Administrative Non-Compliance?

Dr. T. Guaio was ecstatic when he was awarded a second NIH grant. Guaio's first grant, for which he already has an approved IACUC protocol, examines a porcine model of heart failure with a focus on drugs that reduce apoptosis. The new grant also uses a porcine model of heart failure but examines cellular regeneration and gene therapy. Consequently, because of the different research goals, the IACUC at Great Eastern University (GEU) required Guaio to submit two separate IACUC protocols even though the procedures in the two grants were nearly identical.

When an IACUC proposal is submitted through GEU's electronic IACUC system, it is automatically flagged for Designated Member Review (DMR) as the default IACUC review method (unless, of course, a call for Full Committee Review is received). The IACUC office staff are responsible for assigning reviewers; the IACUC Chair provided a list of IACUC members who were deemed qualified to conduct DMR and reviewers are assigned on a rotating basis. Each protocol is assigned scientific members and a veterinary reviewer. As a result, Guaio's protocol on cellular regeneration was reviewed by different IACUC and veterinary reviewers than his first protocol on apoptosis.

About a month after Guaio's cellular regeneration protocol was approved, Mr. Cooper, the Post-Approval Monitor, found a protocol deviation regarding the use of anesthesia. Evidently, during the IACUC review of the cellular regeneration protocol, the veterinary reviewer requested a change in the anesthesia; switching the induction agent from propofol to Telazol, ketamine, and xylazine (TKX), with both protocols maintaining a surgical plane of anesthesia with isoflurane. When Guaio's post-doc fellow, Dr. Matt, initiated studies on the cellular regeneration protocol, he was not expecting any differences between the two protocols and used propofol for the animals listed under the protocol with TKX. There were no problems with the surgery and the animals recovered uneventfully (i.e., there were no welfare concerns).

The IACUC concluded that while this error was *technically* off-protocol work and, therefore, non-compliance, the members struggled with qualifying this as anything other than an administrative error. Both methods of pre-anesthesia were approved in other GEU IACUC protocols (thus, the activities themselves are IACUC approved) and both were recommended by the veterinarians for survival surgery in pigs (i.e., both induction agents are acceptable for the type of surgery conducted).

What are your thoughts? ❐

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A WORD FROM OLAW AND USDA

In this scenario, the IACUC approves two very similar protocols by the same lab to be conducted on swine but with different anesthetic regimens. A lab staff member mistakenly uses an anesthetic not approved for the intended research.

Response from OLAW

The question of whether this incident of mistaken use of an anesthetic requires reporting to OLAW can best be answered by a phone call or email to OLAW.
Even though the anesthetic used was appropriate for a similar IACUC-approved study and the animals recovered without incident, the incident constitutes protocol noncompliance and is reportable[1]. At issue is that the IACUC did not review and approve the anesthetic choice for the specific animal activity and its associated aims. In addition, there was a lack of understanding by all lab staff of what the IACUC approved. OLAW receives many reports of these deviation types every year. An approach that would remedy future recurrences is for the IACUC to have an approved list of anesthetic regimens developed with veterinary input that can be referenced in such protocols.

Response from USDA

In accordance with AWA regulations, and as summarized above, this incident is an example of protocol noncompliance, regardless of the circumstances, and would result in a citation of such during inspection[2,3]. A review of relevant institutional and IACUC policies and practices is recommended to mitigate the potential for similar mishaps in the future. ❐

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References
1. National Institutes of Health, Office of Extramural Research. *Guidance on Prompt Reporting to OLAW under the PHS Policy on Human Care and Use of Laboratory Animals.* Notice NOT-OD-05-034, 2005. http://grants.nih.gov/grants/guide/notice-files/not-od-05-034.html
2. Animal Welfare Regulations 9 CFR § 2.31(d)(8).
3. Animal Welfare Regulations 9 CFR § 2.31(e)(3).

Not Just an Administrative Error

The IACUC at Great Eastern University (GEU) was correct in identifying that this protocol deviation was not a reportable event to OLAW. The error made by Dr. Matt fortunately would not be considered a serious noncompliance issue, a continuing noncompliance issue, or a serious deviation from the Guide (NIH Guide for Grants and Contracts NOT-OD-05-034)[1]. Additionally, the IACUC conducted itself accordingly by investigating the protocol deviation in a timely manner and concluded not to suspend this project.

Despite the decision not to report this off-protocol work to OLAW, there are several responses that should be taken by both the IACUC and Dr. Guaio's staff moving forward. First, the IACUC should be sure to report any minority views that may have been expressed by the committee members on their next Semi Annual Report and OLAW Annual Report. This fulfills their regulatory requirements of the PHS Policy (PHS Policy IV.E.1.D)[2] and promotes healthy discussion among the IACUC members. Second, The IACUC should request that Dr. Guaio conducts protocol meetings for his staff covering any newly approved protocols moving forward. Dr. Guaio should also keep a record of these meetings for the IACUC to review if necessary. These protocol reviews will ensure that his staff avoid errors of miscommunication or oversight in the future. The third consideration for the IACUC is to assess the Veterinary Verification and Consultation (VVC) policy, or lack thereof, at GEU. This type of protocol change, if it was made prior to the procedure being conducted by the PI or his staff, would likely qualify for VVC. The method of anesthesia was a previously approved and acceptable method for this species and could have been changed to make both porcine protocols consistent. Updating the policy to include acceptable anesthesia methods for porcine models would be an effective way to limit a potential noncompliance issue in the future. The fourth and final consideration is that the IACUC revisits its own protocol review procedures. The IACUC, veterinary staff, and/or administrator should consider if a new protocol is part of a package of protocols under one researcher. Reviewing each protocol in a vacuum could lead to consistency challenges for a research team,

COMPLIANCE CONSIDERATIONS

The Protocol Review coordinators offer the following compliance considerations:

1. What constitutes "IACUC review of proposed animal activities"?

The PHS Policy[1] does not mandate the use of a "protocol" form for the review of proposed animal activities; in fact, there is no prescribed method for the mechanism of IACUC review (to ensure the proper treatment of animals). Previously, IACUCs often used the NIH grant application as the source of information for IACUC review and approval of proposed animal activities. The development of an IACUC "protocol" is the work of the IACUC community itself.

The Health Research Extension Act of 1985 mandates "The organization and operation of animal care committee[1]" and charges this committee with ensuring the adherence to the guidelines for (a) the proper care of animals and (b) the proper treatment of animals. Specifically, the proper treatment of animals includes:

- the appropriate use of tranquilizers, analgesics, anesthetics, paralytics, and euthanasia for animals in such research; and
- appropriate pre-surgical and post-surgical veterinary medical and nursing care for animals in such research.

The US Government Principles[1] go on to specify that:

- "Procedures with animals that may cause more than momentary or slight pain or distress should be performed with appropriate sedation, analgesia, or anesthesia."
- "Where exceptions are required in relation to the provisions of these Principles, the decisions should not rest with the investigators directly concerned but should be made, with due regard to Principle II, by an appropriate review group, such as an institutional animal care and use committee."

It isn't until the *Guide*[2] where the use of a "protocol" is mentioned: "The committee is responsible for oversight and evaluation of the entire Program …including review and approval of proposed animal use (protocol review) and of proposed significant changes to animal use…" and "The animal use protocol is a detailed description of the proposed use of laboratory animals."

The *Guide* still does not provide detailed guidance on how appropriate sedation, analgesia, and anesthesia for (in this case) surgical procedures are assigned. For example, the IACUC could approve a policy that dictates the specific sedation, analgesia, and anesthesia regimen(s) required for all major survival surgeries in a given species, and PIs could agree within their IACUC protocols to adhere to that policy.

2. Should the activity be considered non-compliance?

Even if an animal activity has been conducted in accordance with the applicable regulatory expectations (e.g., PHS Policy, the Guide, and Animal Welfare Act and Regulations), that activity can still be considered non-compliance based on institutionally specific requirements. For example, perhaps a violation of an institutional policy or a clearly stated expectation for the care and use of animals (e.g., method for labeling cages or required documentation in the animal housing room) occurred. Whether the non-compliance needs to be reported to the regulatory agencies is often different from how an institution responds internally to addressing the animal concern. An institution can consider an activity to be non-compliant with institutional policies, yet the activity doesn't require a report to, for example, OLAW.

Ultimately, the goal of animal care and use programs includes the "Proper use of animals, including the avoidance or minimization of discomfort, distress, and pain when consistent with sound scientific practices..."[1] Ensuring research teams have the necessary knowledge and expertise to conduct the animal activities includes education on, and adherence to, institutional policies and expectations. Whether or not an activity is considered "non-compliance" should not prevent the IACUC from implementing appropriate mitigation strategies to prevent reoccurrence of an animal activity conducted in a manner that violates a federal regulation and/or an institutional policy or expectation. ❐

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References
1. Public Health Service. *PHS Policy on Humane Care and Use of Laboratory Animals*. (U.S. Department of Health and Human Services, National Institutes of Health, Bethesda, MD, 2015).
2. Institute for Laboratory Animal Research. *Guide for the Care and Use of Laboratory Animals* 8th edn. (National Academies Press, Washington DC, 2011).

and possible unintended non-compliance situations like Dr. Matt's. ❐

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References
1. Office of Laboratory Animal Welfare. *Reporting Noncompliance* https://olaw.nih.gov/guidance/reporting-noncompliance.htm
2. Public Health Service. *PHS Policy on Humane Care and Use of Laboratory Animals* (U.S. Department of Health and Human Services, National Institutes of Health, Bethesda, MD, 2015).

Protocol Compliance and Institutional Best Practices

Principal investigators (PIs) many times tend to have more than one IACUC protocol. Often, it can be for work that appears similar but have distinct differences. In this example, the anomaly in anesthesia is what caused the Post-Approval Monitor to report the deviation in the protocol.

I agree with the IACUC's decision to note the non-compliance, but the IACUC should understand why it may be more than administrative error and how this situation could be avoided in the future. After all, this is what OLAW will want to see in the institution's final report when submitting the letter to their office[1].

Although both propofol and TKX are approved pre-anesthetic agents for survival surgeries on pigs at Great Eastern University (GEU), the PI in this case only listed *one* method (TKX) to be used in the new protocol for cellular regeneration. The moment the post-doc fellow used propofol instead of TKX, it generated the non-compliance. According to NIH/OLAW, a change in use of an anesthetic agent is a significant change that requires IACUC review and approval[2]. There are situations where emergency or immediate intraoperative anesthetic changes may be made if the welfare of the animal is in jeopardy[3]. However, this was not the case in point as these animals recovered from surgery with no complications. Where there are situations when there are multiple IACUC protocols for one PI, training and meticulous review become very important to the research staff assigned to those protocols.

There are a few steps that the PI and the IACUC at GEU can do to mitigate non-compliance from recurring. A PI has a duty to its research team to ensure that they possess the necessary knowledge and expertise to accurately carry out the proposed procedures that are in the protocol[4].

One way to accomplish this is to ensure that all staff possess a copy, or have access to a copy, of the current IACUC protocols. This can be included in the laboratory on-boarding process or accomplished through continued staff training. The IACUC can monitor this by formally confirming that research staff are aware of the protocol(s) they are working on during the semiannual facility inspection. Lastly, the IACUC and the PI should collaborate when writing and reviewing protocols that utilize institutionally- approved methods of anesthesia. The IACUC should create a policy (or guidance) for all appropriate methods of anesthesia for a certain species of animals. To maintain compliance with best institutional practices, the PI should refer to the policy or list each acceptable method of anesthesia on their protocol form to allow the use of other institutional approved methods of anesthesia when necessary. ❐

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References
1. National Institutes of Health, Office of Extramural Research. *Guidance on Prompt Reporting to OLAW under the PHS Policy on Human Care and Use of Laboratory Animals*. Notice NOT-OD-05-034, 2005. http://grants.nih.gov/grants/guide/notice-files/not-od-05-034.html
2. National Institutes of Health, Office of Laboratory Animal Welfare. *What is considered a significant change to a project that would require IACUC review?* FAQ D.9, 2013. https://olaw.nih.gov/faqs/#/guidance/faqs?anchor=question50321
3. *The IACUC Handbook* 3rd edn. (ed. Silverman, J., Suckow, M. & Murthy, S.) (CRC Press, Boca Raton, 2014).
4. Institute for Laboratory Animal Research. *Guide for the Care and Use of Laboratory Animals* 8th edn. (National Academies Press, Washington DC, 2011) p 16-17.