Jerald Silverman, DVM, Column Coordinator

Clinical study or research activity?

Sam Eagle, DVM, a veterinary neurologist, was the deal-maker at the Great Eastern University veterinary school, a USDA-registered and NIH/OLAW-Assured institution that included all vertebrate animals, no matter the funding source for the research in which they were used, in its Assurance. Eagle had friends in all the nearby pharmaceutical companies and human hospitals, and so it was not surprising when he convinced Southedge Hospital, a tertiary care facility, to agree to carry out computed axial tomography (CAT) scans on dogs that came through the veterinary school's small animal clinic and were suspected of having had a stroke. There would be no charge to the animals' owners, as long as they also consented to have periodic functional magnetic resonance imaging (fMRI) studies on their dogs at Southedge, also at no charge to the owners. The initial CAT scan was diagnostic, but the fMRI studies were for Eagle's research and were paid for by Eagle's Everice Foundation grant.

The IACUC at Great Eastern was fully aware of Eagle's collaboration with Southedge and willingly allowed the veterinary school's Clinical Trials Committee to review and oversee Eagle's work at the human hospital. The rationale from the IACUC was that the animals were privately owned and the CAT scans were for diagnostic purposes. As for the fMRI studies, the IACUC took the position that they may have clinical utility, although Eagle proudly advertised it as his research. On the other hand, the school's veterinarians were frustrated that there was no IACUC oversight for exactly the same reason: Eagle readily stated that it was part of his research. Furthermore, the veterinarians did not consider the anesthesia needed for the fMRI studies to be innocuous; rather, they saw it as a potentially dangerous aspect of a research activity that had no direct benefit to the dogs. Eagle neither agreed nor disagreed with them. He said that it was just a matter of personal opinion and that he had no opinion at all on the issue.

What do you think? Is Eagle's work with privately owned animals a clinical study that was really designed for research purposes, or is it a pure clinical study as the Great Eastern IACUC claims? In the former instance, is IACUC approval needed? If so, should approval come from the veterinary school's IACUC, or does Southedge Hospital need to be registered with the USDA and have its own IACUC?

RESPONSE

IACUC should review

Lara A. Weaver, DVM &
Brian J. Moore, MS, DVM

A clinical trial is usually done to determine the safety or efficacy of a diagnostic tool or treatment designed to be of benefit for a clinical condition in the research subject. Ideally, the procedure or drug should address the specific medical condition of and have some direct benefit to the animals enrolled. In this scenario, the dogs were chosen to participate in this study on the basis of clinical indications that they had suffered a stroke. As CAT scans are diagnostically useful in this scenario, this portion of the work could legitimately be considered a clinical procedure and be covered by the Clinical Trials Committee.

The subsequent fMRIs do not have any diagnostic or therapeutic merit, however, and the associated anesthesia poses a real risk to the dogs. The fMRI portion of this study should be considered research, just as Eagle has advertised. Although the Animal Welfare Act[1] does not explicitly address the use of privately owned animals in research, the dogs in this study would meet the Animal Welfare Regulations' definition of "animal." The Public Health Service requires research studies using species listed in the university's Animal Welfare Assurance to have IACUC approval; therefore, regardless of the USDA's position in this situation, Great Eastern's Public Health Service Assurance would dictate that this research be covered by an IACUC protocol[2]. A detailed informed consent document explaining the risks to the owners should also be evaluated during the IACUC review process.

As for the question of which IACUC should review this protocol, again Great Eastern has elected to include "all vertebrate animals, no matter the funding source" in its Assurance, requiring the Great Eastern IACUC to review this protocol. Aside from the regulatory requirements, it may be in the best interests of both the clients and the veterinary school to have Great Eastern's IACUC review the fMRI portion of the study. The Great Eastern IACUC would likely include more veterinarians and should be more accustomed to reviewing protocols of this nature than a committee at a human hospital would be. The review at the veterinary school would also enable the school to have more input in and oversight of the process, which is beneficial to both the animals and the institution. In the event that Southedge does not already have an Assurance or IACUC in place, using the Great Eastern IACUC to review the protocol would also prove to be a more convenient option. Great Eastern could then include Southedge under its Assurance for the purposes of this study and could carry out semiannual inspections of the facility during the time period in which the studies take place.

This unique scenario raises questions that may not have clear-cut answers. In addition to the points raised above, there are also regulatory compliance issues relating to

the transport and housing of the privately owned animals. Though beyond the scope of this discussion, these issues arise in a veterinary school setting on a regular basis and warrant further clarification by regulatory agencies.

1. Animal Welfare Act as Amended (7 USC 2131–2159).
2. Public Health Service. *Policy on Humane Care and Use of Laboratory Animals* (US Department of Health and Human Services, Washington, DC, 1986; amended 2002).

Weaver is Interim Director and Moore is Staff Veterinarian in the Division of Teaching and Research Resources, Tufts University Cummings School of Veterinary Medicine, North Grafton, MA.

RESPONSE

Clinical, not research

Caroline Murray, LVT, BS, LATG, CMAR

It is my opinion that Eagle's work as described with privately owned dogs is a clinical study that has been reviewed by and is being overseen by the Clinical Trials Committee of Great Eastern University's veterinary school. Therefore, it would not fall under the auspices of Great Eastern's IACUC. The dogs are privately owned and do not belong to either Eagle or Great Eastern. In addition, the owners have given informed consent, which should have included the possibility of anesthetic complications and fully described what is meant by 'periodic' fMRI studies.

If the work was a clinical study that was designed for research purposes only, then an approved IACUC protocol and oversight would be necessary. The imaging and anesthesia would have to be fully described, and Southedge Hospital would need to be cited as a satellite location and inspected by the IACUC.

The frustration of the school's veterinarians is understandable, as Eagle's attitude appears to be rather dismissive of their concerns. However, as a veterinary neurologist, Eagle is well within his rights to utilize the information gleaned from these diagnostic tests in his research.

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A word from OLAW and USDA

In response to the issues raised in this scenario, the Office of Laboratory Animal Welfare (OLAW) and the United States Department of Agriculture, Animal and Plant Health Inspection Service, Animal Care (USDA/APHIS/AC) offer the following clarification and guidance:

The primary questions posed in this scenario are when does a clinical evaluation become research, and does the IACUC need to be involved?

The Animal Welfare Act (AWA) requires registration of facilities using live animals in experiments. It is important that the Great Eastern IACUC definitively determine whether the procedures being done are for clinical purposes (for the medical benefit of the individual dog) or for experimental purposes (*e.g.*, a systematic investigation evaluating a new procedure). If it is an experiment, then the IACUC must determine whether the facility is acquiring the animals, and whether it is receiving federal funds to carry out the work. In this scenario, the animals are privately owned and have not been acquired by the facility. Funding is provided by a foundation grant; if this is a federal source (such as the National Science Foundation), then the activity is covered by the USDA and there must be an IACUC-approved protocol for the activity[1].

If the proposed work is supported by the Public Health Service (PHS), then either all of the work must be covered under the Great Eastern Animal Welfare Assurance or Southedge Hospital must obtain its own Assurance. If Great Eastern chooses to add Southedge to its Assurance, Southedge would need to agree to empower Great Eastern's Institutional Official and IACUC to oversee all aspects of the project and to implement provisions of the PHS Policy and recommendations of the *Guide for the Care and Use of Laboratory Animals* at Southedge[2,3]. In addition, OLAW would review and consider the inclusion of Southedge as a performance site under the Great Eastern Assurance prior to the commencement of any work. In similar circumstances, OLAW has observed that IACUCs often choose to add an appropriate staff member from the performance site to the IACUC, or otherwise as a consultant, to ensure that the proposed animal activities do not conflict with the primary use of the facilities for human patients.

If the proposed work is not PHS-supported, and if Great Eastern stated that all vertebrate animals were covered under its Assurance regardless of funding source, OLAW would expect Great Eastern to negotiate an agreement with Southedge as described above prior to the commencement of any work.

Concerning questions about ownership, the PHS Policy doesn't distinguish between the use of institutionally owned and privately owned animals. Although issues of consent are not mentioned in the PHS Policy or the AWA, OLAW and USDA recommend that institutions, in consultation with their legal counsel, devise appropriate consent agreements that fully explain the purpose and procedures involved in clinical trials, the potential benefits and risks to animal subjects and the responsibilities and rights of both owners and the institution.

1. Code of Federal Regulations, Title 9, Chapter 1, Subchapter A - Animal Welfare: Part 1 Definitions and Part 2 Regulations. (§1.1), (§2.31).
2. Public Health Service. *Policy on Humane Care and Use of Laboratory Animals* (US Department of Health and Human Services, Washington, DC, 1986; amended 2002).
3. Public Health Service. *Policy on Humane Care and Use of Laboratory Animals* – Frequently Asked Questions. Protocol Review, Question No. 8. (US Department of Health and Human Services, Washington, DC, 2006; revised 2009). http://grants.nih.gov/grants/olaw/faqs.htm#proto_8.

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Director
OLAW, OER, OD, NIH, HHS

Chester Gipson, DVM

Deputy Administrator
USDA, APHIS, AC

RESPONSE

Needs IACUC oversight

Hillary Herendeen, ALAT, Gillian Braden-Weiss, MLAS & Breanna Caltagarone, MLAS

All animal research, including clinical studies that involve the general public, must meet current regulatory requirements and oversight. Appropriate oversight protects the privilege of carrying out important research while ensuring an adequate standard of care.

The CAT scan is diagnostic of dogs suspected of having a stroke and, therefore, has clinical benefits for the animals enrolled. In contrast, the fMRI appears to have no immediate benefit or diagnostic purpose for the animals involved and includes the added risk of anesthesia. Therefore, the fMRI should be considered a form of research and not a routine diagnostic procedure. We feel that an IACUC should have oversight of this work. This will ensure that both institutions involved are in compliance with current legislation (dogs are included in the Animal Welfare Act[1] (AWA) and Regulations[2] (AWRs)) and will protect the animals involved by assuring appropriate third party risk assessment.

The AWRs (section [2.30(a)]) define a research facility to include "any school (except an elementary or secondary school), institution, organization, or person that uses or intends to use live animals in research, tests, or experiments, and that (1) purchases or transports live animals in commerce, or (2) receives funds under a grant, award, loan, or contract from a department, agency, or instrumentality of the United States for the purpose of carrying out research, tests, or experiments." This definition would include Great Eastern. Eagle is enrolling the animals at Great Eastern, and his funding is awarded through Great Eastern. These facts require that Great Eastern be registered with the USDA and subject to IACUC review. We feel the privately owned dogs being used in Eagle's study are participating as subjects of basic research and are thus covered by the AWA.

If this is a singular situation of ongoing research at Southedge Hospital, we feel the most practical way to provide oversight would be for the Great Eastern IACUC to recognize Southedge as a satellite institution. Great Eastern would then place the hospital within their Animal Program and carry out the necessary programmatic review and site inspection tasks (AWRs section 2.31).

If other animal research projects are underway at the Southedge Hospital site, however, it would make the most sense for Southedge to become an independent entity and have its own Committee and registration with the USDA as having their own Animal Program. The Animal Program should include designating an Institutional Official, who would then appoint a full Committee in keeping with the requirements of the AWRs or in accordance with Public Health Service Policy[3] (if any work is funded by the Public Health Service) and adopt a program of Veterinary Care.

Eagle will benefit from being in compliance, as there would be no space for doubt about the validity of his findings. We do wonder about the ethical ramifications of using a free CAT scan to encourage enrollment into this work, as this is an expensive procedure that owners may view as essential and thus feel pressured to accept the fMRI scans and requisite anesthesia without fully appreciating the risks. Informed consent is very important in enrolling any patient into a clinical trial, including this case.

We conclude that new animal enrollment or periodic scanning of enrolled animals in this work should cease until appropriate action is taken to assure these dogs are included in an Animal Program and covered by an animal use protocol evaluated by the appropriate Committee (at either Great Eastern or Southedge Hospital). In addition, Eagle should be made aware of the impact of his public statements to minimize any misunderstanding of the nature of his research in the future.

1. Animal Welfare Act as Amended (7 USC 2131–2159).
2. Animal Welfare Regulations (9 CFR, Chapter 1, Subchapter A–Animal Welfare Parts 1–4).
3. Public Health Service. *Policy on Humane Care and Use of Laboratory Animals* (US Department of Health and Human Services, Washington, DC, 1986; amended 2002).

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