Lifespan System-wide Policy

Subject:

Lifespan Institutional Animal Care and Use Committee (IACUC) Policy and Procedure Manual

File Under:

ORA RRC 002

Issuing Department:

Lifespan Office of Research Administration

Latest Revision Date:
November 20, 2014

Original Policy Date:

August 25, 2010

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I. **Purpose**: The purpose of this Policy and Procedure Manual is to define and describe the policies and procedures regulating the Institutional Animal Care and Use Committee (IACUC)

II. **Eligibility**: The entire research community of the Rhode Island Hospital, The Miriam Hospital, Emma Pendleton Bradley Hospital, Newport Hospital, collectively known as Lifespan for the purposes of this manual.

III. **Content**: The Manual is attached.

Section 1: Introduction

1.0 Mission Statement

Rhode Island Hospital, The Miriam Hospital, Emma Pendleton Bradley Hospital and Newport Hospital, are collectively known as "Lifespan" for the purposes of this manual. Other organizations and institutions may rely on Lifespan's IACUC, and are also included in the term "Lifespan".

Laboratory animals have played an essential role in the academic medical center setting. Their contribution to our present level of knowledge has been large, important, and indispensible. Virtually every major advance in human and veterinary medicine has depended, at some point, on studies of laboratory animals, and such studies remain essential to a deeper understanding of vital biological and behavioral processes. The decision to use animals in research requires critical thought, judgment, and analysis.

Moreover, the use of animals in research is a privilege granted by society to the research community with the expectation that such use will provide either significant new knowledge or lead to improvement in human and or animal well-being. The use of laboratory animals as subjects imposes special responsibilities on the institution, the investigator, the teacher, the student, and on all others who benefit from the knowledge and resulting advances in science. Lifespan recognizes the importance of animals in research and the scientific and ethical responsibility for their humane care and use.

In considering experimental design in laboratory animal research, researchers at Lifespan are expected to apply the principal of Russell and Burch, in that they will strive to *replace*, *refine*, or *reduce* the use of animals in their work. Replacement refers to selecting methods that avoid using animals. Refinement refers to modifications of husbandry or experimental procedures to enhance animal well/being and minimize or eliminate pain and distress. Reduction involves strategies for obtaining comparable levels of information from the use of fewer animals or for maximizing the information obtained from a given number of animals.

The research protection program for animals is a multi-tiered program involving the Vice President of Research, Executive Management, The Office of Research Administration (ORA), the Research Protection Office (RPO), the IACUC, scientific investigators and research support staff. All those involved with the use of laboratory animals are responsible for insuring the health and well-being of the animals used in research and training at Lifespan. The IACUC is responsible for overseeing the provisions for the care and well-being of animals used for research and training purposes at Lifespan and serves the public by ensuring compliance with all legal and ethical standards regarding the use of vertebrate animals in research and teaching at Lifespan.

1.1 Purpose and Scope of Manual

Lifespan will provide suitable orientation, appropriate materials, adequate resources and training to enable research faculty and staff and IACUC members to carry out their respective duties

consistent with the *Guide for the Care and Use of Laboratory Animals* (the *Guide*), the *Public Health Service Policy on Humane Care and Use of Laboratory Animals* (PHS Policy) and the *Animal Welfare Act* and the *Animal Welfare Regulations* (AWRs).

1.2 Office of Laboratory Animal Welfare (OLAW)

The Office of Laboratory Animal Welfare (OLAW) implements PHS Policy. While OLAW is located organizationally at the National Institutes of Health (NIH) in Bethesda, Maryland, OLAW's responsibility for laboratory animal welfare extends beyond NIH to all PHS-supported activities involving animals. From time to time, OLAW issues policy guidance, interpretation, or general notices regarding PHS Policy, and co-sponsors animal welfare workshops that are held in different locations across the country.

Specific OLAW responsibilities include:

- Implementation of the PHS Policy;
- Interpretation of the PHS Policy;
- Negotiation of Animal Welfare Assurances;
- Evaluation of Compliance with the PHS Policy; and
- Education of institutions and investigators receiving PHS support.

1.2.1 Animal Welfare Assurance

Before the PHS may award a grant or contract that involves the use of animals, the recipient institution and all performance sites involving or using animals must have on file with OLAW an approved Animal Welfare Assurance (Assurance). The Assurance is the cornerstone of a trust relationship between the institution and the PHS. Included in the Assurance are:

- The designation of the Institutional Official responsible for compliance;
- A commitment that the institution will comply with the PHS Policy, with the *Guide*, and with the AWA and the Animal Welfare Regulations (AWRs); and
- A description of the institution's program for animal care and use.

The PHS Policy applies to the use of live, vertebrate animals in any activity supported or conducted by the Public Health Service (PHS). PHS agencies include:

- Agency for Healthcare Research and Quality;
- Agency for Toxic Substances and Disease Registry;
- Centers for Disease Control and Prevention;
- Food and Drug Administration;
- Health Resources and Services Administration;
- Indian Health Service;
- National Institutes of Health;
- Office of Public Health and Safety;
- Office of the Secretary;

- Program Support Center;
- Substance Abuse and Mental Health Services Administration; and
- Office of the Assistant Secretary for Preparedness and Response.

Lifespan has an Animal Welfare Assurance on file with OLAW. The Animal Welfare Assurance number is A3922-01.

1.3 United States Department of Agriculture (USDA)

In 1966, Congress passed the Laboratory Animal Welfare Act (PL 89-544), and the United States Department of Agriculture (USDA) was named the responsible agency for the enforcement of 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, and 1990. The USDA's Animal and Plant Health Inspection Service (APHIS) administers the AWA, its standards, and its regulations.

1.3.1 The Animal Welfare Act

The Animal Welfare Act (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.

1.3.1.1 Inclusions

The AWA (Title 7, Chapter 54, Section 2132(g)) defines the term “animal” to mean any live or dead dog, cat, monkey (nonhuman primate mammal), guinea pig, hamster, rabbit, or such other warm-blooded animal that is being used, or is intended for use, for research, testing, experimentation, or exhibition purposes, or as a pet. With respect to a dog, the term means all dogs including those used for hunting, security, or breeding purposes.

1.3.1.2 Exemptions

The AWA (Title 7, Chapter 54, Section 2132(g)) excludes birds, rats of the genus Rattus, and mice of the genus Mus, bred for use in research, horses not used for research purposes, and other farm animals, such as, but not limited to livestock or poultry, used or intended for use as food or fiber, or livestock or poultry, used or intended for use for improving animal nutrition, breeding, management, or production efficiency, or for improving the quality of food or fiber.

1.3.1.3 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 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.

The AWA mandates that research facilities establish an Institutional Animal Care and Use Committee (IACUC) to oversee the use of animals in experiments. The IACUC is responsible for ensuring that the facility remains in compliance with the AWA and for providing documentation of all areas of compliance to the USDA/APHIS. The AWA also does not permit APHIS to interfere with research procedures or experimentation. To ensure that all licensed and registered facilities continue to comply with the AWA, 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 time frame. 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.

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.

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

The Association for Assessment and Accreditation of Laboratory Animal Care, International (AAALAC) is a private, nonprofit organization that promotes the humane treatment of animals in science through voluntary accreditation and assessment programs.

Lifespan voluntarily participates in AAALAC's program, in addition to complying with the local, state and federal laws that regulate animal research. Participating institutions receive an independent, unbiased expert assessment, and those that meet or exceed applicable standards are awarded accreditation.

Institutions choose to participate in the AAALAC accreditation program for a variety of reasons. Some use accreditation as a symbol of quality—it shows that an institution is serious about setting, achieving and maintaining high standards for animal research programs. AAALAC accreditation also promotes scientific validity. When research involves animals, reliable results depend on healthy animals and superior animal care. And perhaps most importantly,

accreditation demonstrates a willingness to go above and beyond the minimums required by law, and assures the public that the institution is committed to the responsible use and treatment of animals in science.

The institutional accreditation by AAALAC dates to May of 1970. (The original accreditation was for The Miriam Hospital; Rhode Island Hospital first received accreditation in 1996. The two were joined under the Lifespan parent organization in 1994.) AAALAC International has continued full accreditation for Lifespan's Animal Care and Use Program under file number 205.

Section 2: The Institutional Animal Care and Use Committee

2.0 Authority

Institutional Animal Care and Use Committees (IACUC's) derive their authority from the law. The Health Research Extension Act (HREA) of 1985 and the Animal Welfare Act mandate the existence of IACUC's. The laws require the Chief Executive Officer (CEO) of an organization to appoint the IACUC, whose responsibilities are delineated in the law and federal policy and regulations. The Office of Laboratory Animal Welfare (OLAW) considers the CEO to be the highest operating official of the organization. The President and CEO of Lifespan delegates authority through the Institutional Official (IO) to appoint the chair(s) and members of the IACUC.

The Senior Vice President and Chief Research Officer is the appointed IO at Lifespan. The IO is given the administrative and operational authority to commit institutional resources to ensure compliance with the PHS Policy and other requirements and the IACUC reports to the IO.

The IACUC's mandate to perform semiannual program evaluations as a means of overseeing the animal care and use program puts the IACUC in an advisory role to the IO. In its semiannual reports the IACUC advises the IO of the status of the Institution's compliance, establishes plans and schedules for correcting deficiencies necessary to either maintain or achieve compliance, and makes recommendation to the IO regarding any aspect of the Institution's animal program, facilities, or personnel training.

The IACUC's authority to review and approve protocols is independent of the IO, who may not overrule an IACUC decision to withhold approval of a protocol. If the IACUC approves a protocol, however, the Institution is not required or obligated to conduct the research activity. The Institution may also subject protocols to additional institutional review (e.g., department head, Biohazards and Lab Safety Committee, etc.) for initial and de novo reviews.

Lifespan has established an Institutional Animal Care and Use Committee, which is qualified through the experience and expertise of its members to oversee the Institution's animal program, facilities, and procedures.

2.1 Committee Composition

The IACUC is composed of regular voting members, alternate voting members, and non-voting members. The IACUC may include, as necessary, non-voting members and consultants during review discussions. Some IACUC members fulfill specific regulatory requirements (e.g., veterinarian with program responsibility, an individual nonaffiliated with the Institution); others have unique roles by virtue of their position (e.g., Chair, Veterinarian, etc.)

Required categories and membership include:

Veterinarian. The PHS Policy and AWRs mandate the appointment of a veterinarian with direct

or delegated program responsibility to the IACUC. The IO may appoint more than one veterinarian to the IACUC, but the veterinarian with direct or delegated program responsibility must be designated as such. The veterinarian with program responsibility, i.e., Attending Veterinarian, must have training or experience in laboratory animal science and medicine or in the care of the species being used.

Chair. The Chair is appointed by the IO and is an active researcher with a faculty appointment at Brown University (or with significant experience).

Nonaffiliated. The nonaffiliated member(s) represent general community interests. Neither they, nor their immediate family, have an affiliation with Lifespan. These members have equal status (e.g., voting) to every other committee member and are provided the opportunity to participate in all aspects of IACUC functions.

Scientist. PHS Policy requires that the IACUC include a practicing scientist experienced in research involving animals.

Nonscientist. PHS Policy requires that the IACUC include a member whose primary concerns are in a nonscientific area. Examples include, but are not limited to, ethicist, lawyer, member of the clergy, librarian, etc.

The Institution should consider persons with expertise in the disciplines involved in institutional research and teaching programs for service on the IACUC. In addition to the required categories of membership, it is suggested that individuals with expertise in specific areas pertinent to protocol review and program oversight be considered (e.g. statisticians, occupational health experts, information resource specialists, animal health technicians, and scientific research staff).

There is no requirement that any particular member or category of members be present at all IACUC meetings. The institution, however, must have a properly constituted IACUC in order for the IACUC to conduct valid official business.

Alternate members may be appointed to the IACUC as long as they are appointed by the IO or other official with authority to appoint members, and there is a specific one-to-one designation of IACUC members and alternates. An IACUC member and his/her alternate may not count toward a quorum at the same time or act in an official member capacity at the same time. Alternates should receive training identical to the training provided to regular IACUC members.

Lifespan's IACUC meets the compositional requirements set forth in PHS Policy and USDA policies.

2.2 Conflict of Interest

Both the AWRs and PHS Policy state that no IACUC member "may participate in the IACUC review or approval of an activity in which that member has a conflicting interest, (e.g. is personally involved in the activity) except to provide information requested by the IACUC."

For a complete description of the Lifespan policy and procedure regarding the registration and management of conflicts of interest please refer to the policy, ORA GEN 003. The Project Director, Principal Investigator (PD/PI), and any other person, regardless of title or position, who is **responsible** for the design, conduct or reporting of research that is conducted at Lifespan must report on their status of conflicts of interest at least annually. The Principal Investigators of each project are responsible for determining which people (e.g., co-investigators, collaborators, staff, trainees, consultants, etc.) meet the definition of "investigator" and are responsible for the filing of conflict of interest disclosures for each person. The Prinicpal Investigators are also responsible for ensuring that all members of the research team have completed the required COI training.

When they have reviewed a disclosure that may impact the review of a protocol by the IACUC, the Lifespan Research Conflicts of Interest Committee promptly communicates to the IACUC in writing. The IACUC may participate in the development of a management plan of the conflict, if appropriate. In no case may research proceed on a project until the disclosed conflict is reviewed and resolved by the Lifespan Research Conflicts of Interest Committee.

For additional guidance, Lifespan's Corporate Compliance Policy #46, "Interaction with Industry Representatives (Pharmaceutical, Medical, Device and Medical Supply Industries)", Lifespan's Corporate Compliance Policy #09, "Conflicts of Interest" and Lifespan's Materials Management Policy #150, "Institutional Purchasing: Conflict of Interest Guidelines" further describe Lifespan's position on conflicts of interest.

An IACUC member may also have professional or personal conflicts of interest. An IACUC member is said to have a conflict of interest whenever that person, his or her spouse/partner, or dependent child falls under any one of the above conditions, or:

- Is an investigator or sub-investigator on the protocol.
- Is involved in a potentially competing research program.
- Access to funding or intellectual information may provide an unfair competitive advantage.
- A member's personal biases may interfere with his or her impartial judgment.
- Has identified him or herself for any other reason as having a conflict of interest.

IACUC members and consultants will not participate in any IACUC action taken, including the initial and continuing review of any project, in which the member has a conflict of interest, except to provide information requested by the IACUC. IACUC members are expected to self-identify conflicts of interest on the COI form prepared for each full board meeting.

If an investigator submitting a protocol believes that an IACUC member has a potential conflict, the investigator may request that the member be excluded. The Chair (or in his/her absence, the Vice Chair) will present the declared conflict and the Committee will determine whether a conflict exists. Should an IACUC member declare involvement in any way in a research protocol

under review by the IACUC, or state a conflict of interest with the research protocol, then the member(s):

- Decline to serve as a primary reviewer of the application
- May remain in the meeting room to provide information requested by the IACUC;
- Leave the meeting room for discussion and voting; and
- Are not counted towards quorum.

2.3 Confidentiality

During the process of initial or continuing review of an activity (including, but not limited to, any annual reviews or protocol amendments), material provided to the Institutional Animal Care and Use Committee and the Research Protection Office (RPO, administrative office that supports the IACUC) shall be considered privileged information, and the IACUC shall assure the confidentiality of the data contained therein.

2.4 Quorum Requirements

Certain official IACUC actions require a quorum: full committee review of a research project (Policy IV.C.2. and AWR §2.31(d)(2)) and suspension of an activity (Policy IV.C.6. and AWR §2.31(d)(6)).

Lifespan defines a "quorum" as more than half of the regular IACUC voting members.

A protocol is approved only if a quorum is present, and if more than 50% of the attending members vote in favor of protocol approval. For reasons other than conflict of interest, abstentions from voting do not alter the quorum or change the number of votes required. For example: If the IACUC has 19 voting members, at least 10 members must be present at a convened meeting to constitute a quorum and approval of a protocol would require a minimum of six of those 10 votes whether or not there were abstentions.

2.5 Functions of the IACUC

The Institutional Animal Care and Use Committee (IACUC) will:

1. Review at least once every six months Lifespan's program for humane care and use of animals, using the Guide as a basis for evaluation. The IACUC procedures for conducting semiannual program reviews are described in Section 7.1

2. Inspect at least once every six months all of Lifespan's facilities, including satellite facilities, using the "Guide" as a basis for evaluation. The IACUC procedures for conducting semiannual facility inspections are described in Section 7.2.

3. Prepare reports of the IACUC evaluations as set forth in the PHS Policy IV.B.3 and submit reports to the Institutional Official. The IACUC procedures for developing reports and submitting them to the Institutional Official are described in Section 7.3.

4. Review concerns involving the care and use of animals at Lifespan. The IACUC procedures for reviewing concerns are described in Section 8.

5. Make written recommendations to the Institutional Official regarding any aspect of the Institution's animal program, facilities, or personnel training. The procedures for making recommendations to the Institutional Official are described in Section 2.8.

6. In accord with HS Policy IV.C.1-3, the IACUC shall review and approve, require modifications in (to secure approval), or withhold approval of activities related to the care and use of animals. The IACUC procedures for protocol review are described in Section 3.

7. Review and approve, require modifications in (to secure approval), or withhold approval of proposed significant changes regarding the use of animals in ongoing activities as set forth in PHS Policy IV.C. The IACUC procedures for reviewing proposed significant changes in ongoing research or educational projects are described in Section 3.9.

8. Notify investigators and Lifespan in writing of its decision to approve or withhold approval of those activities related to the care and use of animals, or of modifications required to secure IACUC approval as set forth in the PHS Policy IV.C.4. The IACUC procedures to notify investigators and Lifespan of its decisions regarding protocol review are described in Section 3.6.4.

9. Conduct continuing review of each previously approved, ongoing activity covered by PHS Policy at appropriate intervals as determined by the IACUC, including a complete review in accordance with the PHS Policy IV.C.1-4 at least once every three years. The IACUC procedures for conducting continuing reviews are described in Section 4.

10. Be authorized to suspend an activity involving animals as set forth in the PHS Policy IV.C.6. The IACUC procedures for suspending an ongoing activity are described in Section 8.4.2.

2.6 Liability

Under PHS Policy, the primary responsibility for meeting applicable federal and state rules rests with the research facility or PHS awardee institution. The Institutional Official (IO) is the individual held responsible on behalf of the research facility for ensuring compliance. Failure to comply with PHS Policy could result in OLAW's withdrawal of approval of the institution's Animal Welfare Assurance, thereby making the institution ineligible to receive Federal funds for activities involving animals. Failure to comply with the Animal Welfare Act could result in the USDA's withdrawal of Certification and assessment of monetary fines.

2.7 Use of Electronic Mail (Email) for Official Correspondence

Electronic mail (email), like postal mail, is a mechanism for official Lifespan communication. The IACUC will exercise the right to send email communications to all laboratory animal users and the IACUC will expect that email communications will be received and read in a timely manner.

This policy applies to all researchers, staff, students, or any other person listed on an application proposal (ACUP) submitted to the IACUC for review and approval. Official communications using email can include email to a group, or an email message to only one person.

2.8 Making Recommendations to the Institutional Official

The IACUC will make written recommendations to the Institutional Official regarding any aspect of the Institution's animal program, facilities, or personnel training. The procedures for making recommendations to the Institutional Official are as follows:

1. Recommendations regarding any aspect of Lifespan's animal program, facilities or personnel training are formulated at convened meetings of the IACUC.

2. Recommendations are prepared in writing by the IACUC Coordinator, the Attending Veterinarian, the IACUC Chair (or in his/her absence, by the Vice Chair), and/or any IACUC member. A copy of these recommendations is reviewed and approved at a convened meeting of the IACUC. Any minority views are noted and included in the final report.

3. The IACUC Chair or his/her designee submits recommendations, including minority views that are approved by the IACUC to the IO.

Section 3: IACUC Review of Research Proposals

3.0 Protocol Review

The IACUC is responsible for overseeing and evaluating all aspects of animal care and use, and is charged with reviewing proposals that involve animals to ensure that the criteria established in the PHS Policy and the Animal Welfare Regulations (AWRs) are implemented. In its review of proposals, the IACUC's primary goal is to facilitate compliance with applicable laws, regulations, and policies consistent with the performance of appropriate and productive scientific endeavors.

3.1 Eligibility

This policy applies to all Lifespan Employees and all employed members of physician corporations with Administrative, Supervisory and Teaching Services Agreements (AS&T) which agree to research governance, conducting research on-site or off-site with the approval of various compliance committees. Exceptions to the eligibility criteria will be made at the level of the IO, through the use of a separate research governance agreement. In addition, the Lifespan IACUC serves as the committee of record for certain entities under inter-institutional assurance agreements. All Lifespan institutional policies regarding animal care and use apply to those other entities.

Any research project that is conducted by or under the direction of any employee or agent of the institution, in connection with his or her institutional responsibilities, requires Lifespan IACUC approval.

3.2 General Scope of Review

The following kinds of activities involving animals are subject to review by the IACUC prior to initiation:

- Activities conducted by Lifespan staff, students, or volunteers;
- Activities performed on Lifespan premises;
- Activities performed with or involving the use of facilities or equipment belonging to Lifespan.

3.3 Specific Types of Activities

3.3.1 Research

Most of the animal use proposals submitted to the Lifespan IACUC review are for biomedical research. All animals are acquired from commercial vendors, or bred on-site for specific research projects, and housed by the institution.

3.3.2 Teaching

The use of animals in educational settings is subject to IACUC review. Examples include using animals for training and educational programs for residents/fellows allowing practicing physicians to learn new techniques.

All teaching and research activity involving live vertebrate animals must have an approved animal care and use protocol. No activity shall take place without an approved protocol.

3.3.3 Research Projects in Which the Investigator is a Consultant:

In some instances, Lifespan investigators may serve in an advisory capacity for a research project conducted outside the Lifespan community. Lifespan IACUC review is required unless the investigator has a strict consulting relationship in which:

- The investigator is hired on his or her own time;
- The investigator holds no rights to the work; and
- Neither the investigator nor the institution retains any data.

Unless all three of these criteria are met, the Lifespan IACUC must review the project. Review by another institution or facility's IACUC is insufficient.

3.3.4 Research in Foreign Countries

Research conducted by Lifespan investigators in foreign countries falls under the institution's purview and guidelines. Regardless of the setting, the standards for ethical and responsible use of animals in research will not be relaxed even if different customs prevail.

All animal-based research conducted in foreign countries is subject to IACUC review. This includes the use of animals in foreign research institutions and fieldwork involving either domestic or wild animals.

Research projects must be approved by the local equivalent of an IACUC before they are initiated. Where there is no equivalent board or group, investigators must rely on local experts or community leaders to provide approval. The IACUC requires documentation of this local approval, as well as documentation of any necessary permits, before granting final approval for the project.

With regard to activities supported by PHS funds, foreign institutions that serve as performance sites must also have Assurances on file with OLAW.

3.4 Protocol Review Criteria

In order to approve proposed research projects or proposed significant changes in ongoing research projects, the IACUC shall conduct a review of those components related to the care and

use of animals and determine that the proposed research projects are in accordance with PHS Policy, AWRs, and the applicable US Government Principles. Since the PHS Policy further requires that the provisions of the Guide apply, there are many other aspects of research that the IACUC will review, such as food and water deprivation, use of noxious stimuli, and physical restraint. The Guide provides useful guidance on these and other practices.

If the IACUC does not have the scientific and technical expertise to evaluate all aspects of a proposal it may bring in outside expert consultants to provide information. Such consultants will not have a conflict of interest with the research activity and may not vote on any matters pertaining to the protocol. In all cases, the onus should be on the investigator to justify and explain his or her proposed experiments to the satisfaction of the IACUC.

3.5 Protocol Review Procedures

The IACUC reviews all animal proposals regardless of the species, source of funding, or whether they will be subjected to further review by funding sources. All new protocols and existing approved protocols that are submitted for competitive funding renewal must be reviewed by the IACUC using the Full Committee Review process described below.

If a proposed activity may cause more than momentary or slight pain or distress to animals, the AWRs specifically require investigators to consult with the Attending Veterinarian (AV) or his or her designee during protocol development.

The PHS Policy and AWRs recognize two methods of protocol review: Full Committee Review (FCR) and Designated Member Review (DMR).

3.5.1 Full Committee Review (FCR)

Full committee review is required for all new and three year *de novo* applications. Full committee review of protocols requires a convened meeting of a quorum of the IACUC. At least seven days prior to the meeting, the Office of Research Administration provides each IACUC member, including alternate and non-voting members, access to all protocols being presented.

A minimum of two members of the committee are assigned to be the primary reviewers of each application, one of whom must be a veterinarian,. The other members of the committee also review the applications as part of their responsibilities. Any member of the committee may contact the investigator prior to the meeting to request clarification and additional information. All members of the committee participate in the deliberation and decision-making process. At the conclusion of deliberation and discussion the committee members vote on protocol approval. The Committee has the authority to approve, require modifications to secure approval, disapprove, or table (defer until future meeting) any proposed activity. A simple majority vote of the members present is required for action.

The Committee has the authority to approve, require modifications in (to secure approval), disapprove, or table (defer until future meeting) any proposed activity. In cases where the Committee finds a protocol may be approvable despite the lack of substantive information, it

may vote for re-review, and approval, using the Designated Member Review (DMR) process, as described in Section 3.5.2. Approval of the change from FCR to DMR must be unanimous (of a quorum of members (Section 2.4)). All changes of FCR to DMR are recorded in the minutes. Nevertheless, any member of the IACUC may at any time request to see the revised protocol and/or request Full Committee Review of the protocol. If for any reason a designated reviewer (subsequent to FCR) needs to be replaced, an alternate member qualified to complete the review may be designated by the IACUC chairperson (or vice chair in the chair's absence). Under no circumstances will animal work be permitted to resume or begin until final approval is granted.

3.5.2. Designated Member Review (DMR)

Designated member review may be employed for continuation review (progress reports) and requests for revision to approved protocols, and re-review of protocols deemed approvable despite the lack of substantive information (3.5.1, above).

Designated member review (DMR) may be utilized only after all IACUC members have been provided the opportunity to call for full committee review. Accordingly, each IACUC member is provided with, at a minimum, a list of the proposed research protocols undergoing continuing review or a description of proposed changes to previously approved protocols prior to the review. Written descriptions of the research proposals must be made available to IACUC members upon request. Committee members are given a seven (7) day member consideration period to review the continuing review list, 1-3 days for protocol revisions. If any member requests full committee review then that the item is placed on the agenda for the next full board meeting.

Progress reports for continuation and revision requests are processed for DMR review upon receipt, but no approvals are released until the completion of the member consideration period.

The Animal Welfare Executive Committee (AWEC) serves as designated members for the of all continuation reviews (annual progress reports) and requests for revision to approved protocols. Designated member reviewers have authority to approve, require modifications to secure approval, or request full committee review. Designated member reviewers may not withhold approval. When an application, continuation review (annual progress report), or revision request is assigned to more than one designated reviewer. they must all review identical versions of the application, and, if modifications are requested by any one of the reviewers, the other reviewers must be aware of and agree to the modifications. Ultimately, the multiple reviewers must be unanimous in any decision to approve.

3.5.3 Reciprocal Administrative Review

Occasionally, Lifespan researchers will collaborate with colleagues at another institution in such a manner that no live animal work will be done by Lifespan personnel or within Lifespan facilities. Prior to initiation, such research must be reviewed and approved by the IACUC at the institution where the work will be done, as well as the Lifespan IACUC. The Lifespan IACUC will conduct Reciprocal Administrative Review using the DMR review process described above in section 3.5.2. The Executive Committee will serve as designated member reviewers for the

application and all other members will be notified by agenda, allowing the opportunity to request to review the proposal or to require full board review. The institution where the live animal work will be performed must be AAALAC accredited and must have an Assurance on file with OLAW.

3.5.4 Notification of Review Outcome

The IACUC will notify investigators and the institution in writing of its decision to approve or withhold approval of those activities related to the care and use of animals, or of modifications required to secure IACUC approval as set forth in the PHS Policy IV.C.4. The IACUC procedures to notify investigators and the institution of its decisions regarding protocol review are as follows:

- Upon completion of the review process, each Principal Investigator receives a written notification of review decisions (approved, modifications required to secure approval, approval withheld, or tabled) and whether any special monitoring provisions will be required. Records of communications are maintained within the IACUC protocol files.
- Upon completion of the review process, a copy of the meeting minutes is provided to the IO. This informs the IO of all actions taken by the IACUC.

3.6 Required Principal Investigator Certifications and Assurances

In order to submit an application to use animals to the IACUC for review, the Principal Investigator must certify the following:

- I accept responsibility for assuring that this study will be conducted in accordance with the Animal Welfare Act, the PHS Guide for the Care and Use of Laboratory Animals, and applicable federal and state laws and regulations, as well as institutional policies with regard to the humane care and protection of laboratory animals involved in this study.
- I agree to obtain written approval from the Institutional Animal Care and Use Committee prior to making any changes affecting my animal research protocol as described in this application.
- I also agree to promptly notify the committee, in writing, of any problems which may arise in the course of this study, especially adverse effects.
- I assure that all personnel who use this protocol and work with animals have received appropriate training in procedural and handling techniques.
- There are no alternatives to the use of animals to accomplish the scientific goals of this study and there are no alternatives to procedures that may cause more than momentary or slight pain or distress to the study animals other than the use of appropriate and adequate anesthesia, analgesia, or tranquilization.

Additionally, the PI must:

- Ensure that all investigators disclose any significant financial interest, or certify that they have no such "significant financial interest," when the application is submitted to the Research Protection Office for review and approval.
- Accept responsibility for the scientific conduct and design of the project and certify that they will conduct the study in the manner described in the application.
- Agree to provide the required administrative reports if the application is approved and activated.

3.7 Range of IACUC Actions

Upon review of protocols, the IACUC may take one of several different actions depending upon the findings of the committee: approval, modifications required to secure approval, or withhold approval. The IACUC may also defer or table review of a protocol. The PHS Policy and AWRs require the IACUC to notify investigators and the institution in writing of its decision to approve or withhold approval, or require modifications to secure approval of a protocol. If approval is withheld the IACUC must provide the reasons for its decision and give the investigator an opportunity to respond.

- **Approval**

  When the IACUC has determined that all review criteria, based on the PHS Policy and AWRs, have been adequately addressed by the investigator, the IACUC may approve the project, thus granting the investigator permission to perform the experiments or procedures as described.

  The IACUC-approved proposal may be subject to further appropriate review and approval by institutional officials due to financial, policy, facility, or other institutional or administrative considerations. Those officials, however, may not approve an activity if it has not been approved by the IACUC.

- **Modifications required to secure approval**

  The IACUC may require modifications to the protocol before granting approval. If the IACUC determines that a protocol is approvable contingent upon receipt of a very specific modification (e.g., receipt of assurance that the procedure will be conducted in a fume hood), or clarification of a specific point, the IACUC may handle these modifications or clarifications as administrative details that any member or the IACUC Coordinator could verify prior to granting approval.

  If a study is unusually complex or involves untried or controversial procedures the IACUC may wish to impose restrictions, (e.g., approval for the use of a limited number of animals as a pilot study with a written report of interim results, or close monitoring by veterinary or other qualified personnel). If such modifications represent significant departures, the IACUC can ask the investigator to revise the protocol to reflect the modifications imposed by the IACUC.

If the protocol is missing substantive information necessary for the IACUC to make a judgment, or the IACUC requires extensive or multiple modifications, then the IACUC can require that the protocol be revised and resubmitted. If the IACUC wishes to shift to the designated member reviewer mode for the approval of the modified protocol, that shift should be explicitly noted in the meeting minutes, and the requirements for designated review must be met.

- **Withhold approval**

  When the IACUC determines that a proposal has not adequately addressed all of the requirements of the PHS Policy and AWRs, as applicable, or the described activities represent inappropriate or unethical use of animals, the Committee may withhold approval. A designated reviewer may not withhold approval; this action may only be taken if the review is conducted using the full committee method of review.

  As indicated above, a higher institutional authority may not administratively overrule an IACUC decision to withhold approval of a proposal.

- **Defer or table review**

  If the protocol requires significant clarification in order for the IACUC to make a judgment, Committee members with certain expertise are not present, the IACUC wishes to seek external consultation, or any of a number of other reasons prevent the IACUC from conducting its review, then the IACUC may wish to defer or table review until a future FCR.

3.8 Review of Modifications to Approved Protocols

Any proposed changes to approved Animal Care and Use Protocols must be reviewed and approved by the IACUC before they occur (PHS Policy IV.C.1., and AWR §2.31[d][1]). Modifications to approved protocols are reviewed using the Designated Member Review (DMR) process described in section 3.5.2. However, changes that do not substantively alter the protocol or the care and use of animals are handled administratively (see section 3.8.3).

Designated reviewers have the authority to approve, approve after modification, or defer to the convened IACUC for deliberation. Designated reviewer comments and modifications are communicated via email. All IACUC members are notified that the proposed request for change has been processed for DMR review. As part of the notification process, changes are identified as either significant or non-significant (minor). Prior notification is not provided for administrative changes.

Any IACUC member may request full committee review within three business days for significant changes (3.8.1) and within one business day for non-significant (minor) changes (3.8.2). Members who have not responded within the notification period are considered to have consented to the DMR review (i.e. provided silent assent).

3.8.1 Significant Changes

Lifespan interprets significant changes to mean those that have the potential to impact substantially and directly on the health and well-being of the experimental animals. Significant changes are reviewed by at least two designated members, one of whom must be a veterinarian. Designated reviewers are assigned by the IACUC Coordinator, at the direction of the Chairperson.

Changes are considered to be significant when they fall into the following categories:

1. An increase in animal numbers is proposed that is greater than the figure originally approved by the IACUC for the project. For rats and mice, an increase in animal numbers greater than 10% is considered to be a significant change. (Note that any requested increase in animal numbers must be adequately justified before IACUC approval can be granted.)

2. The proposed change would add a vertebrate animal species to the protocol.

3. A survival surgical procedure is proposed to be added to a protocol which was originally approved with no surgical procedures.

4. A major survival surgical procedure is proposed to be added to an approved protocol. (A major survival surgical procedure is considered by the IACUC to be one in which a body cavity is entered or one which could cause an animal to become debilitated post-operatively.)

5. The proposed change involves scheduling of access or restriction of food and/or water other than routine restriction of food prior to surgery.

6. Changes are proposed which would move the protocol to a higher Pain Category (e.g. From Category C to D, C to E, or D to E).

7. Any proposed protocol change which would introduce prolonged restraint of animals.

8. Change of Principle Investigator.

3.8.2. Non-Significant (Minor) Changes

The Institution interprets minor changes to mean those that alter the way animals are used or handled, but do not meet the definition of significant changes as described above. Non-significant (minor) changes are reviewed by at least two designated members, one of whom must be a veterinarian. Designated reviewers are assigned by the IACUC Coordinator, at the direction of the Chairperson.

3.8.3 Administrative Changes:

The following types of changes are considered to be eligible for *administrative* designated review because they do not substantively alter the protocol or the care and use of animals:

1. Additional personnel
2. Change in commercial vendor
3. Relocation of performance site (e.g. lab move or use of a different CAF building/room)
4. Use of cadaver tissue from animals used under another approved IACUC protocol
5. Additional rodent genetic strain, providing that the health status and housing requirements remain unchanged
6. Correct errors in the Animal Care and Use Protocol (ACUP) (e.g. minor mistakes in description of dosage/route that are discovered after initial review, as agreed upon by the veterinarian)
7. Addition of a cost center

The IACUC Coordinator reviews and approves minor administrative changes and all IACUC members are notified of the revision requests post hoc, via a listing on the agenda for the following IACUC meeting. The member notification period for IACUC member comments is not required for these types of activities. Revision requests and designated reviewer comments are sent electronically by email.

3.9 Administrative Action on Termination of Reviewed (Pending/Not Yet Approved) Protocols

The IACUC has the authority to require modification(s) to requests for animal use prior to approving a protocol. To prevent the development of a collection of pending/not yet approved protocols, which results in slower service to all researchers, complicates the oversight process, and interferes with support of active research, the IACUC has established a process for protocol review and approval. The goal of the IACUC and Research Protection Office is to efficiently process protocols in an effort to provide researchers with the maximum amount of time possible to address Committee concerns and clarifications. This policy specifically addresses the duration of time at which point the IACUC will administratively inactivate an application for failure to respond to IACUC requests for further clarification and queries.

The Research Protection Office (RPO) staff will pre-review and process the proposed activity for review. The RPO staff will communicate the review status (as described in Section 3.5). Following IACUC review, RPO Staff will receive PI correspondence, when provided, and forward to the appropriate IACUC activity (full board or Designated Member Reviewer(s)).

The process for PI notification of IACUC administrative actions is as follows (counting from the day of Full-Committee Review as day 0):

Day 0-5 (Week 1): RPO staff will provide IACUC communication to Principal Investigator detailing the modifications required to secure approval, including specific IACUC clarifications, required training, etc. This correspondence will be sent by email and will include a reminder that the PI's response is due within 90 days of IACUC review.

Day 60 (Week 8): RPO staff will send a reminder notice that IACUC requested corrections and/or clarifications have not been received.

Day 90 (Week 12): If no response by the PI is received by this milestone, then the RPO staff will send an email to the PI advising them of the termination action and advising them that a new protocol must be submitted to the IACUC if they wish to pursue the proposed activity.

3.10 Minimization of Pain and Distress

In design of the research, training, or educational activities, it is the responsibility of the PI to consider and include procedures that minimize animal pain or distress.

As required by the PHS Policy and the AWRs, and reiterated in the *Guide*, the IACUC is mandated to critically evaluate research protocols to ensure that pain and distress are minimized in laboratory animals and assure that appropriate steps will be taken to enhance animal well-being. The AWRs stipulate that the IACUC determine that the principal investigator has considered alternatives to procedures that may cause more than momentary or slight pain or distress to the animal and has provided a written narrative description of the methods and sources used to determine that alternatives were not available. The *Guide* states that the IACUC should ensure the protocol addresses:

- Appropriate sedation, analgesia, and anesthesia;
- Criteria for timely intervention, removal of animals from study, or euthanasia if painful or stressful outcomes are anticipated; and
- Details of post-procedural care.

The protocol must provide adequate information for the IACUC to assess the potential animal pain and/or distress resulting from the study and the effectiveness of the pain- and distress-relieving agents proposed for use. Criteria for re-dosing the animal should also be established. The Attending Veterinarian or their alternate must be consulted for any procedure that has the potential to cause more than momentary pain or distress.

Examples of procedures which the *Guide* suggests may have the potential to cause pain or distress include:

- physical restraint,
- survival surgeries,
- food or water restriction,
- death as an endpoint,
- noxious stimuli,
- skin or corneal irritancy testing,
- tumor burdens,
- intra-cardiac or orbital sinus blood sampling, and
- abnormal environmental conditions.

3.10.1 Assessing Pain and Distress

Numerous references indicate that both laboratory animals and humans receive and process noxious stimuli using similar mechanisms. An animal's response to pain is often adaptive to reduce movement to minimize re-injury and aid recuperation. This response, however, may lead to physiological and behavioral changes which impact negatively on both the animal's well-being and the research results.

Fundamental to the relief of pain is the ability to recognize its clinical signs in various species of animals. Due to the inability of animals to verbalize, it is essential that animal care staff and researchers receive adequate training on how to recognize clinical signs of pain and distress. It is often useful to start with a general set of observations for assessing pain and distress, such as change in body weight, physical appearance/posture or changes in unprovoked and provoked behavior. The assessment system should then be modified on a case-by-case basis using specific changes that may be anticipated in a particular study.

3.10.2 Alleviation of Pain and Distress

Accepted best practices for dealing with the possibility of unrelieved pain and distress should be considered and incorporated into protocols unless there is a sound scientific rationale for deviation from those practices. The investigator must also provide an assurance that unrelieved pain will continue for only the minimum period of time necessary to attain the study objectives.

Protocol methodology should be considered that decreases the potential for pain or distress. In addition to thorough searches of the literature, this can be done through the careful use of pilot studies to determine earlier endpoints or less invasive alternatives. The veterinarian must be consulted for all such protocols and should provide guidance to investigators and the IACUC.

Pharmacologic treatment of pain or distress should be given as consistent with the type of pain/distress and the needs of the research question. Non-pharmacologic treatments should also be employed. This may include special housing considerations, dietary and other environmental enrichments, adjustments, and careful supportive care.

It is the responsibility of the investigator to show s/he has considered all the options for minimizing pain and distress that do not compromise the scientific validity of the experiment. The IACUC's deliberations regarding the management of potential pain and distress in a protocol will be documented. Personnel should be trained in pain and distress management. The IACUC should ensure that there is a mechanism in place for prompt reporting of sick animals to the veterinary staff.

3.11 Guidance Documents

From time to time, the IACUC will issue guidance documents (a.k.a., Guidelines) to the animal research community. These guidelines have been written to assist research staff and students in performing vertebrate animal procedures in a humane manner and complying with pertinent regulatory requirements. Under some circumstances deviations from these procedures may be

indicated, but such variances must be approved in advance by the IACUC.

A current list of available guidelines is available at: http://www.lifespan.org/animal-research-helpful-links.html

Section 4: Monitoring of Approved Protocols

4.0 Continuing Review: The Annual Review

Animal Welfare Regulations require an annual review of protocols. PHS Policy requires the IACUC to conduct continuing review of each previously approved, ongoing activity covered by PHS Policy at appropriate intervals as determined by the IACUC, including a complete review, in accordance with the PHS Policy IV.C.1-4, at least once every three years.

At Lifespan, regardless of the species used, the IACUC requires an annual report on the status of each protocol. In doing so, the Investigator verifies that completed activities were conducted in accordance with the approved protocol, describes any proposed departures from the approved protocols, and provides information about activities projected for the upcoming year. In addition, the number of animals used over the course of the previous protocol year is verified.

For each initial or continuing approval the IACUC will indicate an approval period with an approval expiration date specified. IACUC approval is considered to have lapsed at midnight on the expiration date of the approval. The approval date and approval expiration date are clearly noted on IACUC approval letters sent to the PI and must be strictly adhered to. Investigators should allow sufficient time for development and review of renewal submissions.

Review of a change in a protocol does not alter the date by which continuing review must occur. This is because continuing review is review of the full protocol, not simply a change to it.

The regulations make no provision for any grace period extending the conduct of research beyond the expiration date of IACUC approval. Therefore, continuing review and re-approval of research must occur by close of business of the date when IACUC approval expires.

4.0.1 Procedures for Conducting Annual Reviews

Continuing Review is accomplished by requesting the researcher to submit a completed **Progress Report**. A request for this report will be sent 90 days prior to the due date for continuing review by the IACUC. The Research Protection Office (RPO) forwards these requests based on an 11 month review process to ensure timely review and approval. Investigators must submit the following for continuing review:

- the completed progress report form
- health surveillance receipts for all listed personnel (must be completed within the past year)

The progress report form includes questions concerning the status of the protocol (active or inactive), descriptions of any proposed modifications to the protocol, assurances that no alternatives have been developed over the past year, and asks the PI to verify the number of animals used. The PI must complete the annual progress report form and return it to the RPO by the due date listed in the notification. Review of the annual Progress Report is conducted as

described in Section 3.5.2.

If no report is received by the due date, RPO staff will follow up with the investigator via email. This email will inform the investigator that failure to submit a progress report may lead to lapse of IACUC approval. If no report is received by the expiration date, RPO staff will send an expiration notice to the PI. This notice will inform the PI that all research activities must stop until IACUC approval is re-instated. It is the investigator's responsibility to ensure that the continuing review of ongoing research is approved prior to the expiration date. By federal regulation, no extension to that date can be granted. If a progress report is not received within 30 days of the expiration notice, then the project will be administratively closed by the RPO and the investigator will be required to submit a new application for IACUC review and approval at a convened meeting in order to resume the studies. Additionally, the IACUC may consider suspending (as described in Section 8.4.2) or terminating that PI's animal use privileges.

If a protocol is allowed to lapse while the associated vertebrate animals are still being housed on campus, they must be turned over to the custody of the Central Research Facility (CRF). An IACUC-approved holding protocol is present to cover such situations. The CRF Manager will make a determination (after possible consultation with the IACUC Chair and/or the IO) on whether the animals can be safely and humanely maintained temporarily by the CRF staff, or if they should instead be transferred to another study, or euthanized. When the PI has successfully obtained approval of the protocol, animals will be transferred back from the holding protocol, if possible.

4.0.2 The Purpose and Substance of Continuing Review

The purpose of continuing review is primarily threefold:

- To inform the IACUC of the current status of the project;
- To ensure continued compliance with PHS, USDA and institutional requirements; and
- To provide for re-evaluation of the animal activities at appropriate intervals.

Federal requirements, research ethics, and moral obligations of the scientific community to society demand that IACUC's conduct appropriate and meaningful reviews of ongoing animal protocols in the same responsible manner that initial reviews are done. This means that the IACUC will not "rubber stamp" a previously approved protocol during continuing review just because it has undergone a thorough initial review. In a society where use of animals in research, testing, and teaching is viewed with increasing concern, high standards of oversight must be maintained. Within the framework of federal regulations and policies, however, there is need for institutions to develop review procedures that are reasonable, meaningful, and efficient, and that do not burden the IACUC or investigators with unnecessary requirements that do not contribute directly to the welfare of the animals or provide significant information relevant to the role of the IACUC.

4.0.3 Ethical Cost-Benefit Analysis

Animal activities are most frequently justified from an ethical cost-benefit perspective. This means that any animal pain, morbidity, and mortality must be outweighed, or at least balanced, by the potential benefits of the project in terms of its relevance to human or animal health, advancement of knowledge, or the good of society. Ethical cost-benefit assessment should be a major focus during initial and continuing review by the IACUC. This assessment should not, however, be misconstrued as the equivalent of an NIH study section review of scientific merit. Instead, it represents a threshold level of review that documents that the use of animals continues to be justified. Without such assessment, there is lack of accountability, which negates the purpose of continuing review, particularly for projects not funded by the PHS or other funding agencies with rigorous peer review.

The obvious question that arises is why an ethical cost-benefit relationship would change over time. After a protocol is initially approved by the IACUC it is possible that new information may have become available, which allows application of one of the "three R's" (reduction, refinement, replacement). For example, new in vitro techniques or statistical methods may be discovered that could reduce the number of animals required. Or an investigator may find that a lesser degree of morbidity can be used as an experimental end point. Conversely, in some situations, it may be necessary for scientific reasons to increase the number of animals or to allow animals to reach a more advanced stage of morbidity than originally specified in the protocol. In either case, the ethical cost-benefit ratio will be altered, and the IACUC should, therefore, re-evaluate this new relationship. Proposed changes in the protocol can be considered during continuing review and approved as warranted. Admittedly, there are considerations related to scientific continuity and grant requirements that may dictate whether changes in a protocol are possible. Nonetheless, it is incumbent on investigators and the IACUC alike to determine during continuing review whether the 3Rs can be applied further to the protocol.

4.1 The Third-Year Resubmission: *de novo* Review

The PHS Policy requires that a complete IACUC review of PHS-supported protocols be conducted at least once every three years. This triennial review is interpreted by OLAW as a requirement for *de novo* review, meaning that the criteria and procedures for review specified in IV.C. of the PHS Policy must be applied not less than once every three years.

The three year period begins on the actual date of IACUC approval; the IACUC may not administratively extend approval beyond the three years. Since protocol approval period cannot be extended, investigators must be cognizant of the protocol approval period. To aid investigators, the Research Protection Office shall attempt to provide adequate warning of pending protocol expiration. It is the responsibility of the investigator to submit the third-year resubmission by the appropriate deadline date for a scheduled Full Committee Review (FCR) prior to protocol expiration. The IACUC requires a third year resubmission be submitted as a new proposal, using the most recent version of the de novo application form.

4.1.1 Procedures for Conducting Triennial Reviews

Ninety (90) days prior to the three-year anniversary of the animal protocol approval date, the PI is sent a notification requesting a resubmission of the protocol. The PI must resubmit the entire protocol to the RPO. A *de novo* review of the third-year resubmission is conducted as described in Section 3.5. The third-year resubmission must be approved by the IACUC before the expiration date of the original protocol. If a PI fails to submit a third-year resubmission and receive approval by the expiration date of the protocol, the following action is taken:

If a de novo application is not received by the due date, RPO staff will follow up with the investigator via email. This email will inform the investigator that failure to submit a de novo application may lead to lapse of IACUC approval. If no application is received by the expiration date, RPO staff will send an expiration notice to the PI by email within one day. This notice will inform the PI that all research activities must stop until IACUC approval is re-instated. It is the investigator's responsibility to ensure that the continuing review of ongoing research is approved prior to the expiration date. By federal regulation, no extension to that date can be granted. If a de novo application is not received within 30 days of the expiration notice, then the project will be administratively closed by the RPO.

4.2 Comparison of Protocols to Grants

Public Health Service (PHS) agencies will not make an award for research involving live vertebrate animals unless the applicant organization and all performance sites are operating in accordance with an approved Animal Welfare Assurance and have provided verification that the IACUC has reviewed and approved those sections of the application that involve use of vertebrate animals, in accordance with the requirements of the Policy. Additionally, PHS agencies will not make an award for research involving live vertebrate animals to an individual unless that individual is affiliated with an organization that accepts responsibility for compliance with the Policy and has filed the necessary assurance with OLAW.

Regardless of when the review occurs, the investigator should ensure that the research described in the grant proposal application is consistent with any corresponding protocol(s) reviewed and approved by the IACUC. Therefore, a copy of the funded or unfunded grant proposal application is required by the IACUC and reviewed to confirm that all research outlined in the grant is included in the approved IACUC protocol.

4.2.1 Verification of Protocol and Proposal Consistency

The extent of the verification of consistency between grant proposals and IACUC protocols will be a confirmation that the species and procedures relating to use of animals described in the proposal are included in the protocol. This will be a unidirectional comparison of the procedures described in the grants. In conducting the verification, the IACUC focus includes, but is not limited to, the following:

- Are the species used and number of animals requested in the grant proposal included in the IACUC protocol?

- Are animal care and use procedures described in the grant proposal included in the IACUC protocol?
- Are the specific aims in the grant consistent with those described in the IACUC application

Verification of grant and protocol consistency concentrates on animal care and use and **will not** include a judgment of scientific merit.

4.2.2 Timing of Verification

The IACUC will compare the grant to the protocol during the review of the protocol. The verification is not expected to add additional time to the review process. In addition, the IACUC will compare the grant to the protocol when a new funding source for a protocol is proposed, or when the Office of Research Administration, Grants and Contracts requests verification.

4.2.3 Protocol Amendments

There are two types of amendments to animal research protocols that have specific relevance to this policy—(1) a change in funding source and (2) a change in animal use procedures. Submission of an administrative amendment requesting a change in funding source will include a verification of consistency between the new grant and the current protocol to which it is being linked. The verification will include a confirmation that the species, procedures, and specific aims relating to use of animals described in the funding proposal are included in the IACUC approved protocol (see Section 4.2.1).

The IACUC understands that research projects evolve over time and, therefore, the specific direction of a protocol may change from the original description of animal use procedures. These changes should be submitted as a significant amendment to the protocol and should be consistent with the objectives, purpose, or aims stated in the original protocol. It is the Principal Investigator's responsibility to explain how the changes relate to the original protocol. Because the determination of consistency between the grant and original protocol has already been established, there will generally be no need to "re-verify" grant-to-protocol consistency for amendments.

For PHS-supported grants (e.g., NIH, CDC, etc.) it is the responsibility of the Principal Investigator to indicate any significant changes in the use of vertebrate animals in the Progress Report Summary section of their Non-Competing Continuation Progress Report (PHS 2590).

4.2.4 Managing Grant-Protocol Inconsistencies

The IACUC conducts the grant-to- protocol congruency check at the time of initial review and will consult with the Principal Investigator regarding any apparent inconsistency. As noted above, significant changes require that the PI notify the extramural Program Official. Verification of this request and subsequent approval must be shared with the IACUC.

4.3 Post-Approval Monitoring System (PAMs)

4.3.1 Purpose

The goal of compliance monitoring is to work with and support the Lifespan research community and to confirm accurate and consistent protocol performance in a collegial and unobtrusive manner.

Post-approval monitoring of Institutional Animal Care and Use Committee (IACUC) protocols provides assurance to regulatory agencies and to the Lifespan IACUC that animal experiments are performed in accordance with approved IACUC protocols. The Post-approval Monitoring (PAMs) Team confirms consistency and accuracy of approved protocols and practice. IACUC members will volunteer to serve as PAMs team members on a per protocol basis.

4.3.2 Protocol for Compliance Monitoring

PAMs Team Members: The members of the PAMs team will include, but may not be limited to;
Administrative Support, typically the IACUC Coordinator
A veterinarian or a staff member from Veterinary Services
Additional members may be added as needed or desired

Roles:

- PAMs Team: Will work with the investigator and laboratory staff to observe activity, prepare accurate reports, provide recommendations for maintaining compliance, and provide training opportunities.
- Investigators and Laboratory Staff: Will work with the PAMs Team to observe and confirm monitoring procedures with the approved protocol.
- Research Protection Office (RPO): Will provide operational oversight and management of the PAMs Team and the compliance monitoring program, assure the IACUC receives reports or updates on items of concern, and provide training support as required to assure compliance.

Protection Procedures Required: The PAMs Team (and other visitors) will wear the PPE prescribed for the specific activity or laboratory.

SOP Expectations: The IACUC will identify projects which require additional monitoring through the PAMs program at the time of initial review.

4.3.3 Criteria for selection of protocols for monitoring:

a) Protocols involving the use of Category E and D procedures will be monitored at the discretion of the IACUC and veterinarians.

b) The IACUC and/or veterinary personnel will determine which new investigators and new survival surgeries will be monitored within their first year.

c) A small number of active protocols may be selected at random each year for self-assessment. Principal Investigators will review their own protocol and research space for compliance using the PAMs checklist, and will report back in writing to PAMs administrative personnel. RPO staff will use standard audit methods to randomly select protocols for self-assessment.

d) The IACUC will define randomization procedures and may consider limiting duplicate visits to the same investigator within a specified time period.

e) In general, the PAMs Team or designee will schedule monitoring sessions with the Principal Investigator or other laboratory personnel in advance.

f) "For cause" monitoring as requested by the IO, IACUC and/or IACUC Chair may be conducted at any time, with or without advance notice to the Principal Investigator.

4.3.4 Process of monitoring:

a) A letter of introduction will be sent to the Principal Investigator (PI) for the project to be monitored. The PAMs Team or designee will make an appointment with the PI for a preliminary visit, followed by a site visit to the lab to observe procedures of interest. In general the first post approval process protocol review visit will be made by appointment, (non-compliance and/or follow-up visits may be or not be scheduled in advance).

b) The PAMs Team will use the "Protocol Monitoring Checklist" for the routine post approval process protocol reviews.

c) During each monitoring session, the PAMs Team will compare procedures conducted in the laboratory with those listed in the approved protocol and any approved amendments. Documented discrepancies between the procedures performed in the lab and those listed in the protocol will be brought to the attention of the Principal Investigator. Such discrepancies may include:

i) Personnel performing procedures who are not listed in the approved protocol to perform such procedures.

ii) Procedures performed in areas that are not listed in the approved protocol.

iii) Use of anesthetics, analgesics, tranquilizers, antibiotics, or other medications that are not noted in the protocol, or different from those listed in the protocol, or not used in accordance with the protocol.

iv) Procedures listed in the protocol to ensure animal welfare (e.g. post-op monitoring procedures) that are not being performed as approved in the protocol.

v) Survival surgery that is not performed aseptically.

vi) Euthanasia procedures that differ from those listed in the protocol and/or a method for ensuring euthanasia (e.g. after C02 exposure) that are not employed.

d) Other issues of concern may include:

i) Procedures performed by lab personnel who lack the necessary training to perform procedures listed in the protocol.

ii) Incomplete or unavailable supporting documentation for animal care, post-op care or other study procedures.

iii) Conditions unsafe for humans and/or animals.

iv) Use of outdated materials (drugs, suture, etc.).

v) Use of equipment (e.g. anesthetic vaporizers) that is not calibrated.

vi) Animal misuse, mistreatment, or neglect (welfare issues) of animals, or discrepancies which result in animal welfare concerns. Deliberate animal misuse, mistreatment, or neglect, or those which involve willful disregard for appropriate animal care will be immediately reported to the IACUC Chairperson for further investigation in accordance with IACUC policies.

4.3.5 Process of Sharing Information Concerning the Review:

a) The PAMs Team shall discuss monitoring results with the Principal Investigator and other lab personnel. When possible, this should be done before leaving the laboratory. The PAMs team will refer issues that pose an immediate threat to animal welfare to the Veterinary Staff and IACUC Chairperson for immediate resolution.

b) A brief summary of PAMs monitoring activity will be submitted to the IACUC.

4.3.6 Process of Follow-up:

a) The PAMs Team will follow up on any issues that require protocol modification, orientation of new personnel, or training. The PAMs Team will support the laboratory corrective action by facilitating access to the required training and / or guiding the revision of the protocol to bring it into current compliance.

b) On occasion, additional monitoring sessions may be part of the follow-up to ensure proper corrective actions.

c) In most cases, issues shall be addressed by:

i) Amending an existing protocol, or

ii) Reverting to the procedures which are already listed in the approved protocol.

4.3.7 Process of Addressing Concerns:

Investigators who disagree with monitoring results and/or recommendations may address their concerns with the IACUC at a convened meeting.

4.3.8 Record keeping:

A copy of the final compliance monitoring letter shall be kept in the protocol file.

Section 5: Training in the Humane Care and Use of Laboratory Animals

5.0 Training

Personnel working with laboratory animals in Lifespan facilities or submitting Animal Care and Use Protocols are required to attend an orientation meeting with the Veterinary Services Coordinator or a Supervisor of the Central Research Facilities (CRF). At this time, a PowerPoint Presentation will be given which includes an overview of the federal regulatory and accreditation agencies. Each person is instructed on the methods for reporting deficiencies in animal care and treatment and is provided a link to the CRF website where the CRF Policy and Procedure Manual resides. The orientation packet includes the RIH policy on human animal care and handling, general rules and procedures in the animal facilities, reference tables for typical animal species, and membership rosters for the IACUC, Biohazards and Laboratory Safety Committee, and Recombinant DNA Committee. A Lab Animal Privileges and Procedures Training Documentation Form of each person's past experience with animals is completed. This form must be easily assessable within the laboratory and updated as new training is completed. After the orientation presentation, a tour of the animal facility is given. (See also Section 5.2.1). The CRF Supervisors can be reached through the Department Secretary at 444-5788 to schedule an orientation.

In addition to one-on-one training described below, the IACUC mandates that all researchers complete the CITI Program (Collaborative Institute Training Initiative) "Working with the IACUC course". This course contains information on animal care and use legislation, IACUC function, ethics of animal use and the concepts of the Three Rs, methods for reporting concerns about animal use, etc., all of which are critical to the ethical conduct of research using animals.

Each researcher is also required to complete annual CRF training with CRF Supervisors/Veterinary Services or through an internet course with exam, accessed through CITI. Two versions of the course are available (Lifespan Annual Large Animal Training Curriculum and Lifespan Annual Rodent Training Curriculum) These training courses are available on-line through the CITI Program training consortium at www.CITIProgram.org.

The following table provides an overview of the training required for faculty and staff involved in research or training at Lifespan (or Women & Infants) that involves the use of animals or animal tissue.

	Principal Investigators		Research Staff			CAF Staff			IACUC Members
	Hands-On	**Admin(1)**	**Principal Researcher**	**Research Assistants**	**Technicians**	**Vet Supervisors**	**Vet Coordinator**	**Vet Technicians**	
CAF Orientation for New Employees	Required	Required	Required	Required	Required	Required	Required	Required	
Annual Health Surveillance	Required Annually	Required Annually	Required Annually	Required Annually	Required Annually	Required Annually	Required Annually	Required Annually	Required Annually
CITI Training Modules									
Essentials for IACUC Members									Required
Working with the IACUC	Required Every 3 years	Required Every 3 years	Required Every 3 years	Required Every 3 years	Required Every 3 years	Required Every 3 years	Required Every 3 years	Encouraged	
Annual rodent training	Users(2) Annually		Users(2) Annually	Users(2) Annually	Users(2) Annually	Required Annually	Required Annually	Required Annually	
Annual large animal training	Users(2) Annually		Users(2) Annually	Users(2) Annually	Users(2) Annually	Required Annually	Required Annually	Required Annually	
Working with Mice in Research									
Working with Rats in Research									
Working with Rabbits in									

Research									
Working with Swine in Research									
Working with Zebra Fish in Research	Users(2) required at initial review		Users(2) required at initial review	Users(2) required at initial review	Users(2) required at initial review				
Post-Procedure Care of Mice & Rats									
AAALAS Learning Library (4)									
Rodent Surgery	Users(2) required at initial review		Users(2) required at initial review	Users(2) required at initial review	Users(2) required at initial review	Required	Required	Encouraged	
Hands-On Procedural Training									
All procedures performed independently (documented on training form)	Required (3) at initial review		Required (3) at initial review	Required (3) at initial review	Required (3) at initial review	Required (3) at initial review			

Notes:

1) Administrative PIs are those who direct research or training programs, but who are not personally involved in working with animals.

2) Users are defined as anyone who is involved in direct hands-on use of animals, or supervising/training of others who are.

3) Technical proficiency must be documented on the Lifespan Animal Privileges and Procedures Training Form via signature by an expert assessor before procedures may be performed independently on live animals. Expert assessors include anyone with documented proficiency in the procedure, such as a more senior lab member (e.g. PI, senior researcher, lab manager and technician), a CAF staff member, or one of the attending veterinarians.

4) The AAALAS Library is a subscription service. Contact the CRF Main Office at 444-5788 to gain access to the Library

5.1 Who Should Receive Training?

Principal Investigators are responsible for training their staff in the procedures to be performed for each project. Documentation of training is verified during the time of IACUC review.

During IACUC review of protocols, the veterinarians discuss with established laboratory personnel any training needs for new projects, and furnish any appropriate training or arrange training by skilled Lifespan laboratory personnel. If additional training is needed from outside the laboratory, Veterinary Services coordinates any additional training which might be most effectively done by having the new individual work with skilled, established personnel from other laboratories, or personally provide any other needed guidance or training. The *Laboratory Animal Privileges and Procedures Training Documentation* Form is used to document the training of those working with animals. These are updated when the trainer feels that the trainee is qualified to do a procedure without assistance. Types of procedures and trainers' names and dates of training are identified in the forms, which are maintained in the laboratory.

Training is also provided to temporary staff, such as students, volunteers, and visiting scientists. PI's are responsible for identifying these people and assuring that appropriate training is accomplished.

5.2 Training Requirements for Lifespan Laboratory Animal Users

All Principal Investigators who are new to Lifespan, or who are conducting animal research at Lifespan for the first time, must also meet with the IACUC Chair or designee. The Chair/designee presents the ethical principles that guide the operation and deliberations of the committee. This meeting also serves as an opportunity for new Principal Investigators to learn how the IACUC functions so that there will be no unnecessary delays in initiating their research activities.

Protocols will not be approved until all active personnel listed on a protocol are current with their training and orientation. New and untrained staff must be trained before performing work independently. All researchers must maintain a current roster of personnel working on each project, including laboratory training and health surveillance records for all active personnel. Any new employees, students, or volunteers must complete the CRF Orientation. Any employees

who are new or have left the lab need to be reported to the Manager of CRF.

5.2.1 Central Research Facility (CRF) Orientation

CRF Orientation is given by the Veterinary Services Coordinator or a Supervisor of the CRF to all personnel who will interact directly or work in the vicinity of animals. This provides an orientation of the policies and procedures for animal research at Lifespan. The topics covered include:

- Contact information and organizational structure of the Central Research Facilities and other relevant research departments
- Lifespan guidelines for humane animal care and use
- IACUC functions and procedures
- Animal-related risks
- Reporting procedure for animal care and use concerns

5.3 Education and Training for IACUC Members

5.3.1 New Member Orientation

New IACUC member orientation consists of meeting with the IACUC Chair or Vice Chair and the IACUC Coordinator. New members will be orientated to the following: a description of the IACUC and responsibilities; U.S. Government Principles; criteria for membership; authority of the IACUC; protocol review process; monitoring of approved protocols, periodic review; protocol modifications; records; semiannual reviews; roles and responsibilities; and federal regulations.

The objectives of providing this information are the following:

- To introduce members to the role of the IACUC and its evolution;
- To provide the basic information necessary for IACUC members to discharge their responsibilities; and
- To provide a forum for response to, and discussion of, members' concerns and questions.

New IACUC members also complete the Essentials for IACUC Members course through the CITI Program training consortium at www.CITIProgram.org.

5.3.2 Continuing Education

Ongoing training is accomplished via the distribution of pertinent literature, protocol-related discussion of applicable sections of the Guide, PHS Policy and USDA Regulations, participation in OLAW's quarterly webinars, and periodic presentations by in-house staff. The objectives of providing ongoing training for IACUC members is to increase their knowledge, understanding, and awareness of current laws and regulations, new directives, best practice guidelines, and

institutional policies.

Funding is available for member attendance at training workshops, such as those provided by the Massachusetts Society for Medical Research (MSMR) and Public Responsibility in Medicine and Research (PRIM&R). Mandatory training for IACUC members is available on-line through the CITI Program training consortium at www.CITIProgram.org. IACUC members are required to complete the "Essentials for IACUC Members" course. Other optional modules are also available on the CITI website.

Section 6: Occupational Health Program

6.0 Personnel Occupational Health Program (POHP)

The health and safety of individuals working in animal care and use programs is an area of institutional concern. The goal of the Personnel Occupational Health Program is to prevent occupational injury and illness by avoiding, controlling, or eliminating hazards in the workplace. The emphasis of such a program is the prevention of illness and injury, but it also includes provisions for early diagnosis and treatment when necessary.

6.1 The IACUC's Responsibility for Occupational Health and Safety

It is ultimately the Principal Investigator's responsibility to see that all staff members who work with hazardous agents are first trained in their proper use. The Principal Investigator does this with the assistance of appropriate risk management personnel and committees (Biohazard and Laboratory Safety, Recombinant DNA, Radiation Safety). When respiratory protection is mandated by the IACUC, Safety Officer, or Biohazards and Lab Safety Committee, the Safety Department will provide necessary training in the use of PAPRs, respirators, and N95s. If animal care personnel are involved in biohazard precautions, the appropriate CRF Supervisor coordinates training of Central Animal Facility (CAF) individuals with the Principal Investigator.

The hospital safety officers are charged with enforcing biosafety guidelines. In general, investigators are required to follow the recommendations presented in Section IV of the Biosafety in Microbiological and Biomedical Laboratories Manual, published by the Centers for Disease Control and the National Institutes of Health. These recommendations describe four combinations of practices, safety equipment, and facilities for experiments on animals infected with or exposed to agents, which are known to or believed to produce infections in humans. These four combinations, designated Animal Biosafety levels 1-4, describe animal facilities and practices applicable to work on animals infected with agents assigned to corresponding biosafety levels 1-4. The high confinement requirements for Animal Biosafety levels 3 and 4 cannot be met at Lifespan facilities. The Safety Officer is located on the third floor of the Annex Building (phone 444-8064).

6.2 Role of the IACUC in the Occupational Health Program

All protocols proposing the use of hazardous agents in animals (other than radioactive materials) must be approved by the Lifespan and Laboratory Safety Committee (BLSC) and the IACUC for initial and de novo review. As part of its review, the BLSC stipulates the precautions and any necessary monitoring practices which will be put into place to protect personnel from hazardous materials. Projects that will utilize recombinant DNA agents are reviewed by the Lifespan Recombinant DNA Committee (RDC). The RDC specifies animal housing, manipulation and waste handling containment for such experiments. Individual Principal Investigators are licensed by the Lifespan Radiation Safety Committee for the use of particular radioisotopes; they are required to attend radiation safety training sessions in this process. The IACUC may consult with the Radiation Safety Office during protocol review about the appropriateness of precautions

and safeguards; modifications to protocols may be requested by that committee in order to secure approval. CAF Staff are informed of any approved experiments that will use biohazardous agents and are educated as to the safe handling of treated animals and their caging equipment, and disposal of soiled bedding. Laboratory staff are also invited to attend these training sessions. After protocols which will use hazardous agents in animals are approved by the IACUC, the Principal Investigator and the CRF Supervisor(s) communicate the final safety provisions to all individuals involved in the project or the care of animals.

6.3 Elements of the Occupational Health Program

During the orientation session for laboratory and animal care personnel, information about zoonoses, potential exposure to (and protection from) animal allergens, personal hygiene, and occupational health and safety is covered by the Veterinary Services Coordinator or a Supervisor of the Animal Facility. The Veterinarians discuss relevant zoonotic considerations with Principal Investigators at the time of protocol submission and there is a section on zoonoses in the manual of animal care policy and procedures. This manual is available in every laboratory using animals.

6.4 Participation in the Occupational Health Program

The Personnel Occupational Health Program (POHP) is implemented by the Employee & Occupational Health Services (EOHS) staff. Included in the program are all members of the animal care staff, all research laboratory personnel working with animals, and volunteers who work with research animals. Maintenance and housekeeping personnel entering the animal facility will be identified by EOHS who will address potential health risks to personnel that may come in contact with animals in the research environments. Newly hired personnel are interviewed by the EOHS nurses. Medical histories are established, physical examinations are performed, pre-employment evaluation for all personnel hired to work in Central Research Facilities with rats, mice, hamsters, guinea pigs and farm animals includes tuberculosis testing, tetanus immunization, and history of allergies, orthopedic problems, prior work with toxic chemicals, as well as a medical evaluation for ability to wear a respirator mask. Any staff who will work with cats, dogs, or prairie dogs would also be given the option of Rabies immunization. Yearly tuberculosis testing is offered and Influenza and Pertussis vaccination is required for all RIH personnel. Personnel injured or exposed to hazardous material in the animal facilities are sent to the EOHS for evaluation and any necessary medical attention. EOHS maintains a record of these transactions. The program includes annual health surveillance monitoring through the use of a confidential questionnaire for all research personnel, including students and volunteers. The questionnaire is reviewed by EOHS personnel. Newly hired employees complete the form at the time of pre-employment health screening. Employee & Occupational Health Services (EOHS) offices are located in the Grads Dorm on the first floor (phone 444-4038).

6.5 Occupational Health Program Education and Training

There are ethical and legal requirements to inform individuals of workplace health risks that could potentially affect them and appropriate precautions to mitigate those risks. The objectives

of Lifespan's POHP can be achieved only if employees are appropriately trained and understand the hazards associated with their work area and job duties, and how those risks are mitigated through institutional policies, engineering controls, work practices, and personal protective equipment.

All new employees are provided with information concerning OSHA's Hazard Communication Standard (Right-to-Know) during their orientation to the hospital. This orientation is conducted during the hospital's general orientation program for new employees and consists of an overview of the Standard presented via a videotape.

Department managers are responsible for expanding upon the hazardous materials information provided to employees during orientation. Managers are to provide specific training for employees on:

- Hazardous agents used in their departments
- OSHA's Hazard Communication Standard
- Interpreting Material Safety Data Sheets applicable to their work area
- How to interpret cautionary information on container labels
- How to protect themselves when using hazardous materials
- How to deal with a hazardous materials spill, accident, or other emergency
- Applicable Lifespan and departmental policies and procedures concerning hazardous materials, including proper disposal of hazardous waste

Employee's educational background and past experience are taken into consideration when developing training plans. Retraining takes place at least annually, and supplemental training takes place if new hazardous substances enter the work area. Employees are to be familiar with important concepts, understand them, and demonstrate that they know how to safely handle and use workplace chemicals.

Departmental Managers involved with hazardous materials must keep attendance records on all employees who receive training or retraining involving hazardous substances.

Section 7: Semiannual Program Review and Facility Inspections

7.0 Semiannual Reviews

The PHS Policy and Animal Welfare Regulations (AWRs) stipulate that the IACUC must review the program for humane care and use of animals at least once every six months, using the *Guide* as the basis for evaluation. Federal requirements also state that the IACUC must inspect all institutional animal facilities at least once every six months.

7.1 Program Review

The animal care and use program review includes an evaluation of institutional policies and responsibilities (lines of authority and reporting channels), IACUC membership and functions, and IACUC recordkeeping and reporting procedures. It also includes a review of the adequacy and appropriateness of the veterinary medical care program, the training program for personnel, and the occupational health and safety program.

The IACUC will review at least once every six months the institution's program for humane care and use of animals, using the *Guide* as a basis for evaluation. The IACUC procedures for conducting semiannual program reviews are as follows:

Program reviews are conducted using the using the NIH/OLAW Sample Semiannual Program Review Checklist as a guide. Sections of the checklist are covered at normally-convened meetings of the full IACUC, such that the content of the entire checklist is covered twice each year, with completions by April and October. The checklist is designed to evaluate the following:

Institutional Policies and Responsibilities

1. Animal Care and use Program
2. Disaster Planning and Emergency Preparedness
3. IACUC
4. IACUC Protocol Review-Special Considerations
5. IACUC Membership and Function
6. IACUC Training
7. IACUC Records and Reporting Requirements
8. Veterinary care
9. Personnel Qualifications and training
10. Occupational Health and Safety of Personnel
11. Personnel Safety
12. Investigating & Reporting Animal Welfare Concerns

Veterinary Care

1. Clinical Care and Management
2. Animal Procurement and transportation/Preventive Medicine
3. Surgery
4. Pain, Distress, Anesthesia and Analgesia
5. Euthanasia
6. Drug Storage and Control

Each topic is evaluated, and any deficiencies are categorized as minor or significant. All

members are invited and encouraged to participate in the program review and inspection.

Findings from the Program Review, including a Deficiency Correction Schedule (See Section 7.3), are compiled and prepared for IACUC review and discussion at a regular, convened IACUC meeting following the Program Review, usually in May and November. The IACUC Coordinator requests additional comments and minority views from all members for inclusion in the final report to the IO.

7.2 Facility Inspections

The facility inspections consist of physical inspections of all buildings, rooms, and areas where animals are used or housed. The Animal Welfare Regulations for adequate housing also apply to animal study areas where animals are maintained for more than 12 hours.

The IACUC inspects, at least once every six months, all of the institution's animal facilities, including satellite facilities, using the *Guide* as a basis for evaluation. The IACUC procedures for conducting semiannual facility inspections are as follows:

1. Every six (6) months, usually during April and October, the IACUC Coordinator organizes the inspection schedule of the animal facilities and laboratory spaces where live animals are used. These inspections are conducted using the *Guide*, the PHS Policy on Humane Care and Use of Laboratory Animals, and the AWRs as a basis for evaluation. Inspections are usually conducted within a week of the scheduled IACUC meeting for that month. Deficiencies are categorized as minor or significant. All IACUC members are invited, and encouraged, to attend the facility inspections. At a minimum, two (2) members are present for each inspection.
2. A responsible party (e.g., Principal Investigator and lab manager if applicable, hereinafter referred to as PI) is notified, of any minor or significant deficiency identified in their laboratory, facility, or designated space. Responsible parties are required to promptly provide a response to the deficiency notification.
3. Findings from the Facility Inspections, including a Deficiency Correction Schedule (see Section 7.3), are compiled by the IACUC Coordinator and prepared for IACUC review and discussion at a regular, convened IACUC meeting following the inspections, usually in May and November. The IACUC Coordinator requests additional comments and minority views from all members for inclusion in the final report to the IO.

7.2.1 Staffing and Scheduling the Facility Inspections

The IACUC must conduct inspections of facilities at least once every six months. This may be accomplished by assigning specific facilities to subcommittees, which must consist of at least two IACUC members. No IACUC member will be excluded should she or he wish to participate in an inspection. Ad hoc consultants may be used although the IACUC remains responsible for the evaluations and reports. The inspection team should have a working knowledge of the *Guide* and AWRs in order to fully evaluate the facilities that are being inspected.

7.2.2 Performing Inspections

Adherence to the following recommendations will assist the IACUC in performing inspections:

- An updated list of all facilities to be inspected will be maintained by the IACUC Coordinator.
- All proposals submitted to the IACUC will specify locations where animal procedures will be performed.
- The IACUC Coordinator will maintain a list of all facilities including room number, function of the room, and deficiencies identified during the previous inspection. Relevant sections of this list will be provided to each inspection team for the area to be visited.
- The IACUC Coordinator will maintain and provide a list of the approved protocols and animal usage for each facility/area/space to be inspected
- For satellite areas, a contact person will be provided
- Apparent deficiencies will be discussed with the person in charge of the facility to ensure that the team's perception of the situation is accurate. In some cases an apparent deviation will be due to the experiment in progress, e.g., withholding of food prior to surgery.
- The NIH/OLAW Sample Semiannual Facility Inspection Checklist will be used as a reference document.

7.3 Deficiency Correction Schedule

All deficiencies identified during the Facility Inspection and/or Program Review are designated by the IACUC as minor or significant. A significant deficiency is defined as a situation that is or may be a threat to animal health or safety. The IACUC, through the IO, is obligated to promptly report to OLAW any serious or continuing noncompliance with the PHS Policy or any serious deviation from the provisions of the *Guide* (See Section 8.5).

For both categories of deficiencies, a reasonable and specific plan and schedule with dates for correction must be included in the final report. All individuals to be involved in the corrections should be consulted to ensure that the plan is realistic. If the institution is unable to meet the plan, the IACUC, through the IO, will inform USDA/Animal and Plant Health Inspection Service (APHIS) officials within fifteen business days of the lapsed deadline (AWRs). Federally funded projects will have their relevant funding agency informed.

7.4 Documentation

A written report of the semiannual program review and facility inspection is prepared. The AWRs require the report to be signed by a majority of the IACUC members at a convened meeting. The report describes the institution's adherence to the AWRs, PHS Policy, the *Guide*, and identifies specifically any deviations from these documents. The report will indicate whether or not any minority views were filed, and minority views will be included in the final document. The report is sent to the IO and a copy of the report is kept on file for a minimum of three years in the Research Protection Office. Lifespan notifies OLAW of the dates of the semiannual program evaluations and facility inspections in the annual report to OLAW.

Section 8: Animal Welfare Concerns, Unanticipated Problems, and Non-Compliance Situations

8.0 Evaluation of Animal Care and Use Concerns

To help ensure that laboratory animals receive humane care, 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 raised by the public, employees, or anyone engaged in research at Lifespan. The Committee will review each concern in a timely and systematic manner and, when necessary, take prompt, appropriate corrective actions.

8.0.1 Definitions

Adverse Events: Events in which there is direct harm to animals or personnel

Unanticipated Problems: Not all unanticipated problems involve direct harm to animal subjects. Events can occur which are unexpected and result in new circumstances that increase the risk of harm to animals or research/support staff without directly harming them. In each case, while the event may not have caused any detectable harm or adverse effect to subjects or others, they, nevertheless, represent unanticipated problems and should be promptly reported.

NOTE: The death of an animal during transit is considered to be an unanticipated problem, which must be promptly reported to the IACUC.

Violations: Performing procedures which are not approved by the IACUC

8.1 Methods for Reporting

Personnel are required to report adverse events, unanticipated problems, and instances of suspected non-compliance with laws, rules, regulations and policies to the IACUC.

Individuals having concerns involving animal care and use within Lifespan facilities are encouraged to contact the Institutional Official, the Administrative Director, The Research Protection Office, and/or the IACUC, verbally or in writing. IACUC contact information is provided to all researchers who work with animals during their initial orientation with the Central Research Facilities (CRF) Manager. Telephone numbers for veterinary and CRF management staff are posted within each animal facility. Contact information is also posted on the IACUC webpage. Complaints may be submitted anonymously to Corporate Compliance via the Employee Response Line at 888-678-5111, or on the web at http://intra.lifespan.org/compliance/Form.htm

Although written concerns are more convenient to handle, complainants may not be willing to submit them in this manner. In such cases, the individuals who receive concerns should document them fully to ensure that the issues are clear and to prevent misunderstandings.

Lifespan will take appropriate steps to protect the confidentiality of those who report concerns as well as anyone against whom allegations are directed, while allegations are under investigation.

Lifespan policy prohibits unlawful retaliation against employees as a consequence of good faith actions in the reporting or the participation in an investigation pertaining to allegations of wrongdoing.

8.2 Procedures for the Investigation of Animal Care and Use Concerns

8.2.1 Initial Evaluation and Actions

Concerns may include situations or activities ranging from those in which animals are reported to be in immediate, actual or perceived jeopardy to those in which violations of the Animal Welfare Regulations (AWRs) or institutional Animal Welfare Assurance are alleged to be occurring but animals are not in apparent danger. They may focus on allegations of past policy and procedure violations or protocol non-compliance.

The course of action taken by the IACUC should be driven by the potential significance of the alleged situation. For example, conditions that reportedly jeopardize the health or well-being of animals should be evaluated immediately. To cope promptly with such situations, the IACUC Chairperson is authorized to halt procedures which they believe do not comply with institutional policies until the IACUC can be convened to consider the matter formally. Similarly, situations that may involve potential criminal activity or human safety will be reported promptly to hospital security or occupational health and safety officials. Allegations of other ongoing policy or procedural matters may not require such same-day attention, but should not be deferred merely as a matter of convenience. Emergency meetings may be necessary in these cases to ensure prompt consideration of concerns.

8.2.2 Complaint Assessment

Any concerns regarding the care and use of animals brought to the Committee are promptly investigated by the Chair. After initial review of the complaint, the Chair will determine whether the concern requires further investigation and immediate action, further investigation but no immediate action, or no action. If immediate action appears warranted because animal or human welfare may be compromised, the Chair will notify the IO and proceed accordingly. Veterinary medical intervention, suspension of a research activity, and/or notification of appropriate safety, occupational health, or other officials, are examples of actions that may be taken immediately to protect animal or human welfare. In accordance with the AWRs, if an activity is suspended, the IO shall report that action to USDA/APHIS and any federal agency funding that activity. If the PHS supports the activity in any way, the IACUC, through the IO, must promptly notify OLAW.

8.2.3 Investigation

If further investigation is warranted, the Chair will convene an investigative sub-committee. The Chair may enlist the aid of any IACUC member(s) for this purpose. The IACUC Chairperson

will charge the sub-committee with the requirements for information gathering and impose a completion date. The assigned completion date will depend on the IACUC's determination of whether immediate remedial action may be required. The nature of the information required will vary depending on the circumstances, but often involves:

- Interviewing complainants (if known), any persons against whom allegations were directed, and pertinent research and animal facility staff;
- Observing the animals and their environment; and
- Reviewing any pertinent records, (e.g., animal health records, protocol, and other documents).

An initial confidential interview between the concerned individual and the subcommittee is preferred; however, the individual may choose to remain anonymous to all but the contacted member. The ability to retain anonymity is obviously important in any situation where the person fears possible reprisals. The IACUC subcommittee investigates any presented concerns in the same manner, irrespective of the identity status or the degree of subsequent participation by the individual. No adverse action will be taken against any party who reports, in good faith, any violation or apparent or threatened violation.

The sub-committee will provide a report to the IACUC, which summarizes:

- The concern(s),
- The results of interview(s),
- The condition of animals and their environment, and
- The results of records and other document reviews.

The report should also contain:

- Conclusions regarding the substance of the concerns vis-à-vis requirements of the AWRs, the PHS Policy, the *Guide*, and institutional policies and procedures, and
- Recommended remediation, where appropriate.

Supporting documentation such as correspondence, reports, and animal records will be kept on file with the IACUC Coordinator for a period of three years.

The sub-committee report will be presented to the IACUC at the next meeting. The IACUC is charged by the institution as the official channel to receive, evaluate, and respond to such concerns. Reports of concerns, findings, and any corrective actions taken are made by the IACUC in writing to the Institutional Official, OLAW, USDA, and to the project Sponsor where applicable.

8.2.4 Outcomes and Final Actions

Upon receipt and evaluation of the report, the IACUC may request further information or find that

- There was no evidence to support the concern or complaint,
- The concern or complaint was not sustained, but related aspects of the animal care and use program requires further review or other institutional programs may require review, or,
- The concern or complaint was valid.

8.3 Non-Compliance with IACUC Protocol, Policies, Procedures, or Decisions

Protocol non-compliance occurs when procedures or policies approved by the IACUC are not being followed. Examples include performing unauthorized procedures, unauthorized persons participating in a research project, or injecting substances that the IACUC has not approved. When faced with protocol noncompliance, the IACUC's first step, if possible, should be to find a way to bring the protocol into compliance.

If allegations of animal misuse or protocol non-compliance are verified, the IACUC can apply sanctions. If, in the opinion of the IACUC, sanctions are not appropriate, they need not be applied. A clearly minor and unintentional misinterpretation of an IACUC policy that has created no problem for an animal is an example of where a verified allegation of protocol non-compliance might lead to an explanation, not a sanction.

8.4 Consequences of Non-Compliance

Subsequent actions of the IACUC may include:

- Implementing measures to prevent recurrence;
- Notifying the IO of its actions;
- Notifying funding or regulatory agencies, as required; and/or
- Notifying the complainant, any persons against whom allegations were directed, and appropriate supervisory and management staff such as the risk management, public relations office, institutional attorneys, etc.

8.4.1 Institutional Sanctions

Examples of institutional sanctions which may be imposed include, but are not limited to:

- counseling;
- issuing letters of reprimand;
- mandating specific training aimed at preventing future incidents;
- monitoring by the IACUC or IACUC-appointed individuals of research, testing, or training that involves animals;
- temporary suspension of privileges to provide animal care or to conduct research, testing, or training that involves animals, pending compliance with specific, IACUC-mandated conditions;
- permanent revocation of privileges to provide animal care or to conduct research, testing,

or training that involves animals; and
- recommendation to the IO that institutional (e.g., reassignment, termination of employment) sanctions be imposed.

8.4.2 Suspension of Animal Activities

The IACUC is empowered to suspend a project if it finds violations of Lifespan policy, PHS Policy, the *Guide*, Assurance, or Animal Welfare Regulations. Suspension may occur only after review of the matter at a convened meeting of a quorum of the IACUC, and a vote for suspension by a majority of the quorum present. Further, the IACUC must consult with the Institutional Official regarding the reasons for the suspension. The Institutional Official is required to take appropriate corrective action, and report the action and the circumstances surrounding the suspension to OLAW. Because an IACUC action to suspend a project is a serious matter, the action must be reported to OLAW promptly.

8.5 Reporting Requirements

Failure by research personnel to follow Federal and/or institutional regulations, guidelines, policies, and/or procedures may require reporting to the appropriate institutional, local, state, and/or Federal agencies. Violations may include, but not limited to

- Serious or continuing non-compliance with the PHS Policy; and
- Serious deviations from the *Guide for the Care and Use of Laboratory Animals*;

IACUC suspensions may also require reporting to the appropriate institutional, local, state and/or Federal agencies.

8.5.1 Principal Investigator Reporting

The Principal Investigator and protocol personnel must report any serious or continuing non-compliance with an IACUC protocol, policies, procedures, decisions, or deviations from the *Guide*. The report should be addressed to the IACUC Chairperson and e-mailed (preferred) to the IACUC Coordinator or mailed to the Research Protection Office. The self-report of non-compliance should include the following information:

- IACUC project number (CMTT#)
- the relevant grant or contract number(s);
- a full explanation of the situation, including what happened, when and where, the species of animal(s) involved, and the category of individuals involved (e.g., principal or co-principal investigator, technician, animal caretaker, student, etc.);
- a description of actions taken by the PI to address the situation; and
- a description of short- or long-term corrective plans and implementation schedule(s).

8.5.2 IACUC and IO Reporting

The IACUC, through the IO, will submit an annual report to OLAW by January 31 of each year. Lifespan's reporting period is January 1 – December 31. The report will include:

- Any change in the accreditation status of the institution (e.g. if the hospital obtains accreditation by AAALAC or AAALAC accreditation is revoked),
- Any change in the description of Lifespan's program for animal care and use as described in the Assurance, or any change in the IACUC membership. If there are no changes to report, Lifespan will provide written notification that there are no changes.
- Notification of the dates that the IACUC conducted its semiannual evaluations of the institution's program and facilities (including satellite facilities) and submitted the evaluations to the IO.

The IACUC, through the IO, will promptly provide OLAW with a full explanation of the circumstances and actions taken with respect to:

- Any serious or continuing non-compliance with PHS Policy.
- Any serious deviations from the provisions of the *Guide*.
- Any suspension of an activity by the IACUC.

All investigations by the IACUC will be reported internally at the completion of the investigation to the following individuals, as appropriate:

- Principal Investigator (PI)
- PI's Department Chair
- IACUC Chair
- Senior Vice President and Chief Research Officer (IO)
- Administrative Director, Office of Research Administration
- Director, Research Protection Office
- Manager(s), Office of Research Administration, Sponsored Projects(if project is externally funded)
- Director, Central Research Facilities

8.5.3 Response to External Requests for Information

In accordance with applicable policies, guidelines and regulations, upon request, Lifespan will make available to the public all IACUC meeting minutes. Redaction of proprietary and private information is allowed but must be done so judiciously and consistently for all requested documents.

Section 9: Recordkeeping

9.0 Maintaining IACUC Records

The Institution is responsible for maintaining the following:

- The Assurance approved by OLAW;
- Minutes of IACUC meetings;
- Records of IACUC activities and deliberations;
- Minority IACUC views;
- Documentation of protocols reviewed by the IACUC, and proposed significant changes to protocols;
- IACUC semiannual program evaluations and facility inspections, including deficiencies identified and plans for correction; and
- Accrediting body determinations.

All records are to be kept for a minimum of three years, with the exception of records that relate directly to protocols, which must be kept for the duration of the activity and for an additional three years after completion of the activity.

Records documenting such activities as the provision of adequate veterinary care, training, and occupational safety are expected to confirm with the recommendations of the *Guide* and with commonly accepted professional standards.

9.1 Meeting Minutes

Review of proposals by the IACUC invokes a deliberative process, and the PHS Policy and Animal Welfare Regulations (AWRs) require that the institution maintain "minutes of IACUC meetings, including records of attendance, activities of the Committee and Committee deliberations" (PHS Policy IV.E;9 CFR Part 2 Subpart C 2.35 (a) (1). The IACUC has some latitude in the degree of detail in these minutes.

Recorded minutes from IACUC reviews at a convened meeting (FCR, full committee review) are intended to reflect the substantive discussion of protocols. Minutes are intended to contain sufficient information that a reasonable person could understand the nature of the discussion. Meeting minutes are not intended to provide a verbatim transcript of discussion nor to reiterate shared knowledge of the Committee; such as recent discussions about a protocol in previous minutes. Historical evidence of compliance or non-compliance would be recorded in the minutes if it were germane to the discussion. Minutes may include reference to historical discussion by the IACUC from members who have served on the Committee and observed the procedures being proposed, served as reviewers for protocols involving similar procedures (where their questions were answered), or participated in past IACUC discussions about the procedures.

Minutes of each FCR are recorded in writing and include records of attendance, a summary of

the issues discussed and the resolution of issues, and the results of IACUC votes on protocols.

1. Records of Attendance

   Although members may arrive late or leave during a meeting, generally a member is marked as either present or absent. An exception would be when the IACUC member leaves the meeting room during discussion of a protocol on which that member is a participant. This would be indicated as a member "recusal" in the minutes. If the temporary absence of a member drops the number of members present below the quorum no official actions may take place, and this will be noted in the minutes.

2. Activities of the Committee

   Activities of the Committee include, but not limited to, corrections or approval of previous minutes; presentation of program, policy, facility and compliance reports; and decisions on policies, protocols, and amendments.

3. Deliberations of the Committee

   A deliberation of the Committee refers to the discussion and reasons leading to particular IACUC decisions. Minutes should include, as a minimum, a summary of the key points discussed prior to a committee decision.

Completed minutes are distributed to all IACUC members. Minutes are discussed at a subsequent convened meeting of the IACUC, and the Committee votes on approval. A copy of the meeting minutes is provided to the IO. This informs the IO of all actions taken by the IACUC.

9.2 Conflict of Interest Documentation

IACUC members and consultants will not participate in any IACUC action taken, including the initial and continuing review of any project in which the member has a conflict of interest, except to provide information requested by the IACUC. IACUC members are expected to self-identify conflicts of interest on the COI form which is prepared for each full board meeting. The IACUC Coordinator will maintain copies of the COI forms from each meeting.

9.3 Protocols

The PHS Policy and the AWRs require that animal applications and proposed significant changes be retained for the duration of the animal activity and for an additional three years after the end of the activity. Proposals submitted to the IACUC must be kept for three years, even if approval was not granted or animals were not used. The records must show whether or not IACUC approval was given.

9.4 Other Records

Both the PHS Policy and the AWRs require that the institution retain the semiannual Program Review and Facility Inspections Report and any recommendations of the IACUC. PHS Policy also requires that the OLAW Assurance and reports of accrediting agencies (e.g. AAALAC) be kept on file. USDA requires additional records on dogs and cats acquired, transported, sold, or euthanized by the research facility. Animal health records are not usually maintained by the IACUC but are kept in the animal facility or in research laboratories. All these records must be kept for at least three years; and must be accessible to OLAW, USDA/APHIS, and funding agencies for inspection or copying.

Section 10: Acknowledgements

This manual contains content that was adapted from materials obtained from the University of Texas at Austin, the University of Minnesota, the University of Pennsylvania, and the University of Illinois at Urbana-Champaign.

Section 11: Additional Policies

The following IACUC approved policies which directly relate to the care and use of animals are included in the Central Research Facilities (CRF) Policy and Procedure Manual:

Topic	**Location in the CRF Manual**
Pharmaceutical Grade Drugs	VI. F
Conditions for Multiple Major Survival Surgery	VI. I
Expired Medical Products	VI.J
Humane Euthanasia of Lab Animals	VI. K
Required Use of Flow Regulators for CO2 Euthanasia of Rodents	VI.K. 5(b)
Rodent Health Monitoring Program	VI. N
Tumor Implantation	VI.O
Use of Human Source Tissue and Cells in Immunodeficient Animals	VI. P
Prolonged Restraint	VI. Q
Environmental Enrichment	VI. R.
Mouse Tail Biopsy	VI. S
Rodent Toe Clipping	VI. T
Use of Animal Cadavers and Animal Body Parts in Research	VII.K
Avian Embryo Use	VII.M
Animal Usage Policy (counting animals)	VII.N

Section 12: Resources and Contacts

Contact information for the IACUC Chairperson and management staff, along with hyperlinks to animal welfare regulatory and guidance documents will be posted on the IACUC webpage at http://www.lifespan.org/research/administration/animal-research.html

The Public Health Service Policy on Humane Care and Use of Laboratory Animals, Office of Laboratory Animal Welfare is posted on the DHHS website at http://grants.nih.gov/grants/olaw/references/phspol.htm

The Animal Welfare Act is posted on the USDA website at http://www.aphis.usda.gov/animal_welfare/downloads/awa/awa.pdf

The Animal Welfare Regulations are posted on the USDA website at http://www.aphis.usda.gov/regulations/index.shtml

The *Guide* for the Care and Use of Laboratory Animals, Institute of Laboratory Animal Resources is available from National Academy Press and posted on the web at http://www.nap.edu/catalog.php?record_id=12910

The AVMA Guidelines on Euthanasia, 2013, are posted on the AVMA website at https://www.avma.org/KB/Policies/Pages/Euthanasia-Guidelines.aspx?utm_source=prettyurl&utm_medium=web&utm_campaign=redirect&utm_term=issues-animal_welfare-euthanasia-pdf

The BMBL, Biosafety in Microbiological and Biomedical Laboratories Manual, published by the Centers for Disease Control and the National Institutes of Health is available as a PDF on the CDC website at http://www.cdc.gov/biosafety/publications/bmbl5/index.htm

Section 13: Acronyms and Abbreviations

AAALAC- Association for Assessment and Accreditation of Laboratory Animal Care, International
ACUP- Animal Care and Use Protocol
APHIS- Animal and Plant Health Inspection Service, a division of the USDA
AVMA- American Veterinary Medical Association
AWA- Animal Welfare Act
AWRs- Animal Welfare Regulations

CAF- Central Animal Facility
CRF- Central Research Facilities

DHHS- Dept. of Health and Human Services

IACUC- Institutional Animal Care and Use Committee
IO- Institutional Official

NIH- National Institutes of Health

OLAW- Office of Laboratory Animal Welfare, a division of NIH
ORA- Office of Research Administration

PHS- Public Health Service, a division of DHHS
PI- Principal Investigator

RDC- Recombinant DNA Committee
RPO- Research Protection Office, a division of the Office of Research Administration

USDA- United States Dept. of Agriculture