

Discretionary consent

Dr. T. Guaio, a Principal investigator (PI) at Great Eastern University (GEU), used a non-animal model to create a designer drug that pinpoints specific markers

on the surface of cancer cells. Dr. Ty, a private practice veterinarian, and Guaio developed a plan to test the drug on privately owned dogs that visited Ty's veterinary clinic. This was

particularly exciting for Guaio because he lacked experience working with dogs and he had few fiscal resources to support the project. Guaio hoped to obtain preliminary data that could be used to supplement an NIH grant application for funding, and subsequently a New Drug Application (NDA).

Ty was interested in the collaboration because successful outcomes meant healthier animals, happier owners, and better business. As part of the collaboration, Ty provided tumor biopsy tissue to Guaio, who verified the presence of the tumor cell markers. Guaio then provided the designer drug to treat the dogs. In addition, Ty also provided clinical records such as scans and blood chemistry to validate the efficacy of the drug. Guaio used this information to analyze the efficacy of the treatment.

Guaio was awarded an NIH grant based on the preliminary data. When GEU conducted a protocol and grant congruency review, they identified and asked Guaio about the prior dog studies. It was then that GEU's IACUC learned of the work at the veterinary clinic and asked Guaio to an IACUC meeting for a discussion. Guaio maintained that his approach was appropriate since the animals received better than the standard of care for cancer. In addition, Ty did, in fact, inform the owners that he would be treating their dogs with an experimental drug that shows significant promise.

GEU's IACUC disagreed, and determined Guaio to be in non-compliance. The IACUC informed him an IACUC approved protocol and a Memorandum of Understanding (MOU) with Ty was required. The committee also indicated that Ty should have discussed the trial with each dog owner as part of the consent process, and subsequently ask each to sign an informed consent form.

Guaio became quite distraught with the allegations of non-compliance since the data was used to obtain his NIH grant. He maintained that an informed consent form was not necessary because the drug evaluations were supported by discretionary funds independent of GEU and that the animal activities were conducted by Ty, his veterinary colleague. Does Guaio have an argument? □

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A WORD FROM THE USDA AND OLAW

In this scenario, dogs that are client-owned were receiving an experimental drug as part of a veterinary clinical study to treat tumors that contain markers for a specific form of cancer. The investigator failed to obtain IACUC review of the preliminary research activities conducted in collaboration with the private practice veterinarian prior to receiving NIH funding for continuation of the research. There is concern that the early trial proceeded without IACUC oversight and without having a signed owner consent form.

Coverage under the Animal Welfare Act (AWA) depends on the species and purpose for the use of an animal¹. In this scenario, the purpose for the client-owned dogs is to undergo treatment with an experimental drug for a tumor forming condition. This treatment is occurring under the oversight of their private practice veterinarian. In light of this, the dogs are not covered under the AWA because they are under treatment within the context of a veterinarian-client-patient relationship, as defined by the American Veterinary Medical Association². Oversight by the IACUC is therefore not required under the AWA. Regarding owner consent, in the event there is evidence the veterinarian did not inform the owners of the work and consequently did not obtain consent, the issue would fall within the jurisdiction of the State Veterinary Medical Board.

Applications for grant awards to NIH must demonstrate compliance with certain public policy requirements. Among them is oversight of research involving live vertebrate animals³. In the scenario, the PI provided a drug of unknown safety to obtain preliminary data about its efficacy and then included the findings in the NIH grant application without IACUC approval. This is non-compliance that the institution has appropriately identified, as it is the institution that is attesting in the application to its commitment to consistent standards for oversight⁴. Although issues of consent are not mentioned in the PHS Policy, OLAW recommends that institutions, in consultation with their legal counsel, devise a consent agreement that explains the purpose of and procedures

in the experimental study, the potential benefits and risks to the dogs, and the responsibilities and rights of the owner and the institution^{5,6}. Because an NIH award is pending and the veterinary clinic will be the performance site, the institution must add the private veterinary practice as a covered component to its Animal Welfare Assurance with OLAW and secure a memorandum of understanding or written agreement with the practice^{7,8}. As most journals require IACUC review as a prerequisite to publication, an additional concern is publishing the data from the work⁹. □

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References

- 9 C.F.R. §1.1- Definitions: Animal.
- American Veterinary Medical Association - The Veterinarian-Client-Patient Relationship, online at: <https://www.avma.org/resources-tools/pet-owners/petcare/veterinarian-client-patient-relationship-vcpr>
- National Institutes of Health Grants Policy, Part I: NIH Grants – General Information, 2.3.6. Legal Implications of Applications. https://grants.nih.gov/grants/policy/nihgps/HTML5/section_2/2.3.6_legal_implications_of_applications.htm
- Public Health Service. Policy on Humane Care and Use of Laboratory Animals – Frequently Asked Questions. Applicability of the PHS Policy, Question No. A.1. (US Department of Health and Human Services, Bethesda, MD, USA). [online]. <https://olaw.nih.gov/faqs#/guidance/faqs?anchor=question50285>
- Brown, P. A. & Gipson, C. *Lab Anim. (NY)* **38**, 186 (2009).
- Public Health Service. Policy on Humane Care and Use of Laboratory Animals – Frequently Asked Questions. Applicability of the PHS Policy, Question No. A.7. (US Department of Health and Human Services, Bethesda, MD, USA). [online]. <https://olaw.nih.gov/faqs#/guidance/faqs?anchor=question50226>
- Public Health Service. Policy on Humane Care and Use of Laboratory Animals – Frequently Asked Questions. Applicability of the PHS Policy, Question No. A.8. (US Department of Health and Human Services, Bethesda, MD, USA). [online]. <https://olaw.nih.gov/faqs#/guidance/faqs?anchor=question50227>
- National Institutes of Health Grants Policy Statement, Part II: Terms and Conditions of NIH Grant Awards, Subpart B: Terms and Conditions for Specific Types of Grants, Recipients, and Activities 15.2.1 Written Agreement. [online]. https://grants.nih.gov/grants/policy/nihgps/HTML5/section_15/15.2_administrative_and_other_requirements.htm
- Brown, P. A. *Lab Anim. (NY)* **47**, 54 (2018).

A troubling designer drug

Dr. Guaio may have an argument on the tumor biopsy conducted by Dr. Ty. If the tumor biopsy was conducted as a part of routine veterinary care

to understand the tumor type and determine a treatment plan for the dog, it is regulated by the state licensing boards (OLAW FAQ 8). However, in this case it is clear that Dr. Guaio

does not have an argument. The tumor tissue was used to create a “designer drug” that was administered to client owned dogs. Furthermore, Dr. Ty conducted scans and blood chemistries to validate the drug efficacy, which constitutes research and must be IACUC approved. Because these animal studies were not IACUC-approved, GEU should consider providing guidance to Dr. Guaio about the use of data in publication or as a basis for a grant application.

According to OLAW (FAQ 8), the PHS Policy and the Animal Welfare Act and Regulations (AWAR) do not distinguish between animals owned by the institution and privately owned animals, and pets used in research must be covered under an IACUC-approved protocol. This study was not PHS funded; however depending on how the institution’s Assurance is written, PHS policy may apply to all research activities at the institution and would require that Dr. Ty’s veterinary clinic be listed as a covered component on the institution’s Assurance. Regardless of funding, these dogs meet the definition of an animal per Animal Welfare Act (Section 2132(g)) and are subject to the requirements of the AWAR, such that IACUC oversight is required of the research activities.

There are two additional issues, the lack of an informed consent and a Memorandum of Understanding (MOU). Per OLAW (FAQ 7), the institution should have an informed consent prior to conducting the research. Despite the fact this work was not supported by PHS funds, there are legal implications for the institution and Dr. Ty because the dog owner did not have adequate informed consent to participate in the study. Lastly, an MOU should have been secured to outline each parties’ responsibilities for animal care and regulatory oversight. □

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COMPLIANCE CONSIDERATIONS

The Protocol Review coordinators offer the following compliance considerations:

Are Drs. Guaio and Ty’s actions non-compliance?

Dr. Guaio’s procurement of tumor biopsy tissue would not require IACUC review and approval if Dr. Ty is performing a procedure for clinical reasons and excess tissue was given to Guaio¹. However, the collection of tissues for research activities (regardless of the source of funding) requires IACUC review and approval prior to the initiation of the animal activities². Consequently, the collection of tissues under the described circumstances would be considered non-compliance. Furthermore, the administration of an experimental substance, as detailed in the next paragraph, also requires IACUC review and approval, which Guaio did not secure.

Were informed consent forms required?

In this scenario, the collaboration between Dr. Guaio and Dr. Ty constitutes a Veterinary Clinical Study using an Investigational Veterinary Product. The USDA and AVMA have guidelines governing the proper conduct of clinical studies of veterinary products. These guidelines describe the requirement of IACUC oversight for Veterinary Clinical Studies “which involve an activity that would not normally be done for the condition of the animal if it were not enrolled in the study, such as the administration of an experimental drug or collection of samples not normally required”³ and include the principles of Good Clinical Practice (GCP) and obtaining Informed Consent⁴.

The purpose of the Informed Consent is to ensure that “the animal owners understand the risks, potential benefits, and alternatives of enrolling their animal in the study”⁵.

Does Guaio have an argument?

The source of funds supporting the animal activities is irrelevant; the fact that GEU was involved in the Veterinary Clinical Study is the determining factor. Resources from GEU were used in support of the study (e.g., equipment, Guaio’s time, manufacturing the designer drug), which means GEU has an obligation to ensure IACUC oversight of the activities occur. An MOU would have established the roles and responsibilities of GEU and Dr. Ty’s private practice. The MOU would have documented compliance with all pertinent regulations. In addition, the IACUC review and approval of the activities would have verified informed consent was obtained. □

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References

1. NIH/OLAW, Frequently Asked Questions (FAQs) PHS Policy on Humane Care and Use of Laboratory Animals, *Does the PHS Policy apply to use of animal tissue or materials obtained from dead animals?* <https://olaw.nih.gov/faqs#/guidance/faqs?anchor=question50287>
2. Animal Welfare Act, § 2132 https://www.aphis.usda.gov/animal_welfare/downloads/bluebook-ac-awa.pdf
3. AVMA, AVMA Animal Health Studies Database - Learn About Veterinary Clinical Studies, https://ebusiness.avma.org/aahsd/more_info/veterinary_clinical_studies.aspx
4. USDA/APHIS, VETERINARY SERVICES MEMORANDUM NO. 800.301 https://www.aphis.usda.gov/animal_health/vet_biologics/publications/memo_800_301.pdf
5. Greer, W. & Danridge, L. *Lab Anim. (NY)* 47, 92 (2018).

Complicated Relationship

Dr. Guaio may not have been required to obtain IACUC approval, but he should not rest easy. There are several factors that would determine the appropriate oversight including Great Eastern University (GEU)'s policies and PHS Assurance on animal use.

Regarding federal law, the Animal Welfare Act/Animal Welfare Regulations (AWA/AWR) would not apply to the project as they involve client-owned animals under a veterinarian-client relationship to treat a known condition. This project did not include federal funds, nor did it include the purchase or transportation of the dogs so the veterinary clinic would not be considered a research facility by AWA standards^{1,2}. While the drugs were provided by Dr. Guaio, all procedures were conducted by Dr. Ty on client owned animals.

Additional guidance on this scenario comes from the USDA's Animal Welfare Inspection Guide. The "Annual Report" section indicates that "Animal patients participating in clinical trials in the context of medical care under a veterinary client relationship" should not be reported in the research facility's Annual Report³.

There are several factors that could require or encourage the oversight of an IACUC or Veterinary Clinical Studies

Committee (VCSC) outside of the AWA/AWR. First, most institutions have overall policies on animal care and use. Depending on GEU's policy, IACUC approval could have been required as a faculty member and representative of GEU was involved in the study. A violation of GEU policy in the acquisition of data for an NIH grant may mean a report to OLAW about that grant. The American Veterinary Medical Association (AVMA) also encourages the use of IACUC or VCSC oversight when conducting veterinary clinical research studies⁴.

The approved PHS Animal Welfare Assurance would also determine whether an IACUC protocol was required for the work. The language and coverage level of GEU's program under their Assurance could require that all vertebrate work by GEU faculty be covered under their IACUC and Assurance⁵.

The lack of an informed consent form should be concerning for all parties involved. Without a documented description of the benefits and risks involved in the study, there is no way to know whether the clients received the correct information. As a treatment that was moved directly from an in-vitro test to client animals, it would be difficult for Dr. Ty to support the decision to use this drug if adverse consequences were discovered.

In this scenario, the ethical repercussions are immense and could have been avoided by IACUC oversight. There was no ethical review conducted, no in-vivo trials to ensure safety, a possibility of unknown harm to the animal, and the possibility of legal repercussions to both the clinic and institution. Best practice would include oversight by an IACUC or VCSC, an ethical review of the novel treatment for use in client animals, a Memorandum of Understanding with the clinic, and the use of an informed consent between the owners and clinic. □

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References

1. Animal Welfare Act and Regulations 7 U.S.C. 2131-2159; 7CFR 2.22, 2.80, and 371.7 (a) (1.1).
2. Kendall, L. V., Petervary, N., Bergdall, V. K., Page, R. L. & Baneux, P. J. R. *J Am Vet Med Assoc* **253**, 980–984 (2018).
3. USDA APHIS, Animal Welfare Inspection Guide, Section 7.5.3, January 2021, https://www.aphis.usda.gov/animal_welfare/downloads/Animal-Care-Inspection-Guide.pdf
4. AVMA, Establishment and Use of Veterinary Clinical Studies Committees, <https://www.avma.org/resources-tools/avma-policies/establishment-and-use-veterinary-clinical-studies-committees>
5. Silverman, J. *Lab Anim. (NY)* **38**, 185–187 (2009).