

Renewed Responsibility

Dr. Jerry Silverman has been a faculty member at Great Eastern University (GEU) for over 15 years and has had an IACUC approved protocol for the duration. While many protocol questions, IACUC policies, and veterinary guidelines have changed over the years, Jerry's IACUC protocol has remained relatively untouched.

GEU's IACUC adheres to the regulatory expectations for IACUC review and approval and ensures that all IACUC approved protocols undergo a triennial

review. The electronic system used by the IACUC permits Principal Investigators (PIs) to "copy" their IACUC approved protocol to a new submission, wherein PIs are expected to complete any new questions, update the protocol content (e.g., research goals, animal numbers), and submit for review by the IACUC. The review process for renewal applications is the same as for new applications, and all submissions undergo review by at least two IACUC members, a veterinarian, and other safety offices (e.g., Institutional Biosafety Committee (IBC)

and Environmental Health and Safety (EHS)) as applicable.

When GEU's IACUC performed their most recent round of semi-annual inspections, the committee members found what they thought was non-compliance. A few cages of mice, under Jerry's IACUC approved protocol, were flagged as having undergone subcutaneous implantation of osmotic pumps the day before, but the post-operative records did not show that the appropriate analgesia regimen was administered. GEU's current veterinary guidelines require at least 48 hours of analgesia after this type of surgery (one pre-emptive dose just before surgery and one dose 24 hours after the first) and Jerry's records showed that only one pre-emptive dose was given. The veterinarian on the inspection evaluated the animals and commented that the mice appeared bright, alert, responsive, and without any signs of pain or distress.

Upon investigation, the IACUC found that Jerry's protocol was approved with only the one pre-emptive dose of analgesia for the specific pump implantation procedure. Furthermore, the protocol had been approved in this manner for the past 15 years.

Considering that Jerry's animal activities were compliant with his IACUC approved protocol, GEU's IACUC wasn't sure if they could consider the finding a non-compliance, even if the protocol did not align with GEU's current veterinary guidelines. Nonetheless, the IACUC requested that Jerry amend his protocol to increase the post-operative analgesia to 48 hours. This "request" did not sit well with Jerry; he has used this model for over 15 years and does not want to introduce a new variable.

What do you think:

1. Is there any non-compliance in this scenario and, if so, what is it?
2. Should the IACUC require Jerry to add the second dose of analgesia?
3. Are there any other considerations, alternatives that could be employed, or issues that need to be addressed?

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A WORD FROM USDA AND OLAW

In this scenario, a semiannual inspection revealed an incongruence between the pain management approved in the protocol and pain management procedures as listed in Great Eastern University's (GEU) veterinary guidelines. The procedures in the protocol have been unchanged for the past 15 years.

The regulatory requirements under the Animal Welfare Act cannot be applied because this scenario involves mice which are not a covered species¹.

Because the activities of Dr. Silverman's lab align with the IACUC-approved protocol, they are compliant with the PHS Policy and would not be reportable to OLAW². In the years since the protocol was first approved, new standards for pain relief by the IACUC are a commendable 3Rs refinement as discussed in the *Guide*³. It is incumbent on the investigator and the IACUC to determine whether the change in standards can be applied to the protocol. The PHS Policy IV.C.1.b. requires that withholding all or part of the analgesia regimen be "justified for scientific reasons in writing by the investigator"². Conducting a pilot study is an option that may determine whether withholding the analgesic is influencing data integrity and may also indicate if the animals are experiencing pain or distress and contribute to the scientific justification.

Because the IACUC has updated analgesia standards without a mechanism to have them considered during its continuing review of protocols, there is a program deficiency that needs correction and should be included in the semiannual

report to the Institutional Official⁴. More comprehensive post-approval monitoring by the IACUC may have identified the discrepancy sooner. One solution is for the IACUC to approve SOPs for common procedures, like the osmotic pump placement, revise the SOPs as veterinary and scientific standards advance, and review at least triennially⁵.

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Ignorance is not bliss!

There is no non-compliance in this scenario. Dr. Silverman is following his animal protocol as it was approved by the IACUC. It is unclear if at GEU “veterinary guidance” carries the same weight as an IACUC policy or if it is a best practice recommendation. There should be a clear definition of veterinary guidance if it is a requirement. I will answer going forward with the assumption the IACUC requires that veterinary guidance be followed.

Since the veterinary guidance has changed, the IACUC should ask Dr. Silverman to either update his analgesia duration to meet current standards or to give a scientific justification for why he can't. The IACUC reviewers, including the veterinary reviewer, did not catch that Dr. Silverman's animal protocol had not been updated to meet the current veterinary guidelines on their review; so he is not out of compliance. However, IACUC reviewers have the authority to ask for an amendment to any animal protocol at any time and it would be appropriate for the IACUC to ask that the animal protocol be updated. Although the current cohort of mice did not seem to be showing signs of pain, this fact alone is not a justification not to update the protocol. Future cohorts may experience a different level of pain. The lab has been using this analgesic regime for over 15 years. If there have been no veterinary concerns in that time the analgesia may have been adequate or the signs of pain were not observed and understood.

GEU should make sure that the research community knows the current IACUC standards that are expected and should communicate any changes in a timely manner. There should be a clear definition of veterinary guidance, including if it is a requirement.

IACUC reviewers should try to keep up to date on the current standards and require changes during the protocol review period. Researchers should be told that the IACUC may require updates to protocols when there are policy changes that occur outside of the normal review cycle. The Guide for the Care and Use of Laboratory Animals¹ discusses the value of post-approval monitoring (PAM) review. PAM review of approved animal protocols can be helpful in finding procedures that no longer meet the current IACUC expectations and help

COMPLIANCE CONSIDERATIONS

The Protocol Review coordinators offer the following compliance considerations:

Is there any non-compliance in this scenario and, if so, what is it?

1. Dr. Jerry Silverman's animal activities were performed in accordance with his IACUC approved protocol, which is the expected compliance action.
2. Ensuring proposed animal activities align with IACUC expectations (whether it is a new protocol or a triennial renewal) is a shared responsibility that includes the:
 - PI (to propose the activities according to their research needs with consideration of animal welfare);
 - IACUC voting members/reviewers (to ensure the proposed activities address the regulation and all institutional expectations)
 - Veterinarian(s) (e.g., to ensure appropriate use of analgesics, anesthetics, euthanasia, and pre/post- surgical care); and
 - Other safety units (e.g., if use of hazards are involved).
3. IACUCs must perform appropriate reviews of proposed animal activities; GEU's IACUC may have uncovered a larger, programmatic concern, e.g., how many other protocols have been approved with “inadvertent” deviation(s) from IACUC expectations?

Should the IACUC require Jerry to add the second dose of analgesia?

1. The IACUC must review all proposed animal activities in context of the regulations, including:
 - “Procedures with animals that may cause more than momentary or slight pain or distress should be performed with appropriate sedation, analgesia, or anesthesia.”¹
 - “Proper use of animals, including the avoidance or minimization of discomfort, distress, and pain when consistent with sound scientific practices, is imperative.”¹
2. The IACUC, in consultation with the veterinarian(s), should (among other things):
 - Evaluate animal welfare in context of the procedure(s) being performed and determine what analgesia is appropriate
 - Evaluate scientific elements of the research goal that may necessitate withholding analgesia

- Identify opportunities for refinement (as well as reduction and replacement) to further minimize pain, distress, and impact on animal welfare;
- Establish a plan for monitoring animals as well as specific criteria for identifying pain and distress in animals (e.g., establish humane endpoints); and
- Ensure that they are not requiring the use of analgesia when it is not necessary (i.e., when established criteria indicating pain and distress are not observed in absence of the analgesia) to avoid unnecessary/unintentional effects, such as constipation.

Are there any other considerations, alternatives that could be employed, or issues that need to be addressed?

1. When any change in policy or guidelines occurs, institutions should have an established mechanism for disseminating the pertinent information and ensuring all members of animal care and use programs are educated. This includes the IACUC reviewers, who need to be aware of current veterinary and regulatory expectations, at least if they are related to the content of the IACUC protocol applications.
2. Institutions should be careful when utilizing a system whereby components of the animal activities described in IACUC approved protocols reference out to external documents (e.g., policies, veterinary guidance, SOPs) for specific information needed to conduct the animal activities; this method can create opportunities for inadvertent non-compliance. □

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keep labs up to date on any changes in policy.

If a veterinarian is willing to observe the animals and agrees to make an exception for Dr. Silverman's study because the analgesic plan he has been using for many years is acceptable, then the IACUC could accept the veterinarian's recommendation and approve the animal

protocol as currently written (not requiring the amendment).

It is almost always beneficial to write analgesia guidance or policy as a minimum that is required with the caveat that analgesia will be given longer if needed. In this case perhaps the single dose could be approved, and the second dose given only when needed as defined by clinical signs of pain. □

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Putting guidelines, protocols, and inspections into context

There are a few items that stand out in this scenario. First, GEU appropriately reviews proposed animal activities and all IACUC approved protocols undergo a triennial review to adhere to the PHS Policy¹ and Animal Welfare Act Regulations. Next, the post-operative records showed that a pre-emptive dose of analgesic was given, but a second dose was not given 24 hours after the first dose. There is also additional information stating what is included in GEU's veterinary guidelines. On GEU IACUC's website, it clearly states that guidelines outline preferred or "best practice" methods, and that the IACUC will accept alternate methods with adequate justification.

First steps: PIs in these situations typically have records from previous years research, to demonstrate to the IACUC that the methods they use are appropriate. Jerry has been asked this question before by the IACUC since the current veterinary guidelines were implemented several years after he began this project. IACUC staff also consider the possibility that the PI used the "copy" function to complete their triennial review but copied the wrong

version. If he has done this work for over 15 years, there are several versions he could have copied, and depending on when those veterinary guidelines were implemented, the justification could have been missing. Finally, IACUC staff need to confirm when the veterinarian observed these mice during the inspection, e.g. how long after the procedure did their observation occur.

Next: Once IACUC staff review the current approved protocol and confirm if the justification section is missing, they will also review the previous approved versions of the protocol, to verify which drugs were approved for use (e.g. may include sustained release formulations), if the justification was present, and stated that veterinary staff may treat any animals experiencing pain/distress post-surgery. The information stored in an electronic veterinary medical record system will also support these findings, and whether a second dose of analgesic has ever been administered for these study animals.

In conclusion: With this information, GEU's IACUC will be able to determine there was no protocol non-compliance, that a second dose of analgesia was not needed,

and the PI's currently approved protocol needs to be administratively amended to add the missing information. The IACUC staff may also generate a report from their protocol system, to find out if there are other protocols similar to Jerry's. This will inform the committee's decision whether to update their veterinary guidelines. If GEU's IACUC has not already done their semiannual program review, then that is a good opportunity for this discussion to occur. □

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