Protocols for pets: what authority does an IACUC have?

E-2400, an anti-neoplastic drug, was to be used in a clinical trial for dogs with osteosarcoma, a bone tumor often seen in large breeds such as Irish wolfhounds. The proposed plan was for the dog's affected limb to be totally amputated and then the drug would be administered intravenously, once every two weeks for four treatments. The control group of dogs would also have the limb amputated but postoperatively would receive the antineoplastic drug carboplatin, the standard treatment for dogs with osteosarcoma that were seen at Great Eastern University, College of Veterinary Medicine.

The study's principal investigator was Dr. Sheila McCrae and the work was funded through an NIH grant. On her IACUC protocol form McCrae carefully described the general mechanism of action of E-2400, qualifications required for a dog to be entered into the trial, number of animals receiving either E-2400 or carboplatin, blinding procedures, details of the intravenous infusion, observations to be made, possible side effects of E-2400, a copy of the information sheet and consent form to be given to the owner, and so forth. The protocol was destined for full committee review and per the standard procedure of the school's IACUC, it was pre-reviewed by a laboratory animal veterinarian and another member of the committee. The reviewers were impressed by the amount and quality of the details provided by McCrae, but one item was conspicuously missing: a description of the amputation procedure. When she was asked to add it to the protocol, McCrae replied that the surgical procedure is the veterinary hospital's standard of care for dogs with osteosarcoma and it would be performed on all osteosarcoma patients, whether they would receive E-2400 or carboplatin. This response was deemed unsatisfactory by the IACUC administrative office and the pre-reviewers, and they again asked McCrae for a detailed description of the surgery and all perioperative procedures, including anesthesia and analgesia. McCrae, who was usually a very non-confrontational and compliant researcher, believed that the IACUC had overstepped its authority and was asking to review a standard oncological procedure used at the veterinary school. She lodged a formal complaint with the IACUC chairperson, alleging that the requested additional information exceeded the authority of the IACUC.

The McCrae protocol and her complaint were discussed at the next full committee meeting. Do you believe that the IACUC exceeded its authority and how should the IACUC proceed to resolve this issue? ❐

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Details necessary for IACUC assessment?

Although the animals under this study are privately-owned, there is no distinction in terms of regulations between the PHS Policy[1] and the Animal Welfare Act and Regulations (AWAR)[2] when compared to animals owned by the institution. As such, pets used in research must be covered under an IACUC-approved protocol. Additionally, given that this study is PHS-funded, all applicable IACUC approval is required for research activities. This includes endorsement of the "U.S. Government Principles"[3], compliance (where applicable) with the Animal Welfare Act, and requires institutions to use the *Guide for the Care and Use of Laboratory Animals* (*the Guide*)[4] for the basis of assessment and development of institutional policies.

It is important to note that the question of appropriate training and qualifications of Dr. McCrae, correctly, do not appear to be a topic of disagreement for the IACUC. The Academy of Surgical Research's "Guideline for Training in Surgical Research with Animals"[5], which is referenced in *the Guide*, states that "Veterinarians who are certified or trained in laboratory animal medicine, surgery, or anesthesia should be considered competent in their field and should not require additional training." However, the point of debate between the IACUC and the PI concerns the provision of detailed surgical procedures and perioperative procedures and monitoring to the IACUC for review.

As per *the Guide*, "the IACUC is responsible for assessment and oversight of the institution's Program components…". The Program is specifically defined as "all activities conducted by and at an institution that have a direct impact on the well-being of animals, including animal and veterinary care…". As the limb amputation procedure certainly has a direct impact on the well-being of the study animals, it is directly within the purview of the IACUC to request a detailed description of the amputation procedure and all perioperative procedures.

Additionally, the provision of these details will provide both the IACUC and the attending veterinarian with the necessary information to assure that pain and distress is minimized in these patients, as well as the appropriate used of analgesic, anesthetic, and tranquilizing drugs—as is emphasized in the PHS Policy, US Government Principles, *the Guide*, and the AWAR.

Dr. McCrae may be advised that citing an IACUC-approved Standard Operating Procedure (SOP) for amputation in the IACUC protocol is also feasible. IACUCs may approve SOPs that can be cited by investigators in their protocols[6]. The IACUC approval and incorporation of SOPs into IACUC protocols helps reduce regulatory burden for investigators, while providing the IACUC the necessary details of the procedures performed.

Rather than questioning Dr. McCrae's expertise as a veterinarian and oncologist, the IACUC simply needs to be provided with all the appropriate information to evaluate the protocol to the standards of federal regulations. ❐

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Oversight depends on how 'eligibility' is defined

Dr. McCrae is proposing a trial to evaluate the efficacy of a novel anti-neoplastic drug, E-2400, by comparing it to the standard therapeutic drug, carboplatin, used in the treatment of osteosarcoma. Although limb amputation of the dog's affected leg is a step in the overall process of treating osteosarcoma, the question is raised as to whether the IACUC must oversee the surgery as part of the drug trial proposed to the IACUC. The answer to that question depends on whether the surgery is described as an animal activity in the grant submission or when the animals are enrolled in the drug trial.

As described in the scenario, the Principal Investigator (PI) has defined the qualifications required for the animal to be eligible for the study, which is the key to deciding whether the IACUC should oversee the surgery. In addition, through the informed consent process (USDA - Veterinary Services Memorandum No. 800.301), the scientist is ensuring the animal owners understand the risks, potential benefits, and alternatives of enrolling their animal in the study, which is also a critical factor.

Regarding the enrolment of an animal in the study, oversight of the surgical procedure should not be under the purview of the IACUC if the criteria for an animal to be eligible to participate in the drug trial is limited to only those that have undergone the first phase of the standard clinical treatment (i.e., the amputation of the affected leg) for osteosarcoma. In this particular scenario, the onus would be on the PI to ensure only those animals satisfying the enrollment criteria would participate in the blind study with a percent of the animals continuing the standard treatment of receiving carboplatin (i.e., the control group), and others the test drug E-2400. In this case, the IACUC should only consider the potential effects of E-2400 on the welfare of the animals.

Alternatively, if eligible animals include all that have been diagnosed with osteosarcoma, the IACUC may have additional responsibilities. For example, let us assume that after osteosarcoma is diagnosed and during the informed consent process, the animal owner learns that the treatment of the disease includes limb amputation followed by chemotherapeutic treatment. At that time, owners are also informed of a trial intended to evaluate the efficacy of a novel chemotherapeutic drug (E-2400) that they believed will increase the chance of the animal being successfully treated for the disease. In addition, and if the surgical procedure is described in the grant, the owners are informed that because the drug trial is sponsored through the NIH all associated expenses relating to the treatment of the animals will be covered as part of the trial.

In this particular scenario, the IACUC must oversee the effects of the drug trials on the animals since that is the overall scope of the study. In addition, the IACUC has some responsibility associated with the surgical procedure especially since the costs associated with the surgery are being covered by the grant. The IACUC can satisfy this responsibility by asking the PI to assure in the protocol that the surgery will be conducted following an established standard clinical practice in a veterinary hospital by a veterinarian with extensive expertise in the standard treatment of osteosarcoma in dogs. Since the findings from the overall study seeks to identify more efficacious drugs for the treatment of the disease, and not methods for improving the associated standard surgical procedures, the IACUC need only concentrate on the drug trial with the consideration that the surgery is a standard of clinical care that ultimately leads to additional drug treatments. ❐

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IACUC overreach, no bones about it

A robust, well-designed pre-review process can be one of the most important steps in the efficient, complete and consistent review of an animal care and use protocol. When properly performed, a pre-review can shorten the IACUC review period, thus reducing administrative burden on the Committee and the investigators. An overzealous review process can accomplish the opposite, increasing the burden of the Committee and frustrating responsible and conscientious scientists[1]. This seems to be what has occurred at Great Eastern University (GEU)—the IACUC, through its pre-review of Dr. McCrae's protocol, is requesting information outside of its purview, e.g., the review of standard veterinary care.

In determining the scope of their oversight, GEU research administration and the IACUC should determine (1) whether the Public Health Service (PHS) and or the U.S. Department of Agriculture (USDA) has jurisdiction over the activity, (2) what parts

of the activity are required to be reviewed by or overseen by the IACUC, and (3) if there are related topics that the institution may want to consider.

The PHS Policy and the Animal Welfare Act and Regulations (AWARs) do not distinguish between animals owned by the institution and privately owned animals. Privately owned animals used in research supported by the PHS must be covered under an IACUC-approved protocol[2]. An important distinction between conventional biomedical research projects and research involving pets is the presence of a veterinarian-client-patient relationship (VCPR). In the context of a valid VCPR, standard veterinary care of a privately owned animal is not a research activity and does not require IACUC approval or compliance with the PHS Policy or AWAR[3,4]. As part of the VCPR, if the animal undergoes procedures that are medically justified and are the standard of care, even if the results are used for research purposes (e.g., limb amputation), those procedures are not subject to oversight[3]. Dr. McCrae has confirmed that the limb amputation procedure is the standard of care for this disease; therefore, that surgical procedure is not subject to IACUC oversight and should not be included in the review. Conversely, the experimental drug, E-2400, is not the standard of care; therefore, details about this drug should be reviewed by the IACUC.

It would be prudent for the institution to review the informed consent received from clients enrolling their pets in a clinical study. Legal counsel or the risk management group would likely be involved with this documentation, perhaps even public affairs and communication. Though not part of this scenario, if Dr. McCrae decides to include referral practices to increase the patient population in this PHS-supported study, these practices must be listed as performance sites in the GEU's Animal Welfare Assurance[2].

It should be noted that in a biomedical research setting, it is standard for an IACUC to ask for an appropriate description of a major survival surgery (or any procedure). Considering Dr. McCrae has a long-standing record of being a good citizen, when she objected the reviewers should have consulted with subject matter experts (e.g. IACUC office staff) whether they were overstepping their authority. The GEU IACUC may consider being [re-]trained on the limits of IACUC oversight of clinical studies. Dr. McCrae would surely oblige. ❐

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A WORD FROM OLAW

In response to the issues posed in this scenario, the Office of Laboratory Animal Welfare (OLAW) provides the following clarifications:

In this scenario, a PI proposes to test a drug to treat osteosarcoma in canines in an NIH-funded study. The study proposal describes in detail all aspects of the experiment that will be conducted after amputation of the affected limb. However, it does not describe the amputation procedure. When asked to include the amputation procedure during administrative pre-review by the IACUC office, the investigator declines, replying that this request exceeds IACUC authority, as the standard of care SOP will be followed. The scenario asks, "How should the IACUC handle the situation?" However, the key question is whether the amputation procedure must be included in the protocol.

The IACUC is responsible for the welfare of each animal in the research study.[1] Amputation is an integral part of the study and the IACUC must have all the information on procedures to be performed on the animal to evaluate animal welfare. Additionally, it would be necessary to know which anesthetics, analgesics, and fluids were used as well as physiological parameters assessed during surgery, if unexpected complications occur during the research study.

The PI may provide details of the amputation procedure within the protocol or may simply reference the veterinary school SOP for details of the procedure. As described by reviewers, this "helps reduce regulatory burden for investigators, while providing the IACUC the necessary details of the procedures performed." The IACUC may review and accept the established written standard of veterinary care for the surgery and incorporate it in the protocol. ❐

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Complete details for a complete review

The IACUC did not exceed its authority, and is within reason to request additional information from the PI to complete a thorough protocol review as mandated by both PHS Policy[1] and Animal Welfare Act and Regulations[2]. These federal regulations do not differentiate between institution- and client-owned animals, and because the work described in the scenario is PHS-funded research, the institution must maintain an OLAW-approved Animal Welfare Assurance covering all performance sites.

As written, the scenario indicates that the 'proposed plan was for the dog's affected limb to be totally amputated', indicating that the surgery is clearly being conducted for the purpose of the research, therefore it cannot be solely considered veterinary clinical care of a privately owned animal. If amputation is included in the pre-treatment regimen for the effective use of the study drugs, then the procedure should be described in the protocol for IACUC review.

According to *the Guide*[3], the animal use protocol is a detailed description of the proposed use of laboratory animals, and appropriate sedation, analgesia, and anesthesia, and conduct of surgical procedures should be considered in the preparation of the protocol by the researcher and its review by the IACUC. Specifically, the IACUC is charged with evaluating the surgical procedure, perioperative processes, humane endpoints, and relief of pain or distress. Despite the standard oncological procedure from the veterinary school being used, the IACUC cannot effectively assess the items above to ensure the appropriateness of each element for the study in question without a complete description of the surgical procedure to be utilized.

Additionally, the PHS Policy and the AWRs require research institutions to ensure that investigators have appropriately considered alternatives to procedures that can cause more than slight or momentary pain or distress in animals[4]. These alternatives are detailed within the "3Rs": reduction, refinement, replacement. In regards to the study in question, the IACUC needs to evaluate refinement to ensure that current veterinary practices employed at the veterinary school in question reduce or eliminate unnecessary pain and distress in the study animals[1].

The IACUC must also be able to assess personnel qualifications, including knowledge of basic principles of laboratory animal science to help ensure high quality science. Staff veterinarians providing clinical support must have the experience, training, and expertise necessary to evaluate the health and wellbeing of the species used in the context of the animal use at the institution[3].

The IACUC should request that a description of the surgery procedure be added to the protocol prior to approval. Alternatively, in the spirit of reducing regulatory burden, if Great Eastern University, College of Veterinary Medicine maintains its own IACUC-approved protocol, or Standard Operating Procedure for the amputation, Dr. McCrae's IACUC may request a copy of that document for review instead of requiring that the details be entered into the protocol form. The document could then be attached to or included with the protocol file for future reference. ❐

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