under Category E in the annual USDA report, either (unless other protocol procedures the animals underwent warrant it).

We do not know if the study is PHS-funded, but even if it is, there would likewise be no need to report the incidents to OLAW, who acknowledge "that there may be levels of morbidity and mortality…that are not the result of violations of either the policy or the Guide", including "animal death or injuries related to manipulations that fall within parameters described in the IACUC-approved protocol"[2]. Given the inherent potential for some uncontrollable animal loss in the course of research, this wouldn't meet the criteria for reporting to AAALAC, either.

In summary, the PI has proven himself to be a conscientious animal user, and accepting his expert opinion and cautiously accommodating his keenness to proceed should satisfy the needs and obligations of all involved.

1. United States Department of Agriculture. *Animal Welfare Act and Animal Welfare Regulations* (2013).
2. National Institutes of Health, Office of Laboratory Animal Welfare. *Guidance on Prompt Reporting to OLAW Under the PHS Policy on Humane Care and Use of Laboratory Animals*. https://grants.nih.gov/grants/guide/notice-files/NOT-OD-05-034.html

Biogen, Inc., Cambridge, MA.

A Word from OLAW

In response to the issues posed in this scenario, the Office of Laboratory Animal Welfare (OLAW) provides the following clarifications:

This scenario describes the unanticipated deaths of control animals during a procedure that was conducted in the long-running study. The deaths were reported to the IACUC by the conscientious PI. The scenario asks, "How should the IACUC handle the situation?"

In addition to reviewing the report to the IACUC from the PI, the IACUC must further investigate the unexpected deaths to meet its oversight responsibilities under the PHS Policy, the *Guide* and the Animal Welfare Act and Regulations (AWAR)[1–3]. The investigation requires a thorough analysis by the IACUC, in cooperation with the research team, to discern any changes that may have caused the deaths. In this particular study, items to review include: 1) homeostasis of the animals (e.g., fluctuations in room temperature, fluid, or thermal support for the animal), 2) suitability of the animals for the study (e.g., animal conditioning, age, and weight), 3) fidelity to the IACUC-approved procedure (e.g., comparison of the protocol to the procedures and specific anesthesia actually used), and 4) condition of equipment (e.g., examination of maintenance records on all anesthesia and support equipment in use). Although the research team conducted their own investigation of both the equipment and animals, the IACUC may consider expanded consultation with veterinary pathologists, an independent diagnostic evaluation of the anesthesia machine by a certified technician, and a call to the rabbit supplier about any changes in health or genetics of the colony. To encourage continued engagement of the research team, a reasonable approach is to allow the research to continue with enhanced monitoring of the next procedure by the veterinarian and, if available, an anesthesia specialist.

If a cause is established, the IACUC may request amendments to the protocol to incorporate appropriate changes. Additional training may be necessary to improve responses to anesthetic complications and to engage rapid veterinary assistance. The IACUC may also find that the protocol needs to address an expected level of mortality.

If all procedures were performed according to the protocol and the deaths are due to individual rabbits' sensitivity to anesthesia, the incident is not reportable. If some aspect of the procedure was not done in accordance with the protocol or, for example, there was equipment failure, or inadequate thermal control or fluid support, then the IACUC must report to OLAW[4]. If the IACUC is unsure as to whether an incident is reportable, contacting OLAW by phone is the recommended approach.

1. Public Health Service. Policy on Humane Care and Use of Laboratory Animals (US Department of Health and Human Services, Washington, DC, 1986, revised 2015).
2. Institute for Laboratory Animal Research. Guide for the Care and Use of Laboratory Animals 8th edn. 43–44 (National Academies Press, Washington, DC, 2011).
3. United States Department of Agriculture. Animal Welfare Act and Animal Welfare Regulations (2013).
4. National Institutes of Health. Guidance on Prompt Reporting to OLAW under the PHS Policy on Humane Care and Use of Laboratory Animals. Notice NOT-OD-05-034 (National Institutes of Health, Washington, DC, 24 February 2005).

Patricia Brown, VMD, MS, DACLAM
Director
OLAW, OER, OD, NIH, HHS

RESPONSE

Reporting is unnecessary, but preventing further unexpected deaths is key

Steven T Shipley & Jenny Estes

The question of action by the IACUC is twofold – regulatory concerns, and methods to correct the situation/prevent recurrence need consideration. The IACUC needs to first decide if this situation warrants a report to OLAW and/or USDA. For the question of OLAW reporting, PHS Policy IV.F.3 (ref. 1) states that a report is necessary for "serious or continuing non-compliance with PHS Policy," "serious deviation from the provisions of the *Guide*" or "any suspension of an activity by the IACUC". The AWRs §2.31 (d)(7) (ref. 2) state that reporting to APHIS (and the funding agency) is required if an activity is suspended by the IACUC/IO. Osterman's lab conducted all work compliant with an approved protocol and promptly reported the events to the IACUC. They actively cooperated with IACUC and the institution's veterinarians to evaluate the animals, records and anesthesia machines. Based on this scenario, reporting to either OLAW or APHIS is not warranted.

The IACUC now needs to decide how to best proceed by matching their action to the severity of the adverse events. The least intrusive option for the PI would be to simply agree with Osterman and accept that these incidents were bad luck based on the five-year track record of no previous unexpected adverse events. This would allow Osterman to proceed with his research