uninhibited, but there would be an inherent risk of a repeat adverse event since no corrective action would be taken. A much more aggressive option would be for the IACUC to either suspend the protocol or ask Osterman to voluntarily cease his research until he can submit a plan aimed at reducing the risk of anesthetic deaths. This is an overzealous response—Osterman and his team have been very cooperative and there might not be enough specific knowledge within the lab to create a comprehensive plan.

With a reputation for shutting down research after self-reported adverse events, an IACUC risks developing a culture of fear where PIs are not forthcoming with adverse event reporting. The appropriate middle ground in this situation is for the IACUC and veterinary group to work with the PI to develop modifications of animal procedures without suspending protocol activity. This should include having Osterman and his technician-anesthetists work under the auspices of a veterinarian (or veterinary anesthesiologist) for a period of time to refine animal use procedures along with thorough hands-on anesthesia training. This training should provide the technician-anesthetists (who were responsible only for inducing, maintaining, and monitoring anesthesia) with refined plans/algorithms necessary to respond to anesthetic complications before they become life-threatening. Veterinarian-provided training could incorporate more complicated scenarios than the animal anesthesia simulation equipment being used can provide, making problems leading to animal death less likely in the future. Working cooperatively with Osterman this way builds trust and improves relationships between scientists, the IACUC, and the veterinary group, while simultaneously improving animal care.

1. U.S. Department of Health and Human Services. Public Health Service Policy on Humane Care and Use of Laboratory Animals (2015).
2. United States Department of Agriculture. *Animal Welfare Act and Animal Welfare Regulations* (2013).

Division of Comparative Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC.

RESPONSE

The time for active post-approval monitoring is now

Tracy H Vemulapalli

The unexpected death of any research animal is troubling, but especially when it appears that a trend might be forming. While in the case of Osterman's research, only two animals have died, it is incumbent upon the IACUC to determine the root cause of these unexpected deaths. The IACUC must, to the best of its ability, determine whether the root cause is due to inadequate training (a situation likely to incur other deaths) or a non-procedural issue that is unlikely to incur additional deaths (*e.g.*, an individual rabbit with undiagnosed cardiac disease). Osterman was correct in his timely reporting of the events before more unexpected deaths occurred. Rabbits are an "AWA-covered species." In the spirit of open communication, the IACUC should report the two deaths to the USDA while clearly stating that current evidence does not point to a non-compliance at this time[1]. Likewise, if the research is PHS-funded, OLAW should also be informed immediately[2]. The IACUC should report any findings of their subsequent investigations to these same agencies.

To aid in the IACUC investigation, the institution's veterinarians exercised due diligence in performing the necropsies on the two rabbits. The lack of gross anatomic and histopathological findings lends support that the deaths were not due to underlying disease conditions or anatomic anomalies. Likewise, the anesthesia machines appear to be in working order. This lack of findings, however, does not rule out a possible role that the anesthesia might have played in these deaths. For example, hypercapnia associated with physiologic dead space in the anesthesia circuit may not necessarily show up on necropsy. A root cause cannot be determined from the present investigation. Thus, I believe the body of evidence does not support an immediate IACUC suspension of Osterman's research, but, instead, the IACUC should institute active post-approval monitoring (PAM) of Osterman's rabbit protocol.

The Guide states that PAM "helps ensure the well-being of the animals and may provide opportunities to refine research procedures"[3]. Neither the AWAR or the PHS policy refer to PAM specifically by name. PAM can take several forms. One is the so-called "passive" form which relies on investigator self-reporting and the IACUC review of any adverse events reported on the annual and triennial protocol reviews required by the AWAR and PHS Policy, respectively[1,2]. In the case of Osterman's research, a more "active" PAM-approach is warranted because a potential procedural (and thus a training) issue with the implementation of the lab's rabbit-anesthesia protocol might be to blame. IACUC member(s) should observe the pre-anesthetic and anesthetic procedures from start-to-finish. At least one of the IACUC-appointed observers should be sufficiently knowledgeable in rabbit anesthesia. This could be one of the institution's veterinarians or an *ad-hoc* appointed observer, such as a board-certified veterinary anesthesiologist.

Should active PAM reveal deficiencies in the training and practice of anesthetic procedures as the root cause, the IACUC should suspend the protocol activities immediately[1]. To remove the suspension, Osterman should provide the IACUC proof of successful retraining of all staff involved in the rabbit anesthesia procedures. Additionally, it is within the IACUC's purview to stipulate that a continuation of active PAM is required as a condition of protocol reinstatement.

1. United States Department of Agriculture. *Animal Welfare Act and Animal Welfare Regulations* (2013).
2. U.S. Department of Health and Human Services. Public Health Service Policy on Humane Care and Use of Laboratory Animals (2015).
3. Institute for Laboratory Animal Research. *Guide for the Care and Use of Laboratory Animals* 8th edn. (National Academies Press, Washington, DC, 2011).

Department of Veterinary Pathobiology, College of Veterinary Medicine and Biomedical Sciences, Texas A & M University, College Station, TX.