On hold: what to report after a study is halted?

As any anesthetist or anesthesiologist knows, there is always a risk of complications when a patient is put under general anesthesia. This risk became reality when Dr. Giorgio Ionnelli's dog died while undergoing an experimental cardiac surgical procedure. The veterinary technician administering and monitoring the isoflurane anesthesia tried, but she was unable to revive and save the animal when its blood pressure dropped acutely, and the animal went into cardiac arrest.

Ionnelli voluntarily halted his study until the school's veterinarians and the IACUC could investigate the incident. After a thorough review, the investigators reported that they found no problems with the surgeon's performance, the technician's efforts to revive the dog, or the readouts from the blood pressure and electrocardiographic monitors. They suspected that the anesthetic vaporizer, which had been serviced recently, was providing an excessive amount of isoflurane gas at each setting of the machine. This suspicion was confirmed after an inspection by another technician from the company that had serviced the vaporizer. The machine was repaired and recalibrated, but the IACUC was faced with the question of what to report to the federal government, if anything. Some IACUC members and Ionnelli believed this was a single instance of a mechanical failure and not noncompliance with the *PHS Policy*[1] or the *Guide*[2]. However, the chairman of the IACUC said that because Ionnelli voluntarily halted his study, and the IACUC did not disagree with that action, the stoppage was analogous to a suspension by the IACUC and it had to be reported as such to OLAW and the USDA. The veterinarians were unsure of what advice to give to the IACUC. Although Ionnelli's IACUC-approved protocol clearly stated that after induction, anesthesia would be maintained at three percent isoflurane, and that was what was recorded on the anesthesia monitoring sheet, they knew that the numbers on the vaporizer showing the percent of isoflurane being delivered were not meant to be taken as the standard for judging the depth of anesthesia. Rather, they believed it was the job of the person monitoring the animal to adjust the anesthetic depth as needed.

What should the veterinarians tell the IACUC? What, if anything, should the IACUC report to OLAW and the USDA? Is there anything that might be done to help prevent a repeat of this problem? ❐

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The benefits of reporting

This scenario describes equipment failure that unfortunately lead to the death of an animal. This falls under OLAW's Guidance on Prompt Reporting to OLAW under the PHS Policy on Humane Care and Use of Laboratory Animals[1], which requires reporting of "*conditions that jeopardize the health or wellbeing of animals, including natural disasters, accidents, and mechanical failures, resulting in actual harm or death to animals*".

However, this scenario does not state whether the study is PHS funded; the IACUC would therefore need to refer to their Animal Welfare Assurance to determine their criteria for reporting to OLAW. If the study was not funded by PHS and the institution's Assurance states that only PHS-funded studies need be reported, then no reporting is required. However, if the Assurance is vaguely written, the institution should report this incident to OLAW. Under OLAW's Guidance, "*Reporting promptly to OLAW under IV.F.3 serves dual purposes. Foremost, it ensures that institutions deliberately address and correct situations that affect animal welfare, PHS supported research, and compliance with the Policy. In addition, it enables OLAW to monitor the institution's animal care and use program oversight under the Policy, evaluate allegations of noncompliance, and assess the effectiveness of PHS policies and procedures*".

Even though the IACUC investigation determined that this incident was not the result of a noncompliance or an animal welfare concern, there are benefits to reporting. The institution can describe how they have conscientiously addressed and corrected the issues related to this accident, including interviewing all personnel involved, having the machine re-inspected by its manufacturer, and reviewing the protocol to ensure compliance with actions taken during the surgery. By describing the investigative process, this demonstrates to OLAW that the institution is following processes outlined in their Animal Welfare Assurance and is committed to maintaining high standards in their program. Additionally, OLAW representatives can provide further guidance, if warranted, on follow up activities to prevent future issues.

Many institutions may see reporting to OLAW as a negative to their animal care and use program. They might for example worry about increased attention from activist groups or feel burdened by extra administrative work due to internal processes involved with reporting. But reporting can provide positive interactions with external regulatory agencies that are intended to assist institutions with maintaining compliance with animal welfare regulations. The veterinarians should recommend that the incident be reported to OLAW, including all the steps taken to ensure that appropriate processes were in place and functioning at the time of the event. The reporting of this incident should be discussed with the IACUC and the Institutional Officer as well.

Finally, a voluntary halt of studies is not the same as a suspension. A vote to suspend the protocol would require a convened IACUC meeting with a quorum of members. Therefore, this voluntary halt would not be reportable to the USDA. ❐

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Not a suspension, but still reportable

As illustrated in this scenario, surgery and anesthesia of animals, even when performed by trained individuals, carries the risk of complications resulting in morbidity and mortality. OLAW acknowledges this reality in guidance NOT-OD-05-034: "there may be levels of morbidity and mortality in virtually any animal-related activity, including those associated with the care and use of animals in research, testing, and teaching that are not the result of violations of either the Policy or the *Guide*"[1].

A WORD FROM APHIS AND OLAW

In response to the issues posed in this scenario, the US Department of Agriculture-Animal and Plant Health Inspection Service (USDA-APHIS) and the National Institutes of Health-Office of Laboratory Animal Welfare (NIH-OLAW) provide the following clarifications:

In this scenario, a dog unexpectedly dies while undergoing an experimental cardiac surgical procedure and the institution's IACUC must decide if the incident is reportable to USDA and NIH.

USDA-APHIS response

The issue in this scenario is whether the research facility is obligated to report to USDA an event involving a dog that died unexpectedly while undergoing an experimental cardiac surgical procedure.

There are four items research facilities are required to report to APHIS under the Animal Welfare Act (AWA) regulations: an annual report on animal usage[1], a change of operation affecting its status as a research facility[2], an animal activity suspension by the IACUC during a convened meeting with a quorum present[3], and a failure to correct a significant deficiency identified by the IACUC during a semiannual inspection[4]. Here, the investigator voluntarily halted the study following the animal's death to allow for review. The review determined that the veterinary technician followed the approved protocol for anesthetizing the animal, and that a properly serviced anesthetic vaporizer machine malfunctioned, leading to the animal's death. Although there was some question about whether the veterinary technician independently monitored the animal's depth of anesthesia beyond relying on the machine's reported levels, under these circumstances, there is not a regulatory obligation to report the event.

However, a facility may elect to voluntarily report an incident to USDA. Voluntary reporting allows proactive identification, correction, and prevention of issues that may negatively impact animal welfare, and provides an opportunity for a research facility to keep its USDA inspector up-to-date on activities at the facility.

NIH-OLAW response

The IACUC conducted an investigation of the incident and found that the surgical procedures, anesthetic monitoring, and routine maintenance of the anesthetic equipment were all appropriate. They determined that the cause of death was due to a faulty anesthetic vaporizer. Adverse events such as this where an animal is harmed or dies as the result of equipment malfunction are considered reportable to OLAW[5]. If institutions with an OLAW-approved Animal Welfare Assurance are in doubt about whether an incident is reportable, OLAW encourages a preliminary call from an authorized institutional representative and will provide guidance on the specific circumstances. The incident does not meet the requirements for a suspension because Public Health Service Policy (IV.C.6) states that: "The IACUC may suspend an activity only after review of the matter at a convened meeting of a quorum of the IACUC and with the suspension vote of a majority of the quorum present"[6]. ❐

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The *Guide for the Care and Use of Laboratory Animals*[2] states that effective post approval monitoring (PAM) strategies include "regular review of adverse or unexpected experimental outcomes affecting the animals". These strategies help fulfill the Health Research Extension Act and the Animal Welfare Act requirement that the IACUC inspect animal care and use facilities, including sites used for animal surgeries, every 6 months. Further, the *Guide* recommends a monitoring program that supports a culture of care focusing on the animals' well-being as well as encourages an educational partnership with investigators. After the dog died, the PI, veterinarians, and IACUC fulfilled best practices and regulatory requirements for PAM by voluntarily halting the study pending full investigation of this adverse event.

According to the Animal Welfare Act (AWR 2.31(d)(6))[3] and the Public Health Service Policy on Humane Care and Use of Laboratory Animals (IV.C.6)[4], a suspension of activity can occur only after review of the matter at a convened meeting of a quorum of the IACUC and a majority vote of the quorum to suspend. The immediate and voluntary halt of the study by the PI pending further investigation of the adverse event does not meet the criteria for suspension. In addition, the investigation identified no regulatory noncompliance, but rather an equipment issue that occurred despite timely preventive maintenance. While these conclusions do not support reporting, NOT-OD-05-034 does contain one example of reportable situations that could be interpreted to fit this event: "conditions that jeopardize the health or well-being of animals, including natural disasters, accidents, and *mechanical failures*, resulting in actual harm or death to animals". Therefore, the IACUC should report the event to OLAW. The OLAC report and IACUC meeting minutes should detail the investigation summary, measures taken to address the finding and any additional preventive measures taken.

Additional preventive measures include follow-up communication with the vaporizer company to ensure adequate training for all technicians servicing the units. Measures should also address the question of whether the veterinary technician felt constrained by the protocol to maintain a vaporizer setting that resulted in too deep a plane of anesthesia. Assuming necropsy did not identify any underlying

pathology predisposing the dog to intra-operative complications, veterinarians should review the entire anesthetic and analgesic regimen and *all* monitoring parameter trends (heart rate and blood pressure plus respiratory rate, temperature, oxygen saturation, end-tidal CO_2) with veterinary staff and the investigator. Refinements should focus on balanced anesthesia and development of anesthesia record templates that allow the anesthetist to easily track trends and respond to them immediately. This response may include consulting a veterinarian if there are any intra-operative concerns with the level of anesthesia or analgesia being provided by the protocol-approved regimen. Finally, the protocol should be modified to include a range of doses for anesthetics and analgesics that support the flexibility necessary to adhere to the veterinary standard for judging and adjusting the depth of anesthesia as needed. ❐

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3. Animal Welfare Act and Regulations, 9 CFR, Chapter 1, Subchapter A.
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No harm in picking up the phone and making the call

The circumstances surrounding the unanticipated death of any research animal should always be reviewed critically. However, the IACUC Chair should not compare an investigator voluntarily halting a study (for any reason) to a suspended protocol, an action that can only be determined by a quorum of a fully constituted IACUC[1]. On the other hand, Ionnelli should be commended for voluntarily halting the study and for promptly contacting and collaborating with the IACUC to identify the cause of the dog's unanticipated death. We assume this study is conducted at a PHS-assured institution and funded from an NIH grant, hence the concerns about contacting OLAW.

Multiple sections of the Animal Welfare Act Regulations[2] clearly outline the need for the veterinarians and/or IACUC to both provide and monitor adequate training and use of anesthesia (§ 2.31, 2.33 and 2.40); therefore the veterinarians could also provide the IACUC with additional information concerning all methods by which all personnel are expected to monitor the depth of anesthesia. The IACUC's investigation suggests the veterinary technician acting as anesthesiologist was using the machine in the prescribed manner and administering the isoflurane at what she thought was the appropriate dose. However, the details surrounding the length of time the animal was anesthetized were not provided and it's not perfectly clear if the anesthesiologist could have adjusted the dose fast enough to save the animal. Perhaps it was deduced by the simple process of elimination (i.e., diagnosis of exclusion), but it's also not clear how or why the investigative team determined the vaporizer was most likely miscalibrated and providing excessive isoflurane. Collectively, the investigator and staff appear to have followed the approved protocol and all relevant IACUC policies and standard operating procedures (not stated but implied), and therefore the unanticipated death of this research animal appears to be caused predominantly by a malfunctioning piece of surgical equipment.

We agree with the IACUC Chair that OLAW should be contacted. There was no wrongful intent or obvious deviation from the approved protocol, but as outlined in NOT-OD-05-034, a reportable incident to OLAW includes harm or death to an animal due to an accident or a mechanical failure[3]. Additionally, OLAW's stance on reporting noncompliance due to equipment failure was recently reinforced in a Protocol Review column of Lab Animal—in that scenario, OLAW commented that it is the IACUC's responsibility to oversee the investigation into the cause(s) of unanticipated animal deaths and further commented that unanticipated deaths due to equipment failure must be reported to OLAW[4]. As outlined in the Animal Welfare Inspection Guide and described in detail in a relatively recent Tech Note, this anesthesia-related incident of noncompliance should also be reported to the USDA to promote transparency and two-way communication[5].

This matter should be discussed with the Institutional Officer, re-evaluated at a meeting of the IACUC, and then reported. OLAW and the USDA (as well as AAALAC, if this is an accredited institution) should be contacted promptly and informed that equipment failure—in this case, the miscalibrated vaporizer—caused the unanticipated death of a research animal. The matter was investigated thoroughly, everyone involved (Ionnelli, veterinarians, staff, and IACUC) acted judiciously and conscientiously, and therefore there is no harm in picking up the phone to ask OLAW and the regional USDA representative for guidance. ❐

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