.C. 2131 et. seq.) and other applicable Federal laws, guidelines, and policies.\*

II. Procedures involving animals should be designed and performed with due consideration of their relevance to human or animal health, the advancement of knowledge, or the good of society.

III. The animals selected for a procedure should be of an appropriate species and quality and the minimum number required to obtain valid results. Methods such as mathematical models, computer simulation, and in vitro biological systems should be considered.

IV. Proper use of animals, including the avoidance or minimization of discomfort, distress, and pain when consistent with sound scientific practices, is imperative. 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.

V. Procedures with animals that may cause more than momentary or slight pain or distress should be performed with appropriate sedation, analgesia, or anesthesia. Surgical or other painful procedures should not be performed on unanesthetized animals paralyzed by chemical agents.

VI. Animals that would otherwise suffer severe or chronic pain or distress that cannot be relieved should be painlessly killed at the end of the procedure or, if appropriate, during the procedure.

VII. The living conditions of animals should be appropriate for their species and contribute to their health and comfort. Normally, the housing, feeding, and care of all animals used for biomedical purposes must be directed by a veterinarian or other scientist trained and experienced in the proper care, handling, and use of the species being maintained or studied. In any case, veterinary care shall be provided as indicated.

VIII. Investigators and other personnel shall be appropriately qualified and experienced for conducting procedures on living animals. Adequate arrangements shall be made for their in-service training, including the proper and humane care and use of laboratory animals.

IX. Where exceptions are required in relation to the provisions of these Principles, the decisions should not rest with the investigators directly concerned but should be made, with due regard to Principle II, by an appropriate review group such as an institutional animal care and use committee. Such exceptions should not be made solely for the purposes of teaching or demonstration.

### III. INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE

#### 1. Role and Charge of the Institutional Animal Care and Use Committee (IACUC)

An Institutional Animal Care and Use Committee (IACUC) is a federally mandated committee with the job to oversee the animal care program at any given institution. It has been approximately 12 and 2 years, respectively, since the implementation of the current PHS Policy and Part 2 of the USDA regulations which first defined the federal requirements for IACUCs. Since then, the IACUC has evolved as the premier instrument of animal welfare oversight within the majority of biomedical research institutions in the US.

The UCH IACUC is led by the chairperson of the committee and the committee reports directly to the Institutional Official (IO) of the Health Center- the Associate Vice President of Research Compliance. Members of the IACUC are appointed by the Chief Officer of the UCH or his/her designee. The committee membership is federally mandated and must include:

- A doctor of veterinary medicine who is certified or has training or experience in laboratory animal science and medicine or the use of the species in question
- At least one practicing scientist experienced in research involving animals
- At least one public member to represent general community interests in the proper care and use of animals. Public members should not be laboratory animal users, be affiliated with the institution, or be members of the immediate family of a person who is affiliated with the institution
- At least one non-scientist member

The committee is responsible for oversight and evaluation of the animal care and use program and its components. Its functions include: inspection of facilities, evaluation of programs and animal-activity areas; submission of reports to the IO; review of proposed uses of animals (i.e., protocols); training program for animal users; and establishment of a mechanism for receipt and review of concerns involving the care and use of laboratory animals; suspension of animal activities (if necessary); and make recommendations to the IO regarding any aspect of the animal care program.

There is no federal or state mandate dealing with how often an IACUC should meet, except the statement that “the IACUC must meet as often as necessary to fulfill its responsibilities, but it should meet at least once every 6 months”. Our IACUC meets once per month, generally on the last Thursday of the month. IACUC meeting dates are posted on the IACUC website (<http://research.uchc.edu/animal/iacuc/meeting-schedule/>). Generally, the deadline to submit new applications and modifications that are required to be reviewed at a full committee is at noon on the 10<sup>th</sup> of the month.

Federally mandated functions of an IACUC are as follows:

1. Review, at least once every six months, the research facility’s program for the humane care and use of animals, using the 2011 *Guide for the Care and Use of Laboratory Animals* (PHS) and 9 CFR, chapter 1, subchapter A (USDA) as a basis for evaluation.
2. Inspect, at least once every six months, all of the institution’s animal facilities using the 2011 *Guide for the Care and Use of Laboratory Animals* (PHS) and 9 CFR, chapter 1, subchapter A (USDA) as a basis for evaluation. Satellite holding facilities and areas in which surgical manipulations are performed must always be included.
3. Prepare reports of the IACUC evaluations and submit the reports to the Institutional Official (IO).

4. Review, and if warranted, investigate concerns involving the care and use of animals resulting from public complaints and from reports of non-compliance received from laboratory or research facility personnel or employees.
5. Make recommendations to the IO regarding any aspects of the animal program, facilities, or personnel training.
6. Review and approve, require modifications, or withhold approval of animal care and use protocols. Continuing review of activities required not less than annually and a complete review (e.g., resubmission) are required at least once every 3 years.
7. Review and approve, require modifications in, or withhold approval of proposed changes regarding the use of animals in ongoing activities.
8. Be authorized to suspend an activity involving animals in accordance with specifications in IV.C.6 of PHS *Policy* and/or 9 CFR. This action may only be taken after review of the matter at a convened meeting of a quorum of the IACUC and a vote for suspension by the majority of the quorum present.

In addition to the above federally-mandated Functions of an IACUC, the UCH IACUC has been charged with the following institution-mandated functions:

1. The IACUC shall serve as an advisory committee to the Associate Vice President of Research.
2. The IACUC shall concern itself with the budget of the Center for Comparative Medicine (CCM) and the status of the animal care per diem charges.
3. The IACUC shall concern itself with recommendations to the Space Committee for allocation and space utilization.
4. The IACUC shall concern itself with procedures and technology to maintain disease-free health animals.
5. The IACUC shall concern itself with the long-term development of the facility and broad policy issues, such as scientific and ethical use of animals in research.
6. The IACUC shall be responsible for recommending procedures and policies which will ensure compliance with federal and state regulations concerning the use of animals in research.
7. The IACUC shall be responsible for recommending procedures and policies which will ensure full accreditation status by the American Association for Accreditation of Laboratory Animal Care (AAALAC).
8. The IACUC shall be responsible for reviewing and approving training curricula required by appropriate federal and state regulations.

## 2. Composition of the UCH IACUC

### Current IACUC Members

Dr. Joseph Lorenzo, Chair	Dr. Andrei Medvedev
Dr. Stephen Clark, Vice-Chair	Ms. Alison Pohl
Dr. Stephen Crocker, Vice-Chair	Dr. Lynn Puddington
Dr. Ramaswamy Chidambaram	Mr. Daniel Sasso
Dr. Dashzeveg Bayarsaihan	Deacon Thomas Sutak
Dr. Melissa Caimano	Dr. Ronald Wallace
Ms. Marisa Evans	Dr. Catherine Wu
Dr. Laura Haynes	Dr. Siu-Pok Yee
Ms. Kelly Hoyt	

## 3. Application for Animal Care and Use Protocols

One of the primary functions of the UCH IACUC is to review animal care and use protocols. An adequate review of a protocol depends upon the IACUC receiving a thorough, well-written document that conforms to USDA and PHS policies as well as recommendations set forth by AAALAC and the *Guide*.

### *New applications*

All new animal care and use protocol must be submitted electronically via the Topaz animal protocol development and review system. Once the protocol is submitted, it will be reviewed for completeness and general concerns by the IACUC office. If it is determined that the application form is incomplete or requires changes, it will be returned to the submitter to be completed. Once the IACUC office receives a sufficiently complete protocol application, it will be reviewed in order to evaluate whether it meets criteria for a DMR review or if the submission must go to the full committee of the IACUC. Either way, the protocol application is sent to reviewers and placed on the IACUC agenda.

### *Yearly reviews*

All animal care and use protocols must have a yearly review. The review protocol is in Topaz and it is called "Create Interim Protocol". This is a bit of a misnomer, but it is for the required annual review. All active protocols are required to have a yearly review. Failure to provide information for the yearly review may result in a suspension of the protocol until the form is received.

### *Modifications*

Modifications to approved protocols must be appropriately documented, reviewed, and approved. Modifications are submitted to the IACUC by the electronic protocol development and review system. The IACUC Coordinator, based on IACUC Policy, determines if the modifications are minor or significant. Minor modifications are reviewed and approved administratively. IACUC Coordinator will send the modification to the appropriate reviewer for review and approval. If the modification is determined to be major (significant), then the modification is reviewed by DMR, FCR, or the new Veterinary Verification and Consultation (VVC) review method. Criterion for each route of review is also detailed in IACUC Policy. If



there are any questions regarding a modification's status as minor or significant or the route of review required, the IACUC Chair will make the decision.

Minor modifications would include addition of qualified personnel, addition or deletion of funding sources, addition or deletion of room locations, <100% increase in rodent animal numbers, <25% increase in non-rodent animal numbers, the need to repeat an experiment, and the addition of animal strains including the addition of transgenic lines. Minor modifications that are solely administrative in nature (addition of funding sources, addition/deletion of personnel, changes in room assignments, addition/deletion of accounts, etc.) are reviewed by the IACUC Administrator. Other minor modifications typically would be reviewed by the IACUC member who reviewed the original document or the IACUC Chair. Major (significant) modifications would include a change in purpose or specific aim of study, change in Principal Investigator, >100% increase in rodent animal numbers, >25% increase in non-rodent animal numbers, addition of survival surgery, addition of painful procedure, housing of animals in a location that is not part of the animal program overseen by the IACUC, any changes that have the potential to impact personnel safety, changes in, and additions of, experimental procedures.

FCR review criteria would include addition of major survival surgery, addition of painful procedures, use of death as an endpoint, and requests for exceptions to any regulations. DMR review criteria would include change in purpose or specific aim of a study, change in Principal Investigator, housing of animals in a location that is not part of the animal program overseen by the IACUC, changes that have the potential to impact personnel safety, and addition of minor survival surgeries. VVC review criteria would include changes to anesthesia and analgesics, addition of non-invasive sampling, addition of experimental substances (note: this may also require a safety review), change of euthanasia to any AVMA-approved method, and addition of sample collection times.

#### *Renewals*

3-year renewals follow the same procedures as new applications. This is done to satisfy both the USDA and PHS regulations. Under no circumstances may protocols be granted an "administrative extension"; once a protocol is expired, all work on that protocol must cease until a replacement animal care and use protocol has been approved for the work. PIs will typically be notified at least 4 months prior to the expiration of a current protocol with reminders with a "due date" for a renewal protocol.

#### **4. Reporting of Animal Welfare Concerns**

The following is the IACUC's official policy on reporting animal welfare concerns, as required by the AWA and PHS policy:

UCH's IACUC is committed to the humane care and use of laboratory animals. To ensure that laboratory animals receive humane care and use or treatment in accordance with the highest ethical standards, laws, regulations, and policies governing animal research, the IACUC must review and, if warranted, address any animal-related concerns by the public or UConn Health employees. The following will outline the established procedure to ensure that concerns are communicated to the IACUC. The IACUC must review each concern in a timely and systematic manner and, when necessary, take prompt and appropriate corrective action.

Reports of animal welfare concerns may be made anonymously, if desired. However, if the complainant would like to know the resolution of the investigation, s/he must provide a name. All reports will be handled confidentially, although anonymity cannot be guaranteed.

This policy is subject to the UCH Whistle Blower's Protection Policy.

**Action:**

1. Letter-sized posters outlining how to report animal care and use concerns are available and posted throughout the health center: in the main department offices and on each floor where animal rooms are located. Concerns may be sent to the following:

Non-compliance Report Line	UCH Service	888-685-2637
IACUC Office		860-679-4129
Center for Comparative Medicine		860-679-2731
IACUC Chair		860-679-8199

2. When alleged incidences of non-compliance are reported to the IACUC, these incidences will be investigated with the utmost concern for confidentiality and due process, without compromising the welfare of the animals.

3. If the incidence directly involves animal health and safety, a CCM veterinarian will assess the health and well-being of the animal(s) and will verify the concern. If there is animal suffering, the veterinarian will take immediate action, including supportive care or euthanasia. While a good faith effort will be made to contact the Principal Investigator (PI), the immediate animal welfare situation may necessitate that immediate action be taken without the PI's knowledge.

4. Once the animal(s)'s welfare is assessed and addressed (or in those situations where animals are not directly involved), the alleged concern or issue will be evaluated by the IACUC Chair, the Attending Veterinarian, the IACUC Administrator and/or the IO generally within 5 working days of receiving a report of an animal welfare concern.

a. If they determine a complaint does not warrant further investigation, the IACUC Chair will inform the IACUC of the incident and its resolution at the next convened meeting.

b. If they determine a complaint warrants investigation, the IACUC Chair will inform the PI and appoint a subcommittee of IACUC members to lead a formal investigation of the complaint. Once the investigation is complete, a report will be generated for the full IACUC to evaluate.

c. The IO will then, if a reportable non-compliance has occurred, inform the NIH Office of Laboratory Animal Welfare (OLAW) to comply with the OLAW requirement for prompt reporting (NOT-OD-05-034). The IO will inform the affected PI(s) of this notification.

5. It is the responsibility of the IACUC subcommittee to review the concern and determine the appropriate requirements for the investigation in a timely manner (generally within 5 working days of the formation of the subcommittee) and communicate with the PI involved in the complaint.

6. Once the subcommittee informs the IACUC of the results of the investigation, and it is reviewed and agreed by the full IACUC, then the IACUC will inform the PI and the IO of the results of the investigation.
7. A final report of reportable non-compliance will be sent to OLAW by the IO. If the non-compliance activity requires reporting to the USDA Animal and Plant Health Inspection Service, this will also be done at this time. Concurrent with notification to federal agencies, AAALAC will also be informed of the non-compliant event.
8. If the complainant disclosed their name, they will then be contacted by the IACUC coordinator with the results of the investigation.
9. If allegations of misuse of laboratory animals or non-compliance with federal, state, or institutional policies or regulations have been established by the investigation, the potential consequences to the involved individual(s) may include: mandatory retraining, suspension of animal protocol(s), termination of animal protocol(s), or permanent withdrawal of IACUC approval to use laboratory animals.

## **5. Investigator Responsibilities Regarding IACUC Approved Protocols**

It is the responsibility of the principal investigator (PI) to maintain the “approval” status of his protocol(s). The IACUC coordinator will generally give advanced notice when protocols need yearly reviews (annual reviews are started the month they are due) and 3-year renewals (approximately 4 months and 2 months prior to expiration date) and will provide help when requested. There is no such thing as an “extension” of animal protocol approvals — such actions are strictly prohibited in USDA and PHS regulations. Please do not request extensions of the approvals of your protocols.

It is the responsibility of the PI to ensure that professionally acceptable, ethical, and humane standards governing the care, treatment, and use of laboratory animals will be followed. The PI must also ensure that discomfort, and injury to animals will be limited to that which is unavoidable in the conduct of scientifically valuable research and that appropriate anesthetic, analgesic, and tranquilizing drugs will be used to relieve all unnecessary pain and distress for the subject animals during teaching, research, testing, and post-operative care.

It is the responsibility of the PI to ensure that protocols do not unnecessarily duplicate previous experiments.

It is the responsibility of the PI to ensure that personnel conducting procedures on the animals will comply with all the pertinent institutional, state, and federal laws, rules, and policies; that personnel are adequately trained in the procedures they are required to perform during the course of their work; and that personnel are enrolled in an occupational health and safety program.

It is the responsibility of the PI to ensure that any changes in the protocol procedures or personnel will be submitted to, and approved by, the IACUC prior to implementation. The PI is also responsible for having a current copy of the approved protocol posted in a place where all individuals working on the protocol have access to it.

It is the responsibility of the PI to notify the IACUC coordinator regarding any unexpected study result(s) that impact the animals— including any unanticipated pain and/or distress, morbidity, and mortality.

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It is the responsibility of the PI to cooperate with the IACUC and attending veterinarian(s) in their supervision of all laws, rules, and policies and to cooperate fully with semi-annual reviews and any compliance audits performed by the IACUC.

## IV. CONCEPTS OF VETERINARY CARE

### 1. Use of Anesthetics, Analgesics, and Tranquilizers

An integral component of veterinary medical care is prevention or alleviation of pain associated with procedural and surgical protocols. Pain is a complex experience that typically results from stimuli that damage tissue or have the potential to damage tissue. Pain is a stressor and, if not relieved, can lead to unacceptable levels of stress and distress in animals. The proper use of anesthetics and analgesics in research animals is an ethical and scientific imperative. *Recognition and Alleviation of Pain and Distress in Laboratory Animals* (NRC, 1992) is a source of information about the basis and control of pain.

Earlier, the clinical signs of pain in animals were listed; knowledge of these signs is fundamental to the relief of pain in the animals. The selection of the most appropriate analgesic or anesthetic should reflect professional judgment as to which best meets clinical and humane requirements without compromising the scientific aspects of the research protocol. Preoperative or intra-operative administration of analgesics might enhance post-surgical analgesia. As the selection of the most appropriate analgesic depends on many factors, the attending veterinarians of the health center should be consulted on analgesia options.

Some classes of drugs— such as sedatives, anxiolytics, and neuromuscular blocking agents— are not analgesic or anesthetic and do not relieve pain; however, they might be used in combination with appropriate analgesics and anesthetics. Neuromuscular blocking agents are sometimes used to paralyze skeletal muscles during surgery in which general anesthetics have been administered.

#### *Anesthetic Drugs Guidelines for Rodents/Rabbits (mg/kg of body weight):*

Drug	Category	Mice	Rats	Gerbils	Guinea Pigs	Hamsters	Rabbits
Atropine	Anti-cholinergic	0.02-0.05 IM, SQ, IV	0.02-0.05 IM, IP, IV	0.02-0.05 SQ, IM, IP	0.02-0.05 SQ, IM, IV	0.02-0.05 SQ, IM, IV	
Ketamine + Xylazine	Dissociative Anesthetic	90-120 + 15 IM	40-90 + 15 IM	50 + 2 IP	40-50 + 5 IP	150-200 + 10 IP	
Ketamine + Xylazine + Acepromazine	Dissociative Anesthetic	30-35 + 5-6 + 0.75-1 IM	22-44 + 2.5 + 0.75 IM	May precipitate seizures			35 + 05 + 0.75 IM
Ketamine + Acepromazine	Dissociative Anesthetic	100 + 2.5 IM	30-75 + 2.5-3 IM		125 + 5 IM	150 + 5 IM	
Ketamine + Xylazine + Atropine or Glycopyrrolate							33-40 + 5 + 0.2 IM

Pentobarbital	Barbiturate	Neonate: 5 IP 35-70 IV 40-90 IP	30-40 IP	25-30 IP	25-30 IP	40-85 IP	
Isoflurane (vapors must be controlled-see page 99)	Inhalant Anesthetic	1.5-4% to effect	1.5	4% to effect	1.5	4% to effect	1-3% to effect

*Postoperative Analgesics for Rodents/Rabbits (mg/kg body weight):*

Analgesic	Mice	Rats	Gerbils	Guinea Pigs	Hamsters	Rabbits
Buprenorphine	0.05-1.0 IP/SQ 6-12 hours	0.2-0.5 IP/SQ 8-12 hours	0.1-0.2 SQ 8-12 hours	0.05 SQ 6-12 hours	0.05-0.5 SQ 8-12 hours	0.02-0.05 SQ or IM
Buprenorphine, extended release	0.5-1.0 SQ	10.-1.2 SQ				
Butorphanol	0.05-5.0 SQ q 4 hours	0.05-2.0 SQ q 4 hours				
Meperidine	10-20 SQ/IP 2-4 hours	25-50 SQ 2-3 hours		10-20 SQ/IM 2-3 hours	20 SQ/IM 2-3 hours	
Pentazocine	10 SQ 2-4 hours	10 SQ 2-4 hours				
Fentanyl patch						25 ug/hour patch for up to 72 hours
Meloxicam	5-10 IM	2 SQ or IM				
Flunixin	2 SQ	1.1-2.5 IM				
Ketoprofen	2-5 SQ	2-5 SQ				

It should be noted that non-pharmacologic control of pain is often effective; the attending veterinarians should be able to provide you with information regarding these options.

## 2. Euthanasia

Euthanasia is derived from the Greek terms “eu” meaning good, and “thantos” meaning death. The term is used to describe the ending of the life of an animal in a way that minimizes or eliminates pain and distress. Unless a deviation is justified for scientific or medical reasons, methods must be consistent with the 2013 AVMA Euthanasia Guidelines (<https://www.avma.org/kb/policies/documents/euthanasia.pdf>). In evaluating the appropriateness of methods, some of the criteria that should be considered are: the ability to induce loss of consciousness and death with no or only momentary pain, distress, or anxiety; reliability; non-reversibility; the time required to induce unconsciousness; species and age limitations; compatibility with research objectives; and the safety and emotional effects on personnel.

Euthanasia might be necessary at the end of a protocol or as a means to relieve pain or distress that cannot be alleviated by analgesics, sedatives, or other treatments. Protocols should include criteria for initiating euthanasia, such as degree of a physical or behavioral deficit or tumor size that will enable a prompt decision to be made by the veterinarian and the investigator to ensure that the end point is humane and the objective of the protocol is achieved.

Unacceptable methods of euthanasia include: air embolism, blow to the head, burning, chloral hydrate (unacceptable in dogs, cats, and small mammals), chloroform, cyanide, decompression, drowning, exsanguinations (unless performed under general anesthesia), direct immersion into formalin, household products and solvents, hypothermia, neuromuscular blocking agents, rapid freezing (unless anesthetized), strychnine, and stunning.

The CCM facilities have EuthanEx Rodent Euthanasia Smartbox Auto CO<sub>2</sub> Systems for research staff use – specifically for mice and rats. They are CCM-modified rodent cage tops outfitted with tubing to deliver CO<sub>2</sub> regulated by a pre-set flow meter. The regulators are on timers and all levels are set by CCM staff. No adjustments should be made to the flow meters.

To perform decapitation on neonatal rodents (<7 days old), the pups must be properly restrained or anesthetized and decapitation can be done by surgical scissors or sharp blade. The PI is responsible for using appropriate instruments with adequate sharpness. For decapitation using a guillotine, CCM provides annual maintenance for sharpening and repair.

It is essential that euthanasia be performed by personnel who are skilled in methods for the species in question and that it be performed in a professional and compassionate manner. Death should be confirmed by personnel who can recognize cessation of vital signs such as heart rate and respiratory rate in the species being euthanized. Please note that death by CO<sub>2</sub> requires confirmation of death by such a visual examination and a secondary physical method should be considered (e.g., removal of vital organ [heart], pneumothorax, exsanguination, etc.). Generally acceptable methods of euthanasia for commonly laboratory species are as follows:

Species	Acceptable or Acceptable with Conditions Methods of Euthanasia (2013 AVMA Panel Guidelines)
<b>Amphibians</b>	Barbiturates, Tricaine methane sulfite, Benzocaine hydrochloride, Double pithing
<b>Cats</b>	Barbiturates, Inhalant anesthetics, Potassium chloride with general anesthesia, Carbon dioxide, Carbon monoxide
<b>Dogs</b>	Barbiturates, Inhalant anesthetics, Potassium chloride with general anesthesia, Carbon dioxide, Carbon monoxide
<b>Fish</b>	Barbiturates, Inhalant anesthetics, Tricaine methane sulfite, Benzocaine hydrochloride, 2-phenoxyethanol
<b>Nonhuman Primates</b>	Barbiturates
<b>Rabbits</b>	Barbiturates, Inhalant anesthetics, Potassium chloride with general anesthesia, Carbon dioxide, Carbon monoxide
<b>Rodents</b>	Barbiturates, Inhalant anesthetics, Potassium chloride with general anesthesia, Carbon dioxide, Carbon monoxide

### 3. Physical Restraint

Physical restraint is the use of manual or mechanical means to limit some or all of an animal's normal movement for the purpose of examination, collection of samples, drug administration, therapy, or experimental manipulation. Animals are restrained for brief periods in many research applications.

Animals can be physically restrained briefly either manually or with restraint devices. These devices should be suitable in size, design, and operation to minimize discomfort or injury to the animal. Prolonged restraint should be avoided unless it is essential for achieving research objectives and is approved by the <https://www.avma.org/kb/policies/documents/euthanasia.pdf>. Less-restrictive systems that do not limit an animal's ability to make normal postural adjustments should be used when compatible with the protocol objectives. The following are important guidelines for restraint:

- Restraint devices are not to be considered normal methods of housing
- Restraint devices should not be used simply as a convenience in handling or managing the animals.
- The period of restraint should be the minimum required to accomplish the research objectives
- Animals to be placed in restraint devices should be given training to adapt to the equipment and personnel



- Provision should be made for observation of the animal at appropriate intervals, as determined by the IACUC; and
- Veterinary care should be provided if lesions or illnesses associated with restraint are observed.

#### **4. Multiple Major Survival Surgery Procedures**

Major surgery penetrates and exposes a body cavity or produces substantial impairment of physical or physiologic function. Multiple major survival surgery procedures on a single animal are discouraged but may be permitted if scientifically justified by the user and approved by the IACUC. If multiple major survival surgery is approved, the IACUC will pay particular attention to animal well-being through continuing evaluation of outcomes. Cost savings alone is not an adequate reason for performing multiple major survival surgical procedures according to federal regulations (Animal Welfare Regulations).

The 2011 *Guide* contains recommendations for the use of aseptic techniques for rodent survival surgery. These recommendations apply to all live vertebrate animals used in research and, thus, include laboratory rats and mice as well as other rodents and vertebrates.

Surgical procedures on rodents can be done in a dedicated surgical facility or in a laboratory. If done in a laboratory, the surgery must be conducted on a clean, uncluttered lab bench or table surface in a low traffic area. The surface should be wiped with a disinfectant before and after use and covered with a clean drape. Intra-operative care should aim to maintain a near-normal state of the animal's physiology.

All people involved with a study need appropriate training to adequately perform the duties required of them. Adequate surgical training must be provided to ensure that good surgical technique is practiced including asepsis, gentle tissue handling, minimal dissection of tissue, appropriate use of instruments, effective hemostasis and suturing techniques.

#### **5. Food or Fluid Restriction**

When experimental situations require food or fluid restriction, at least minimal quantities of food and fluid should be available to provide for development of young animals and to maintain long-term well-being of all animals. Restriction for research purposes should be scientifically justified, and a program should be established to monitor physiologic or behavioral indexes, including criteria for temporary or permanent removal of an animal from the experimental protocol.

Animals on food or fluid restriction should be weighed at least once a week; more frequent weights might be needed for small animals such as rodents. The least restriction that will achieve the scientific objective should be used. In the case of conditioned-response research protocols, use of a highly preferred food or fluid as positive reinforcement, instead of restriction, is recommended.

## 6. Routine Animal Husbandry

Proper housing and management of animal facilities are essential to animal well-being, to the quality of the research data and teaching or testing programs in which animals are used, and to the health and safety of personnel. Many factors are considered when planning for adequate appropriate physical and social environment and housing of research animals. These include:

- The species, strain, and breed of the animal and individual characteristics, such as sex, age, behavior, experiences, and health
- The ability of the animals to form social groups with conspecifics through sight, smell, and possibly contact, whether the animals are maintained singly or in groups
- The design and construction of housing
- The availability or suitability of enrichments
- The project goals and experimental design
- The intensity of animal manipulation and invasiveness of the procedures to be conducted
- The presence of hazards or disease-causing materials, and
- The duration of the holding period.

Animals are housed with a goal of maximizing species-specific behaviors and minimizing stress-induced behaviors. For social species, this normally requires housing in compatible pairs or groups. The environment in which animals are maintained should be appropriate to the species, its life history, and its intended use.

An animal's space needs are complex and consideration of only the animal's body weight or surface area is insufficient. The *Guide* has recommendations regarding space for a variety of laboratory animals and are currently used as the minimum standard for CCM animal housing. CCM has guidelines/SOPs available as to what constitutes routine husbandry procedures for all species used at the health center. Any deviation from these guidelines, and the standards set forth in the *Guide*, requires scientific justification and approval from the IACUC.

## 7. Controlled Substances

Controlled substances require special handling at UConn Health. The following are requirements for controlled substance use:

Scheduled drugs must be securely locked behind 2 locked storage areas. Federal regulations promulgated by 21 CFR 1301.72 states: "... housing schedule I or II drugs .... secure building or room ... and (for) small quantities, a safe or steel cabinet .... If (the safe or cabinet) weighs less than 750 pounds, is bolted or cemented to the floor or wall in such a way that it cannot be readily removed...."

Controlled substances must be returned to CCM when expired. Federal regulations promulgated by 21 CFR 1207.21 state: "..... schedule drugs ..... (must be) disposed of by an authorized disposal agency ..."

Logsheets are needed for dispensing controlled drugs. Federal regulations promulgated by 21 CFR 291.505 state: "... accurate records traceable to specific (individuals) are maintained showing dates, quantity, and batch or code marks of the drugs dispensed. These records must be retained for a period of 3 years from the date of dispensing..."

To meet the need for researchers who don't have their own DEA license, CCM will dispense drugs for approved research use on a fee-for-service basis.

## **8. Outdated/Expired Materials**

Drugs used on laboratory animals cannot be expired. Regulations promulgated by APHIS/AC Policy #3 state: the use of expired medical materials such as pharmaceuticals “is not considered to be acceptable veterinary practice and does not constitute adequate veterinary care”. Therefore, no expired drugs, fluid replacements, or surgical/medical materials are allowed for use in animals utilized for research, testing, or teaching purposes. There are some exceptions to this requirement; please contact the IACUC office if expired or outdated materials must be used in laboratory animals.

## **9. Use of Non-Pharmaceutical Grade Compounds**

The use of non-pharmaceutical grade chemical compounds in experimental animals under certain circumstances has been, and will continue to be, a necessary and acceptable component of biomedical research. OLAW and USDA consider that the use of non-pharmaceutical grade compounds should be based on:

- scientific necessity;
- no availability of an acceptable veterinary or human pharmaceutical-grade compound;  
and
- specific review and approval by the IACUC.

Investigators and IACUCs should consider relevant animal welfare and scientific issues including safety, efficacy, and the inadvertent introduction of new variables. Cost savings alone do not adequately justify the use of non-pharmaceutical-grade compounds in animals. Although the potential animal welfare consequences of complications are less evident in non-survival studies, the scientific issues remain the same and the principles and need for professional judgment outlined above still apply. This includes the use of 2,2-tribromoethanol (Avertin).

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## V. Center for Comparative Medicine (CCM)

### 1. Contact Information

Main CCM number		x2731
Director and Attending Veterinarian	Dr. R. Chidambaram	x2248
Assistant Director	Ms. Kelly Hoyt	x2741
CCM Administrative Assistant	Ms. Linda Black	x2731
Administrative Coordinator	Ms. Susan Cohn	x2303
Animal Care Supervisor	Ms. Sara Fraize	x4075
Veterinary Services	Ms. Lisa Chuba	x4726
	Ms. Jessica Butler	x8751

If you need any additional information not found in this training manual regarding the use of animals at UCH, please contact CCM at x2731.

### 2. Animal Facility Access

Access to the CCM facilities requires that individuals have completed initial animal users training or have completed continuing training, whichever is appropriate. In addition, individuals must be enrolled in the UCH Occupational Health Surveillance (OHS) Program and be listed as an animal user on an approved animal care and use protocol. Lastly, animal users must have had a pre-animal use medical evaluation by EHS.

Once an individual has fulfilled all of these requirements, s/he must inform the CCM administrative assistant to request access to the facility by email. The Public Safety office will be notified by CCM and the individual requesting access will make arrangements to go to public safety to have a new ID badge or have a new ID badge activated with CCM access. This ID badge is your responsibility; if it is lost, CCM and Public Safety must be notified immediately. Card sharing is **NOT ALLOWED**.

This activated ID card will allow access to the CCM facility. Access to individual animal rooms is given by CCM personnel; you must contact CCM when individual room access is required. Doors to the animal rooms or main CCM facility must **NOT** be propped open.

If an individual fails to maintain their training and/or OHS requirements, access to the facility will be terminated until training and/or OHS enrollment is completed.

### 3. General CCM Facility Rules

- No food or drinks are allowed in animal rooms.
- No smoking is allowed in the animal facility.
- No children, pets, or unauthorized visitors are allowed into the animal housing facility.
  
- All animal users must follow the established traffic flow patterns:
  - 0 is the cleanest traffic flow number in the facility
  - 8 is the dirtiest traffic flow number in the facility
  - If you enter any room, you may not enter a room with a lower traffic flow number within 24 hours without showering.
  - These traffic flow numbers are posted on each animal room door

- Non-USDA regulated species may not be housed outside the facility for >24 hours unless permission to do so has been given by the IACUC.
- USDA regulated species may not be housed outside the facility for >12 hours unless permission to do so has been given by the IACUC.

#### **4. Personal Protective Equipment (PPE)**

All individuals must adhere to the person protective equipment (PPE) posted on the door of the animal room to be entered. PPE may include masks, gowns, gloves, face shields, safety glasses, bonnets, booties, and/or respirators. Open-toe shoes and shorts should not be worn in the facility.

##### Masks versus Respirators

Masks are meant to protect against splashes only in either direction. Respirators are designed to protect the respiratory system as well as protecting against splashes. Respirator use is highly recommended; however, in order to use respirators at the Health Center, an individual must fill out a respiratory questionnaire and send it to Employee Health (EHS). EHS will evaluate the responses given on the questionnaire and determine if the individual is able to use a respirator. If EHS feels the individual meets the criteria for using a respiratory, notification will be sent to the Office of Research Safety (ORS) which will contact the individual requesting the use of a respiratory to arrange for a fit test. This fit test must be performed annually.

#### **5. Animal Imports, Exports, and Quarantine**

##### Import from approved vendors

All animal orders are submitted through the Granite on-line ordering system. If any individual requires training on how to use the Topaz computer system, please contact CCM to arrange for this training. Animal orders must be placed by noon on Wednesday to be received the following week. Currently, approved vendors include Harlan, Taconic, Jackson Labs, Charles River Labs, Milbrook, Covance, Liberty, and NASCO. For any further help, please contact CCM.

##### Import from unapproved vendors

Mice are able to be imported from non-approved vendors by quarantine test and release method or by re-derivation. Animals are also allowed based on the health status for short-term experimental use. Researchers requiring mice from unapproved vendors must contact Veterinary Services and submit an Import Request Form with all necessary information.

##### Exports

Animal exports are performed when requested by the PI. Please contact Veterinary Services if you need to export animals to another institution.

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## Per Diem Rates

Current per diem rates (as of 3/1/15) are as follows:

	Mouse	Rat	Guinea pig	Hamster	Rabbit	Frog
Regular	0.72	1.14	2.00	1.75	3.00	≤ 20L= 0.25 >20L = 0.50
Quarantine	0.95	1.52				
Rederivation-internal	1.14	1.85				
Rederivation-external	1.45	2.27				
ABSL-2	1.14	1.97	2.50	2.10	4.50	
Metabolic	1.65	2.18				
Set up	3.70	3.70	4.25	4.25	5.50	≤ 20L= 3.70 >20L = 4.25

## Cage Identification

Topaz cage cards are generated by CCM for all active cages; these cage cards have a unique bar-coded number. Every cage must have a Topaz generated cage card. PIs must contact the CCM office for additional cage cards which may be needed (e.g., future weaning).

## Quarantine

Mice imported from non-approved vendors will be placed into a quarantine room. Mice imported to be re-derived will be placed in a room with restricted access to CCM personnel only. Mice for import for short-term experimental use require the approval of the Attending Veterinarian and should have an approved IACUC protocol. These mice will be placed into a room with limited access and a strict quarantine policy. Please contact Veterinary Services for information specific to your mice.

## 6. Animal Care and Notifications

### Reporting Sick Animals

If CCM personnel find a sick animal, they will place a yellow “sick report” sticker with a unique sick report number which is on a plastic transparent card placed over the cage card. The research contact person associated with that cage card will be contacted by CCM via email. Veterinary Services will work with the contact person regarding the treatment or disposition of the sick animals.

Research personnel should be aware that certain sick animals should be reported to the veterinarian if found by research staff. This includes, but is not limited to, animals that are moribund, bleeding, suffering from debilitating diarrhea, exhibiting self-induced trauma, showing ambulatory difficulties, and inability to gain access to food or water. Researchers are responsible for notifying the CCM with any unusual or unexpected morbidity and/or mortality associated with their research protocol in order to comply with the CCM Policy on Unexpected Morbidity and Mortality.

### Pregnancy and Weaning

If CCM personnel find a pregnant animal, they will place a pink “pregnancy/weaning” sticker on a plastic transparent card which is then placed over the cage card. If no dates are recorded on this sticker, the animals are pregnant. If dates are on the sticker, it will reflect the date of birth (DOB) and date of weaning (DOW). Research staff are responsible for weaning animals according to the approved IACUC Policy on Cage Density and Weaning Activities for Mice. If animals are not weaned by the research staff, CCM will wean the animals and the researchers will be charged for this service.

### Medicated Water Treatment

If the IACUC approved protocol dictates the use of medicated water, CCM will place a blue “medicated water” sticker on a plastic transparent card which is placed over the cage card. Please contact the CCM animal care supervisor if medicated water is necessary for your animals. CCM will administer the medicated water treatments and the researchers will be charged for this service.

### Malocclusion

If an animal has malocclusion, CCM will place a yellow “malocclusion” sticker on a plastic transparent card which is placed over the cage card. CCM will trim the malocclusion as necessary for the health of the animal. Researchers will be charged for this service.

### Breeding Diet / Special Food

If an animal requires a special diet, CCM will place a green “special diet” sticker on a plastic transparent card which is placed over the cage card. Please contact the CCM animal care supervisor if a breeding or special diet is necessary for your animals.

### Death Report

If CCM personnel find a dead animal, they will place an orange “death report” sticker with a unique death report number on a plastic transparent card which is placed over the cage card. Research staff will be contacted with the death report number by email. Carcasses will be placed in the necropsy refrigerator along with the death report. Researchers are responsible for notifying the IACUC with any unusual or unexpected morbidity and/or mortality associated with their research protocol in order to comply with the IACUC Policy on Unexpected Morbidity and Mortality.

## 7. Animals and Hazards

If a researcher needs to expose the animals to any biological or chemical hazards (including carcinogens, suspected carcinogens, and unknown chemicals), s/he needs to coordinate with the Biological Safety Officer (BSO) to develop a safety protocol specific to the experiment to be performed. Animals requiring ABSL-2 for biohazard containment will be housed in the biocontainment suite. Animals exposed to chemical hazards will be housed in the chemical isolation room. Veterinary Services must be given at least 3 days' notice prior to the start of the experiment. Use of hazardous agents requires that the research staff work closely with Veterinary Services and the BSO and comply with all directives throughout the course of the experiment.

### Biohazards

If animals are exposed to an infectious agent (including human cells) during the course of the experiment, an additional orange cage card will be labeled with the international biohazard symbol sticker and the safety protocol HAZ number. All cages with biohazards require a safety protocol approved by the Biological Safety Officer. Please note that this card is placed in front of the cage card.

### Carcinogens / Chemical Hazards

If animals are exposed to a potential carcinogen or chemical hazard during the course of the experiment, an additional orange cage card will be labeled with the carcinogen, suspected carcinogen, or chemical hazard sticker and the safety protocol HAZ number.

## 8. Animal Transfers

If an approved protocol has expired, and the researcher must continue to breed the animals, the cages may be transferred to the appropriate institutional animal holding protocol. Researchers must contact the Attending Veterinarian (AV) in order to do this and must provide the AV with the following information: the number of animals needing to be transferred, the species, the transgenic strain (if applicable), and the names of the research staff who will be responsible for any breeding (including genetic analysis) of the transferred animals. The AV will give this information to the IACUC office and a modification to the institutional holding protocol will be generated and approved according to established procedures. Once this modification to transfer the animals is approved, it will be approved for 3 months to allow the original PI time to write a new animal care and use protocol and have it approved by the IACUC. Animals transferred to this holding protocol will be euthanized, or otherwise disposed of, once the 3 month expiration date is reached. A PI may request a one-time 3 month extension submitted in writing to the IACUC office.

Animals may also be transferred between protocols. The PI who is supplying the animals to be transferred must inform the IACUC office ([ooacc@UCH.edu](mailto:ooacc@UCH.edu)) that the animal will be transferred to ensure that the animal is being transferred to an approved animal care and use protocol. Animals which have had experimental procedures performed may not be transferred between protocols; exceptions to this must have approval by the IACUC. In addition, any protocol which has USDA-regulated species being transferred must explicitly state that the transfer of animals is an approved animal disposition method and this may require a modification to the protocol. Researchers should contact the IACUC office if they have any questions regarding animal transfers between experimental protocols.



## 9. Cage Density Requirements for Mice

Overcrowded cages are unacceptable and are a violation of PHS Policy and do not adhere to the guidelines promulgated by the *Guide for the Care and Use of Laboratory Animals*. Researchers should maintain familiarity with the IACUC Policy on Cage Density and Weaning Activity for Mice. There is a maximum allowance of 125 grams total mouse mass per cage with few exceptions. If weaning is necessary in a cage, CCM personnel will place a "PLEASE WEAN" label on the cage and wait for approximately 24 hours for the research staff to wean the animals; after this time, CCM personnel will wean the animals and the researchers will be charged for this service. Exceptions to the cage density policy require prior approval by the IACUC.

## 10. General Animal Husbandry

- Mice and rats are housed in individually ventilated cages. When using ventilated racks, never force a cage into its slot. Please ask for help if you experience any difficulties returning a cage to its position on the rack.
- All ventilated cages are changed once every two weeks. In some cases, this may be more or less frequent depending on the sanitation of the cage (e.g., diabetic animals, breeders).
- All rodents are fed *ad libitum* with irradiated rodent diet.
- The rodent health surveillance program is performed with sentinel animals using a dirty bedding method. The sentinel animals are placed on the bottom shelf of each rack and are clearly labeled with a red transparent card. Please **DO NOT REMOVE THEM OR CHANGE THEIR POSITION ON THE RACK**. After an 8-10 week exposure, the sentinel animals are analyzed and samples are sent for serologic profile testing at Charles River Laboratories. This is done quarterly and results can be obtained from CCM Veterinary Services. If any positive results are noted, the AV will inform research staff of the testing.

## 11. Surgery Rooms and Equipment

The use of the CCM facility surgical suites and equipment are reserved on a first-come, first-served basis. Researchers will need to contact Veterinary Services to inquire about services and the availability of the surgery rooms and equipment. Researchers are charged for the use of surgical suites, equipment, and supplies.

## VI. Self-Assessment Questions

1. Which is not a function of the IACUC?
  - A. Purchase healthy animals on behalf of the investigators
  - B. Conduct reviews of the animal care and use program on a 6-month basis
  - C. Inspect the animal facilities on a 6-month basis
  - D. Review and approve animal use protocols submitted by investigators
2. The USDA AWA regulations do not currently apply to:
  - A. Non-human primates
  - B. Dogs, pigs, and sheep
  - C. Non-vertebrates, laboratory-bred mice and rats, and birds
  - D. Hamsters and gerbils
3. Which of the following institutions must follow PHS guidelines for animal research?
  - A. Those that use vertebrate animals for research, teaching, or testing
  - B. Those that use any animals for research, teaching, or testing
  - C. Those that accept USDA research funds
  - D. Those that accept PHS funding
4. Unlike the USDA AWA regulations, when applicable, PHS Policy applies to:
  - A. All animal species used in research
  - B. All animal species except mice and rats
  - C. All vertebrate species used in research
  - D. Invertebrate species used in research
5. Before making a change in your animal procedures, you must:
  - A. Be confident that the IACUC would have approved it upon review
  - B. Get approval for the change from the IACUC
  - C. Consult with the Institutional Official
  - D. Consult with the appropriate chief or dean of research
6. If procedures involving more than momentary or slight pain or distress to animals are proposed, the AWA Regulations and Standards require:
  - A. A consultation with a veterinarian in the planning stages of the animal experiments
  - B. That a veterinarian be appointed as a consultant on the project
  - C. A consultation with the IACUC chairperson in the planning stages of the experiments
  - D. That the IACUC chairperson be appointed as a consultant on the project

7. Which of the following is **not** true regarding the assurance provided by an investigator to the IACUC that alternatives to painful/distressful procedures are not available?
- A. If a database search is used, the name of the database, date of the search, time period covered, and keywords or search strategy must be given in the narrative
  - B. The assurance must be written, usually as part of the animal protocol form
  - C. All three “Rs” by Russell and Burch must be addressed, not just replacement
  - D. A report of the lab’s experience with the current technique may be used in place of an alternatives search
8. Which of the following is **true** regarding the USDA AWA Regulations and Standards and duplication of experiments?
- A. The investigator may decide if duplication is necessary
  - B. The IACUC is not allowed to decide if duplication is necessary
  - C. The institution can overrule an IACUC decision and allow a duplicative experiment
  - D. Unnecessary duplication of experiments is not allowed
9. Humane endpoint criteria describe when it is time to:
- A. Submit an updated animal protocol form
  - B. Notify the IACUC of the need for more animals to achieve statistical significance
  - C. Intervene in a study, sometimes by euthanizing the animal
  - D. Seek medical care from a veterinarian
10. Euthanasia is:
- A. The act of killing animals by methods that preserve physiologic function after death
  - B. The act of killing animals by methods that induce rapid unconsciousness and death without pain or distress
  - C. The act of killing animals for experimental purposes
  - D. The emotional state of a human or animal under distress
11. Annually, an institution must report the number of animals used by pain/distress category to:
- A. The United States Department of Agriculture (USDA)
  - B. Public Health Service (PHS)
  - C. Association for the Assessment and Accreditation of Laboratory Animal Care, International (AAALAC)
  - D. American Association for Laboratory Animal Science (AALAS)

12. Who is given institutional responsibility for deciding if an individual researcher is properly trained to perform animal procedures, as required by law?
- A. The investigator
  - B. The research technicians who perform the animal experiments
  - C. The IACUC
  - D. The institutional official in charge of the research program
13. All personnel performing animal procedures must be properly trained to do so:
- A. Before any procedures are performed
  - B. By the end of the experiments
  - C. Unless they have doctoral level or medical degrees
  - D. Unless they receive a waiver from their supervisor
14. Which statement is **false** regarding the occupational health and safety program?
- A. Risk assessment for hazards is a necessary component of the program
  - B. The program should include health care procedures
  - C. Personnel should receive training about the program
  - D. The program may be limited to employees
15. In the animal protocol form, the investigator should:
- A. Identify hazardous agents to be used in the proposed animal study
  - B. Verify that personnel are informed or enrolled in the OHSP
  - C. Assure that personnel exposure to hazardous agents will be avoided or minimized
  - D. All of the above
16. Which of the following is **false** concerning prolonged restraint of animals?
- A. It should not be considered a normal method of housing
  - B. The period of restraint should be the minimum required to achieve objectives
  - C. It can be justified as a convenience for research staff
  - D. The restraint method used should be the least restrictive possible

17. When proposing to restrict food or water for animals, which of the following is **true**?
- A. Short-term restriction is allowed without scientific justification
  - B. Restriction for periods longer than pre-surgical preparation is considered to cause pain and distress
  - C. IACUC approval is necessary only for long-term restriction
  - D. Animal monitoring procedures are necessary only for restriction periods greater than 24 hours
18. Which of the following is **true** regarding allegations of misuse or mistreatment of animals or non-compliance with federal mandates on animal welfare?
- A. Individuals should first report an allegation to the institutional official
  - B. Allegations must be investigated by the IACUC
  - C. Allegations are investigated only when made by the institution's employees
  - D. When allegations are proven true, only the institutional official can impose disciplinary procedures
19. Surgery that penetrates and exposes a body cavity of produces substantial physical impairment is described as:
- A. Minor
  - B. Major
  - C. Survival
  - D. Non-survival
20. Which of the following would not be accepted by the IACUC as the sole justification for performing multiple major survival surgeries?
- A. Cost savings
  - B. Scientific need
  - C. Conservation of rare or endangered species
  - D. Clinical need due to medical complications
21. A dedicated surgery suite must be used for which type of surgery?
- A. Non-survival surgery
  - B. Major survival surgery on rodents
  - C. Major survival surgery on non-rodent mammals
  - D. Major non-survival surgery on non-rodent vertebrates

22. Which of the following statements is **false** regarding post-operative analgesia?
- A. If a procedure is expected to cause pain in a human, it must be assumed to cause pain in an animal
  - B. If an animal does not overtly display pain following a procedure, it does not need an analgesic
  - C. A veterinarian must be consulted on the analgesic agent, dose, route, frequency, and duration of treatment
  - D. Post-operative analgesia may be initiated by the use of analgesics prior to surgery
23. Which of the following statements is **true** regarding care of an anesthetized animal during surgery?
- A. Intra-operative care does not need to be documented for USDA-covered species
  - B. Intra-operative care refers to the quality of surgical and aseptic technique
  - C. Intra-operative care should aim to maintain a near-normal state of the animal's physiology
  - D. If adequate intra-operative care is provided, vital signs monitoring can be omitted
24. Which of the following statements is **true** regarding the description of surgical complications in the protocol form?
- A. May omit describing possible surgical complications if the same surgical procedure has been performed previously without problem
  - B. May state only that all surgical complications will be referred to the veterinary staff
  - C. Can use professional qualifications to assure that surgical complications will not occur
  - D. Should describe expected surgical complications and methods of addressing each complication
25. Which of the following statements are **false** regarding controlled substances / pharmaceuticals?
- A. Controlled substances commonly used in the health center must be kept secure
  - B. Expired pharmaceuticals may be used on laboratory animals
  - C. Controlled substances must be disposed of through a federally-authorized disposal agency
  - D. Logsheets for dispensing controlled drugs must be kept for 3 years

**ANSWERS TO THESE QUESTIONS FOLLOW ON THE NEXT PAGE**

## ANSWERS

1. **A.** Purchase healthy animals on behalf of the investigators (see pp. 32-33)
2. **C.** Non-vertebrates, laboratory mice, and laboratory rats (see pp. 15)
3. **D.** Those that accept PHS funding (see p. 19)
4. **C.** All vertebrate animals used in research (see p. 19)
5. **B.** Get approval for the change from the IACUC (see p. 34)
6. **A.** A consultation with a veterinarian in the planning stages of animal experiments (see p. 7)
7. **D.** A report of the lab's experience with the current technique may be used in place of an alternatives search (see p. 5)
8. **D.** Unnecessary duplication of experiments is not allowed (see p. 5)
9. **C.** Intervene in a study, sometimes by euthanizing an animal (see pp. 5-9)
10. **B.** The act of killing animals by methods that induce rapid unconsciousness and death without pain or distress (see p. 43)
11. **A.** The United States Department of Agriculture (see p. 15)
12. **C.** The IACUC (see p. 33)
13. **A.** Before any procedures are performed (see p. 11)
14. **D.** The program may be limited to employees (see pp. 11-13)
15. **D.** All of the above (see pp. 11-13)
16. **C.** It can be justified as a convenience for the research staff (see p. 44)
17. **B.** Restriction for periods longer than pre-surgical preparation is considered to cause pain and distress (see p. 44)
18. **B.** Allegations must be investigated by the IACUC (see pp. 34-35)
19. **B.** Major (see p. 44)
20. **A.** Cost savings (see p. 44)
21. **C.** Major survival surgery on non-rodent mammals (see p. 44)
22. **B.** If an animal does not overtly display pain following a procedure, it does not need an analgesic (see p. 42)
23. **C.** Intra-operative care should aim to maintain a near-normal state of the animal's physiology (see p. 44)
24. **D.** Should describe expected surgical complications and methods of addressing each complication (see pp. 5-6)
25. **B.** Expired pharmaceuticals may be used on laboratory animals (see p. 46)

## VII. Approved IACUC Policies

The UCH IACUC currently has 43 approved policies with which researchers are expected to comply. The following is a list of these policies. All policies can be accessed from the web at <http://research.UCH.edu/animal/iacuc/policies/>.

<b>IACUC Policy</b>
Cage Identification
Code of Ethics for the Care and Use of Animals
Death as an Endpoint
Retro-Orbital Bleeding
Expired Drugs and Biomaterials in Research Involving Animals
Using DMR after FCR
Animal Transportation
Reporting Animal Welfare Concerns
Protocol Reviews
Compliance with the <i>Guide</i>
Counting Animal Use in Approved Protocol
Notification of Suspension of Protocols
Utilizing DMR for New Protocol Submission
New Protocol Submission
Collecting Samples for Genomic Analysis
Use of Complete Freund's Adjuvant (CFA)
Reporting Unusual or Unexpected Morbidity or Mortality
Training Requirements when Using USDA Regulated Species
Training New IACUC Members
Semi-Annual Program Review and Facility Inspections
Inter-Agency IACUC Reviews
Use of Tribromoethanol (Avertin)
Cage Density Control and Weaning Activity for Mice
Food Placement for Impaired Rodents
Annual Reviews and Expired Protocols
Animal Transfers to Institutional Holding Protocol
Animal Training and OHS Requirements
Animal Holding in Investigator Laboratories
Post Approval Monitoring
Animal Stabilization
Assigning Reviewers to New Protocols
Animal Transfers to Approved Protocols using USDA Species
Rodent Toe Clipping
Transgenic / Gene Targeted Animals
Rodent Tumor Production
Animal Housing and Enrichment
Expiration Dates on Drug Mixtures used in Animals



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CO <sub>2</sub> Euthanasia of Laboratory Rodents
Training Requirements when Training Performed by Lab Personnel
Modification Review and Approval
Unexpected Unavailability of Commonly Used Therapeutic Agents
Documentation of Post-Surgical/Procedure Monitoring
IACUC Membership

## VIII. Resources:

### 1. Internet resources

Animal Welfare Act	<a href="http://www.nal.usda.gov/awic/legislat/usdaleg1.htm">www.nal.usda.gov/awic/legislat/usdaleg1.htm</a>
Animal Care Regulations	<a href="http://www.aphis.usda.gov/ac/publications.html">www.aphis.usda.gov/ac/publications.html</a>
Animal Care Policy Manual	<a href="http://www.aphis.usda.gov/ac/polmanpdf.html">www.aphis.usda.gov/ac/polmanpdf.html</a>
PHS Policy	<a href="http://www.grants.nih.gov/grants/olaw/olaw.htm">www.grants.nih.gov/grants/olaw/olaw.htm</a>
2013 Report of the AVMA Panel on Euthanasia	<a href="http://www.avma.org/resources/euthanasia.pdf">www.avma.org/resources/euthanasia.pdf</a>
US Government Principles	<a href="http://www.nih.gov/grants/olaw/references/phspol.htm#USGovPrinciples">www.nih.gov/grants/olaw/references/phspol.htm#USGovPrinciples</a>
The <i>Guide</i>	<a href="http://www.nap.edu/readingroom/books/labrats/">www.nap.edu/readingroom/books/labrats/</a>
To order your own copy of the <i>Guide</i> :	send request to: <a href="mailto:OLAW@od.nih.gov">OLAW@od.nih.gov</a>
IACUC Home page	<a href="http://iacuc.UCH.edu">http://iacuc.UCH.edu</a>
CCM Home page	<a href="http://ccm.UCH.edu">http://ccm.UCH.edu</a>

### 2. Top ten actions for new animal users

As new animal users, you have a responsibility to ensure that you use laboratory animals in an appropriate and ethical manner. The [Institutional Animal Care and Use Committee \(IACUC\) office](#) is available to all animal users who have questions regarding the proper use of laboratory animals and regulations that affect the use of laboratory animals. The IACUC wants to ensure that all animal users get the information they need.

**In order to use laboratory animals here at the Health Center, *all vertebrate animal users* must do the following:**

1. Enroll in animal training. If an individual will be using live, vertebrate animals they **MUST** have animal training. This is both federal law (Animal Welfare Act, HREA of 1985, PHS Policy) and institutional policy.
2. Enroll in the occupational health surveillance program. Please take the time to read the occupational health website- it provides a wealth of information from how to enroll in the program to potential risks associated with common laboratory animal species. This is both federal law (PHS Policy) and institutional policy.
3. Familiarize yourself with the approved policies of the UCH IACUC. Everyone who works with animals is expected to comply with all IACU policies. Failure to do so may lead to the revocation of your ability to use laboratory animals.

4. Maintain your animal training documentation. Everyone who works with animals must maintain a training documentation form for procedure training received. The form can be found on the web at <http://research.uhc.edu/wp-content/uploads/sites/1137/2015/08/IACUctrainingrecordsform1.docx>.
4. Familiarize yourself with the federal regulations that govern the use of vertebrate animals. All animal users, especially Principal Investigators, should be cognizant of these regulations. Ignorance of the laws governing animal use is not an excuse to not follow these laws and policies. Violation of federal laws governing the use of live vertebrate animals is reportable to the Office of Laboratory Animal Welfare, National Institutes of Health, and the United States Department of Agriculture, and your funding agency. It is in a Principal Investigator's best interest ***not*** to allow this to happen.
5. Write and submit animal care and use applications prior to using animals. Federal laws are clear: all research involving the use of live vertebrate animals ***must be approved*** by an Institutional Animal Care and Use Committee (an IACUC). It is the responsibility of the Principal Investigator to submit an application to the IACUC. Failure to do so is a serious violation of federal law and is reportable to the Office of Laboratory Animal Welfare, National Institutes of Health, and the United States Department of Agriculture, and your funding agency. It is in a Principal Investigator's best interest ***not*** to allow this to happen.
6. Read the section on the ethics of animal use. Using animals in an ethical and responsible manner is expected at the Health Center. The issues of animals and ethics and the use of animals in biomedical research are ones that are important for all researchers and personnel who use animals to take some time to think about. It is not the intent of the IACUC to tell you how you should feel about these topics; however, it is important that information be available to the research and animal care community so that each individual can explore these topics.
7. Notify the IACUC of any ***unexpected study result(s) that impact the animals***; including any unanticipated pain and/or distress, morbidity, and mortality. It is the Principal Investigator's responsibility to do this.
8. Inform the IACUC of any animal users that will be using live, vertebrate animals. The IACUC needs to confirm that the individuals have adequate training and are enrolled in the occupational health surveillance program. Individuals must also be added to the protocol(s) they will be working on by ***submitting a modification*** to the IACUC for that protocol(s). It is the responsibility of the Principal Investigator to ensure that this is accomplished.
9. Read The IACUC Connection newsletters. New documents are posted to the website ([http://research.uhc.edu/animal/iacuc/iacuc\\_newsletter/](http://research.uhc.edu/animal/iacuc/iacuc_newsletter/)). Read the older issues that are on the website- they contain information that is helpful to you as a PI and/or animal user.
10. Read the Animal Users Training Handbook. This document, located on the web, will give you supplemental information to what was presented in the initial animal users training. We are required by federal law to provide this information.

### 3. Occupational Health Surveillance Program

In order to be compliant with both *PHS Policy on the Humane Care and Use of Laboratory Animals* and the UCH Policy on Occupational Health Surveillance Program for Principal Investigators, Researchers, Technicians, Center for Laboratory Animal Care Staff, and Students Utilizing Animals in Research or Educational Programs, you and everyone listed on your protocol as animal users **must enroll** in the UCH Occupational Health Surveillance Program for Animal Users.

It would be helpful to all animal users to perform a preliminary risk assessment prior to filling out the Mandatory Annual Certification of Enrollment (MACE). All you need to do is click on the species that you are using. You can find this risk assessment on the web at <http://research.uchc.edu/animal/iacuc/ohshome/risk-assessment/>.

#### In order to enroll, please:

1. Ensure you have a UCH network account. You cannot enroll in the OHS program without it.
2. Log into a computer with your UCH network account.
3. Go to the OHS enrollment webpage at <http://research.UCH.edu/animal/iacuc/ohshome/surveillance>.
4. Complete the MACE form that is on the page and submit.

Respirators may be helpful in preventing allergies to laboratory animals. Unless directed by the Office of Research Safety that a respirator is required for a specific task, your choice to wear a respirator will be considered voluntary. If you choose to protect yourself with a respirator, you will need to review information from OSHA at the following link: [http://www.osha.gov/pls/oshaweb/owadisp.show\\_document?p\\_table=STANDARDS&p\\_id=9784](http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=9784).

You will also need to consult in EHS, or with the Biological Safety Officer (BSO), about how to do this. For respirators, medical clearance and fit testing will be required. Medical clearance for respirators is obtained through EHS. Medical clearance is separate from the OHS program and involves filling out a separate questionnaire - call ORS at 860-679-2723 to get a copy of the respirator questionnaire. Send the Respirator Questionnaire directly to EHS (MC-6210). Respirator fit testing and training is performed by the Office of Research Safety and must be done after written medical clearance is received from EHS.

Please note that ***no new protocols or annual renewal protocols will be approved until all personnel associated with these protocols are enrolled in the Occupational Health Surveillance Program for Animal Users***; therefore, please make this a priority in your laboratory.

### 4. Using recombinant DNA (rDNA) or Hazardous Materials.

The UCH is required, as a condition of both Institutional and individual PIs' funding, to comply with the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (a.k.a. *NIH Guidelines, NIH r/s NA Guidelines, nihG*). Use of r/s NA must be either registered with the Institutional Biosafety Committee (IBC) or exempted to the *NIH Guidelines*. The contact person for doing this is the IBC Coordinator, Dr. Ron Wallace ([rwallace@uchc.edu](mailto:rwallace@uchc.edu), x3781), who can also tell you if your experiment is exempt or not. Sometimes people look at experiments and because they see they are safe, they reason that they are exempt to the *NIH Guidelines*. This is not always the case. Sometimes safe experiments are not exempt.

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Your IACUC protocol will be reviewed for human occupational health, safety, and compliance issues by the IBC Coordinator, who is also the Biological Safety Officer (BSO). Those protocols that have human occupational health, safety and/or compliance issues must be approved by the BSO before the IACUC will grant approval. These issues will mainly be for *in vivo* experiments, which are the purview of the IACUC. Occasionally, *in vivo* issues transfer into the lab for *in vitro* analysis. Those *in vitro* issues that originate *in vivo* will also be addressed by the BSO. You will be notified by the IACUC after the Committee meeting if such issues exist in your protocol and asked to contact the BSO with information, clarifications, to fill out an application for the IBC, or to fill out an IACUC Animal Safety Protocol. Please note that the IBC is a separate committee from the IACUC. It is possible that you will be asked to fill out both forms for the Animal safety protocol and for IBC registration. There has been confusion, because the BSO collaborates with PIs or designees on both documents, that after the BSO was encountered once, all of the requirements had been met. Please see that all of the requirements listed by the IACUC in its review are addressed by their respective committees. In order to be in compliance, fiscal packages for grants will not be set up without all approvals indicated on the routing sheet and research with r/s NA must not start without IBC approval and research with animals must not start without IACUC approval.

The following is a partial list of experiments typical to IACUC protocols and modifications and their exempt or non-exempt status in the *NIH Guidelines*. Even if you know that your experiment is exempt, please document how this is true in your IACUC protocol to avoid being contacted by the BSO for verification and documentation.

<b>Description of Experiment or Procedure</b>	<b>Needs IBC Registration</b>	<b>niHG Exempt</b>	<b>Notes for IACUC Protocol</b>
Transgenic (Tg) or Gene Targeted (GT) rodents will be constructed for you in the GTTF at UCH.	X		Please make a table of all of your Tg/GT strains and indicate where they were constructed or from where acquired.
Tg or GT rodents will be acquired from a <i>domestic</i> institution or vendor.		X	Please make a table of all of your Tg/GT strains and indicate where they were constructed or from where acquired.
Tg or GT rodents will be imported from outside the US.	X		Please make a table of all of your Tg/GT strains and indicate where they were constructed or from where acquired.
You will construct your own Tg or GT rodent strains.	X		Please make a table of all of your Tg/GT strains and indicate where they were constructed or from where acquired.
You will cross Tg or GT rodent strains with other strains.  *Not exempt, but in most cases your description in the IACUC	X*		Please make <i>another</i> table of all of your Tg/GT strain crosses. Please indicate if each parent was constructed using plasmids or viral vectors or if unknown. Please indicate if potentially hazardous

protocol/modification will become the IBC registration.			sequences were incorporated into either parent.
You will transfer non-infected, non-transfected, non-Tg/GT eukaryotic cells into animals. If cells are human, see table below.		X	Please state in your IACUC protocol that the transferred cells are not recombinant or infectious unless they are human.
You will introduce rDNA into animals either directly or using viral vectors.	X		Please indicate this in your IACUC protocol.
You will transfer recombinant cells (transfected by any means) or that come from a Tg/GT animal into other animals.	X		Please indicate this in your IACUC protocol.
You will infect animals with recombinant, infectious organisms or viruses.	X		Please indicate this in your IACUC protocol.
You will transfer untransfected hESC into animals. (see table below)		X	Please indicate this in your IACUC protocol. ESCRO approval is required.
You will transfer recombinant hESC (transfected by any means) into animals. (see table below)	X		Please indicate this in your IACUC protocol. ESCRO approval is required.

Exemptions for Tg/GT animals are in Section III-E-3 and Appendix C-VI in the nihG. Most of the transfer of recombinant materials into animals experiments fall under Section III-D-4 of the nihG. The requirement for registering crosses of Tg/GT animals comes from a letter of clarification from NIH/OBA.

The following is a partial list of experiments typical to an IACUC protocol that need safety documentation: either a sentence in the protocol, or an animal safety protocol (independent of an IBC registration).

<i>Description of Experiment or Procedure</i>	<i>Needs IACUC Safety Protocol?</i>	<i>Notes for IACUC Protocol</i>
Use of paraformaldehyde or formalin in perfusion or fixation (carcinogen, sensitizer). Check 'yes' for formaldehydes in the hazard section of the IACUC protocol.	No	State in IACUC protocol that you will use this in a chemical fume hood. If you cannot, please consult the BSO.

Use of anesthetic gases (isoflurane) with a chamber or other than with a vaporizer and scavenger. Check 'yes' for isoflurane in the hazard section of the IACUC protocol.	No	State in IACUC protocol that you will use this in a chemical fume hood. If you cannot, please consult the BSO.
Use of toxicologically hazardous or uncharacterized chemical compounds and toxins. Check 'yes' for hazardous chemicals in Hazards section of the IACUC protocol	Yes	Please define chemical acronyms using the full chemical name, the CAS# and/or supply the MSDS.
Use of ionizing and non-ionizing radiation producing instruments and/or radioactive materials	Possible	Please indicate whether or not you are in contact with the Office of Radiation Safety regarding this use.
Use of human or non-human primate tissues, blood or body fluids, including cultured human cell lines (e.g. hESC, HeLa, HEK 293, etc.) for transfer into animals or any other purpose.	Yes	Under the OSHA Bloodborne Pathogen Standard, Universal Precautions and/or BSL-2 containment must be used with animals that contact these materials.
Use with animals of organisms or viruses pathogenic for humans, animals or plants. This includes recombinant organisms and viruses, select agents and most viral vectors even if replication incompetent.	Yes	Please indicate the name(s) and strain(s) of the organism(s) or virus(es) and the time course of infection and clearing. You may also be required to register your lab.
Use of disease carrying vectors (arthropods, etc.)	Yes	Please specify species/strain of vectors and containment conditions.

A positive answer in both tables generally means that both requirements will need to be fulfilled. Because the IBC meets at currently non-published times, it may be more efficient to prepare the IBC registration in advance or in parallel with the IACUC protocol and IACUC Animal Safety Protocol. Please consult the biosafety web site or contact the BSO for details and answers to questions about this. In addition, if hESC are involved, please allow time for consideration by the ESCRO committee.

## 5. Contact Information

Trying to find information on:	Contact this individual:	Contact information:
<b>IACUC ADMINISTRATIVE</b>		
Animal regulations, laws, policies	Alison D. Pohl, IACUC Coordinator Marisa Evans, Research Compliance Monitor	<a href="mailto:pohl@uchc.edu">pohl@uchc.edu</a> ; <a href="mailto:maevans@uchc.edu">maevans@uchc.edu</a>
Adverse events involving animal research	Alison D. Pohl, IACUC Coordinator Marisa Evans, Research Compliance Monitor	<a href="mailto:pohl@uchc.edu">pohl@uchc.edu</a> ; <a href="mailto:maevans@uchc.edu">maevans@uchc.edu</a>
Information regarding your protocol	Alison D. Pohl, IACUC Coordinator Marisa Evans, Research Compliance Monitor	<a href="mailto:pohl@uchc.edu">pohl@uchc.edu</a> ; <a href="mailto:maevans@uchc.edu">maevans@uchc.edu</a>
Animal training class registration	Alison D. Pohl, IACUC Coordinator Marisa Evans, Research Compliance Monitor	<a href="mailto:pohl@uchc.edu">pohl@uchc.edu</a> <a href="mailto:maevans@uchc.edu">maevans@uchc.edu</a> <a href="mailto:ooacc@uchc.edu">ooacc@uchc.edu</a>
Occupational Health Surveillance	Marisa Evans, Research Compliance Monitor Marc Croteau, M.D., Director Occupational Med	<a href="mailto:pohl@uchc.edu">pohl@uchc.edu</a> <a href="mailto:croteau@uchc.edu">croteau@uchc.edu</a>
<b>SAFETY/COMPLIANCE ADMINISTRATIVE</b>		
IACUC Safety Protocols for Chemical, Infectious, Bloodborne Pathogens Issues	Ron Wallace, Biosafety Officer See section 4, Using rDNA and Hazardous Materials, above.	<a href="mailto:rwallace@uchc.edu">rwallace@uchc.edu</a>
IACUC Safety Protocols for Chemicals	Dan Sasso, Chemical Safety Officer	<a href="mailto:sasso@uchc.edu">sasso@uchc.edu</a>
R/S NA use	Ron Wallace, Biosafety Officer	<a href="mailto:rwallace@uchc.edu">rwallace@uchc.edu</a>
Biosafety issues	Ron Wallace, Biosafety Officer	<a href="mailto:rwallace@uchc.edu">rwallace@uchc.edu</a>
Institutional Biosafety Committee	Ron Wallace, IBC Coordinator	<a href="mailto:rwallace@uchc.edu">rwallace@uchc.edu</a>
CT Dept. Public Hlth. registration	Ron Wallace, Biosafety Officer	<a href="mailto:rwallace@uchc.edu">rwallace@uchc.edu</a>
Select Agents program	Ron Wallace, Biosafety Officer	<a href="mailto:rwallace@uchc.edu">rwallace@uchc.edu</a>
Radiation / Radioactive materials	James Fomenko, RSO	<a href="mailto:fomenko@uchc.edu">fomenko@uchc.edu</a>



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Laser Safety	James Fomenko, RSO	<a href="mailto:fomenko@uchc.edu">fomenko@uchc.edu</a>
Blood Borne Pathogens	Steve Jacobs, Asst. Director EH&S Ron Wallace, Biosafety Officer	<a href="mailto:Jacobs@uchc.edu">Jacobs@uchc.edu</a> <a href="mailto:rwallace@uchc.edu">rwallace@uchc.edu</a>
Chemical hazards	Steve Jacobs, Asst. Director EH&S	<a href="mailto:Jacobs@uchc.edu">Jacobs@uchc.edu</a> ; x2723
Hazardous waste	Steve Jacobs, Asst. Director EH&S	<a href="mailto:Jacobs@uchc.edu">Jacobs@uchc.edu</a> ; x2723
Shipping hazardous materials	James Fomenko, RSO Ron Wallace, Biosafety Officer	<a href="mailto:fomenko@uchc.edu">fomenko@uchc.edu</a> <a href="mailto:rwallace@uchc.edu">rwallace@uchc.edu</a>
Respiratory fit testing	All members of EH&S	ORS office: 860-679-2723
<b>URGENT ISSUES</b>		
Chemical/Biological <b>Spills/ Exposures</b> in CCM <b>controllable</b> by personnel present	Director CCM & PI of Protocol; for exposures, EHS or JDH ED (off hour	x2731 EHS, OPP x2893 JDH ED hospital x2588
Chemical/Biological <b>Spills / Exposures</b> in CCM <b>NOT controllable</b> by personnel present	Contact the Office of Research Safety x2723 - Steve Jacobs and/or Ron Wallace and/or Dan Sasso; then contact those above.	ORS office: 860-679-2723
<b>EMERGENCIES</b> where <b>Fire, EMT/ Rescue, Police</b> personnel are required. Fire, Man/Woman Down	Call x7777, then contact those above.	860-679-7777 x7777
If animals appear to be sick	Veterinary services	<a href="mailto:veterinaryservices@uchc.edu">veterinaryservices@uchc.edu</a>
Problems with IACUC Safety Protocols where human <b>safety is in question</b>	Ron Wallace, Biosafety Officer	<a href="mailto:rwallace@uchc.edu">rwallace@uchc.edu</a>
Animal Welfare Issues (animal mis-treatment, neglect, etc.)	Alison D. Pohl, IACUC Coordinator R. Chidambaram, Director CCM	<a href="mailto:pohl@uchc.edu">pohl@uchc.edu</a> x2731
Animal Allergies	Marc Croteau, Director Occ Med/EHS Ron Wallace, Biosafety Officer	<a href="mailto:croteau@uchc.edu">croteau@uchc.edu</a> <a href="mailto:rwallace@uchc.edu">rwallace@uchc.edu</a>

# UConn HEALTH

Office of the Vice President for Research

<b>CCM ADMINISTRATIVE</b>		
Ordering animals	Susan Cohn, CCM Coordinator	<a href="mailto:cohn@uchc.edu">cohn@uchc.edu</a>
Problems with Animal Ordering	CCM	X2731
Imports / Exports of animals	Lisa Chuba Jessica Butler	<a href="mailto:chuaba@uchc.edu">chuaba@uchc.edu</a> <a href="mailto:jbutler@uchc.edu">jbutler@uchc.edu</a>
Give 3 days notice for setting up animals in Biocontainment or Chemical Isolation	Veterinary Services	<a href="mailto:veterinaryservices@uchc.edu">veterinaryservices@uchc.edu</a>
Procedural training with research animals	Veterinary services	<a href="mailto:veterinaryservices@uchc.edu">veterinaryservices@uchc.edu</a>
<b>NON-COMPLIANCE ISSUES</b>		
Non-compliance with IACUC protocols	Alison D. Pohl, IACUC Coordinator Joseph Lorenzo, IACUC Chair	<a href="mailto:pohl@uchc.edu">pohl@uchc.edu</a> <a href="mailto:jlorenzo@uchc.edu">jlorenzo@uchc.edu</a>
Scientific Misconduct	Wesley Byerly, Associate VP Research Compliance / IO	<a href="mailto:byerly@uchc.edu">byerly@uchc.edu</a>

## Contact Websites:

The best thing about websites is that you can usually find the information you need faster and easier than what you might think! Try these websites for information:

IACUC	<a href="http://research.uchc.edu/animal/iacuc/">http://research.uchc.edu/animal/iacuc/</a>
Center for Laboratory Animal Care	<a href="http://research.uchc.edu/animal/ccm/">http://research.uchc.edu/animal/ccm/</a>
Environmental Health & Safety	<a href="http://research.uchc.edu/rcs/ehs/">http://research.uchc.edu/rcs/ehs/</a>
Biosafety	<a href="http://research.uchc.edu/rcs/ehs/biosafety/">http://research.uchc.edu/rcs/ehs/biosafety/</a>
Chemical Safety	<a href="http://research.uchc.edu/rcs/ehs/">http://research.uchc.edu/rcs/ehs/</a>
Radiation Safety	<a href="http://research.uchc.edu/rcs/ehs/radiation-safety/">http://research.uchc.edu/rcs/ehs/radiation-safety/</a>
OHS information and enrollment form	<a href="http://research.uchc.edu/animal/iacuc/ohshome/surveillance/">http://research.uchc.edu/animal/iacuc/ohshome/surveillance/</a>
ORSP (grant information)	<a href="http://research.uchc.edu/sps-proposals/">http://research.uchc.edu/sps-proposals/</a>
Employee Health Services	<a href="http://health.uconn.edu/occupational-environmental/clinical-services/uconn-employee-health-services/">http://health.uconn.edu/occupational-environmental/clinical-services/uconn-employee-health-services/</a>

## IX. References

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3. 21 CFR Chapters 291, 1207, 1391— Controlled Substances, 2003.
4. *Public Health Service Policy on Humane Care and Use of Laboratory Animals*, Office of Laboratory Animal Welfare, 2015.
5. Animal Care Resource Guide, United States Department of Agriculture, 2000.
6. Hume, C.W. 1957. Introductory paper to UFAW Symposium on Humane Techniques in the Laboratory, May, 1957, London.
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8. Notes from “IACUC 101” attended March 28-30, 2004, Boston, Massachusetts.
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10. Silverman, J., Suckow, M. and Murphy, S. *The IACUC Handbook*, CRC Press, 2000.
11. Occupational Health and Safety in the Care and Use of Research Animals, National Research Council, 1997.
12. “Working with the IACUC: Writing an Animal Protocol”, American Association for Laboratory Animal Science, 2002.