

Jerald Silverman, DVM, Column Coordinator

## How should an IACUC handle high mortality rates?

Madison Schute, who was responsible for training new members of her laboratory, walked slowly to her meeting with a subcommittee of the Great Eastern University IACUC. The issue was whether or not a new person in her laboratory was trained adequately to perform intracerebral (IC) injections in mice. During a regular semi-annual inspection the IACUC inspectors found that almost half of all mice given intracerebral injections by the new lab member had died, whereas those administered by more experienced personnel were doing fine. Now Schute and the new research technician had to face an inquiry by the subcommittee.

Schute told the subcommittee that the new research technician was trained following her lab's standard IACUC approved procedures. That is, training began by the new person observing a skilled technician performing the technique. Then the new person, with Schute's oversight, practiced the technique on dead mice, progressing to doing the procedure with animals under non-recovery anesthesia, and finally to performing the injection under general anesthesia from which the animals recovered. In Schute's opinion the new technician was fully qualified to perform the procedure. The subcommittee thought otherwise, saying that the proof could be found in the unfortunate results of the injections

when compared to the results from other lab members. Additionally, the subcommittee said the problem was compounded by Schute not advising the IACUC or any school veterinarian that there was a problem. Schute responded that she did not think that there was a problem because 30–50% mouse mortality was not unusual for a new person performing IC injections, and the IACUC protocol even listed extra animals to account for experimental failures.

Do you think that Schute's explanation is credible or does her lab have more of a problem than she realizes? How would you proceed with handling the finding from the semiannual inspection?

### RESPONSE

#### More oversight and communication might be needed

Julie Fitzgerald, DVM, MS, DACVPM, CPIA, MAJ, VC

In our opinion, Schute has more of a problem than she realizes. Comparatively the new technician has a higher mortality rate than other technicians performing the same manipulation. This leads to the conclusion that the technician is not technically proficient. As stated in the Institutional Animal Care and Use Committee Guidebook, "training is a classic performance standard where the emphasis is on the outcome"<sup>1</sup>. While Schute has assured the Great Eastern University IACUC that the employee was properly trained using IACUC approved methods, it is ultimately the responsibility of the IACUC to ensure that personnel conducting procedures on research animals are appropriately qualified and trained.

We recommend that the technician be suspended from performing the procedure

in question until he or she can be retrained. As recommended in the *Guide for the Care and Use of Laboratory Animals*, training may need to be tailored to accommodate the educational background and experience of the individual<sup>2</sup>. Following laboratory standard operating procedures may not always be sufficient. If necropsies were performed to determine the exact cause of death of the mice, this could pinpoint the problem area that the retraining should focus on. Once retrained, this technician should continue to be closely monitored and the IACUC should request a periodic status update. Additionally, even though Schute is the training coordinator, she may have delegated the task of training to subordinate employees. The personnel that trained the new staff member should also be observed to make sure that proper techniques were taught.

Another point to make is that training and communication should never be the responsibility of one individual. The Great Eastern University animal care staff, including veterinarians and veterinary technicians, should also be actively involved in training at the University. We also feel that more open communication

between Schute and the veterinary staff could have prevented some of the animal deaths. Once it was determined that there was an increase in the mortality rate for procedures performed by this technician, Schute should have addressed the issue with veterinary staff and temporarily excused the technician from performing the technique.

Schute's opinion that there is no problem is also cause for some concern. It may be a good idea for the IACUC to review Schute's qualifications and experience for this procedure, to ensure that she can adequately oversee training for her laboratory. Finally, the Great Eastern University IACUC should consider reviewing their post approval monitoring program, which could have identified this issue earlier.

1. ARENA/OLAW. *Institutional Animal Care and Use Committee Guidebook* 2nd edn. (OLAW, Bethesda, MD, 2002).
2. Public Health Service. *Policy on Humane Care and Use of Laboratory Animals* (US Department of Health and Human Services, Washington, DC, 1986, revised 2015).

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**RESPONSE**

**Adverse events and deficiencies**

**Lucy Kennedy, DVM, DACLAM**

Let's first look at whether the training itself was adequate. Although our regulatory and guidance documents address training requirements, it's often in broad terms and the implementation is left up to each institution. In the *Guide for the Care and Use of Laboratory Animals*<sup>1</sup>, however, it specifically states that "the IACUC, together with the AV, is responsible for determining that personnel performing surgical procedures are appropriately qualified and trained in the procedures." In many institutions, the research facility provides training in general surgical, preparatory, and post-op techniques. However, the most qualified person to train the actual surgical technique is often in the lab. As long as it is documented clearly, this is an appropriate training modality for protocols in which the veterinary staff may not have the explicit expertise necessary to teach the procedure. Schute's description of her training program with the new lab member appears generally acceptable to me. At this point, any records of that training or proficiency assessments that the lab performed should be brought to the IACUC.

Based on the information that the IACUC has thus far, we do not know enough to determine exactly what happened with these mice. My plan moving forward would be to join and watch the next set of surgeries that the lab member is performing. At that time, I could evaluate not only the surgical technique, but all of the other factors that could be affected mortality: appropriate anesthesia, sterile technique, anesthetic and post-operative monitoring, and analgesic use. Necropsies of the dead mice, if available, would provide important information about what might have happened.

For the sake of this situation, let's just say that the lab member has adequate proficiency in all of these topics, and we're left with the statement made by Schute: that this particular procedure comes with a learning

**A Word from OLAW**

*In response to the questions posed in this scenario, the Office of Laboratory Animal Welfare (OLAW) offers the following guidance:*

The Office of Laboratory Animal Welfare (OLAW) acknowledges the thoughtful advice of the commenters and supports the importance of research personnel receiving adequate training and education prior to conducting procedures on animals. One of the commenters suggests reclassifying the mice that died into USDA Category E. Both the PHS Policy and the *Guide for the Care and Use of Laboratory Animals* expect procedures that may cause pain or distress to be performed with appropriate sedation, analgesia, or anesthesia, unless justified for scientific reasons<sup>1,2</sup>. Some IACUCs choose to monitor compliance with this expectation by assigning USDA pain categories to non-regulated species, but this is not required. IACUCs may develop other methods to comply with the Policy and the *Guide*.

1. Public Health Service Policy on Humane Care and Use of Laboratory Animals, IV.C.1.b. (US Department of Health and Human Services, Bethesda, MD, 1986; revised 2015, NIH Publication No. 15-8013 <http://grants.nih.gov/grants/olaw/references/phspol.htm>).
2. Institute for Laboratory Animal Research. *Guide for the Care and Use of Laboratory Animals* 8th edn. p. 26 (National Academies Press, Washington, DC, 2011).

**Patricia Brown, VMD, MS, DACLAM**

*Director  
OLAW, OER, OD, NIH, HHS*

curve that results in 30–50% mouse mortality. I would then label this an adverse event and a significant deficiency. The steps that need to follow involve investigation at the protocol level. The mice that have already died may need to be retroactively classified into USDA Category E. Additionally, the lab should re-categorize the percentage of mice expected to die without intervention into Category E, adding appropriate scientific justification for this failure rate. I would also ask the lab to increase the number of non-survival training mice they use, and to create a detailed monitoring plan for early intervention for future mice that are declining in health.

Lastly, perhaps the most significant deficiency was the lab's failure to notify veterinary staff of the sick or dead animals. It is sometimes challenging to get lab groups to understand that this communication needs to occur even if the negative outcome is expected. It's possible that the veterinary staff could have intervened and changed the outcome, either with treatment or earlier humane endpoints. The IACUC's plan for following up on the significant deficiency should include retraining of all members in this lab on communicating with the veterinary staff or IACUC whenever any significant changes to animal health and welfare occur.

1. Institute for Laboratory Animal Research. *Guide for the Care and Use of Laboratory Animals* 8th edn. (National Academies Press, Washington, DC, 2011).

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**RESPONSE**

**Postapproval monitoring could have identified problems earlier**

**Karen Lieber, RVT, RLATG**

The first issue that requires investigation is whether the approved IACUC protocol actually states that 30–50% mortality is expected for new staff; simply having additional animals approved to account for 'experimental failures' does not in itself indicate that this high mortality is expected. *The Guide* states that "the institution should provide appropriate education and training to members of research teams...to ensure that they have the necessary knowledge and expertise for the specific animal procedures proposed...before beginning animal work"<sup>1</sup>. This could certainly be

interpreted to mean that the IC-injection skills of the new staff must reach an acceptable success rate *before* survival procedures can be performed. In this case, the IACUC inspectors noted that the animals injected by the more experienced lab personnel were “doing fine.” Given this, it would seem unreasonable to accept the 50% mortality rate simply due to inexperience, unless the lab has provided specific data and references confirming that this is consistent with other labs/protocols using the same procedure. If such references or justification for such high mortality rates does not exist in the protocol, then noncompliance is indeed present.

In this circumstance, where training of lab staff is performed by senior lab members rather than an IACUC/animal resources trainer, the institution is not relieved of their responsibility to ensure “continuing IACUC oversight of

animal activities (as) required by Federal laws, regulations and policies”<sup>1</sup>. An SOP describing the training protocol should be created with detailed information on the training process, including a description of the progression from dead animals to survival animals must be described, along with an explanation of how the proficiency of the trainee is assessed at each time point during training. This could involve using dye for dead animal and non-survival injections, followed by necropsy/histological examination to assess the location and depth of the injection. Ultimately, the IACUC and/or veterinary staff should oversee final assessment of proficiency to perform survival surgeries.

This scenario exemplifies the need for a Postapproval Monitoring (PAM) program. Such a program would likely have noted the high mortality and, regardless of whether it is described in the protocol,

could have recommended changes to the training process that could improve survival rate. Possible non-training issues, such as whether the new member was injecting the same substance and volume as the members without mortality issues, could be investigated. If a different compound was used, then investigation into possible contamination could be recommended. Potential refinements, such as use of a small surgical incision to visualize the skull and/or a stereotaxic apparatus to help assure accurate placement of the needle could also be suggested.

1. Institute for Laboratory Animal Research. *Guide for the Care and Use of Laboratory Animals* 8th edn. (National Academies Press, Washington, DC, 2011).

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