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[1], 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 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.

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[1,2]. 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).

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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

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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"[1]. This could certainly be