OFFICE OF RESEARCH OVERSIGHT

FOR-CAUSE REVIEW REPORT

Investigation of a Research Feline's Death while under Anesthesia

VA Northeast Ohio Healthcare System
Cleveland, OH

January 15, 2020

Veterans Health Administration

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ORO FOR-CAUSE REVIEW REPORT

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On-Site Review Dates: October 22-24, 2019
Date of Report: January 15, 2020

EXECUTIVE SUMMARY

On August 29, 2019, the Office of Research Oversight (ORO), Veterans Health Administration (VHA), was notified by VA Northeast Ohio Healthcare System (VANOHS) personnel that a cat housed in the facility's Animal Research Facility (ARF) for research purposes had died unexpectedly on July 30, 2019; the cat was under general anesthesia for imaging with a new micro computed tomography (CT) scanner during a training demonstration. Based on initial information received by ORO about the incident and a need for additional clarification on aspects of that information, ORO determined that an on-site review to evaluate the circumstances surrounding the cat's death was warranted. Accordingly, ORO conducted an on-site For-Cause Review of the incident at VANOHS on October 22-24, 2019. Based on its review, ORO concluded that there was a failure to provide adequate veterinary guidance to personnel anesthetizing the cat. This lack of appropriate guidance resulted in the cat being administered anesthesia via an anesthetic gas delivery system that was inappropriately configured for use with the cat, resulting in the cat's death. Furthermore, VANOHS inadvertently neglected to provide timely written notification of this reportable event to the National Institutes of Health Office of Laboratory Animal Welfare (NIH-OLAW) and the Association for the Assessment and Accreditation of Laboratory Animal Care, International (AAALAC). ORO also identified that training activities involving the use of other species were conducted without the required approval of the facility's Institutional Animal Care and Use Committee (IACUC). In addition, during the course of its review, ORO made an incidental safety finding that facility personnel failed to ensure appropriate configuration of the fire alarm system to allow perception of alerts by a deaf ARF employee in all areas of routine duty. Within 30 days of receipt of this report, VANOHS personnel will be required to develop a remedial action plan specifying the actions to address the findings in the report and timely completion dates. While on-site, ORO requested that VANOHS personnel develop an interim action plan to address the incidental safety finding rather than waiting until issuance of this report.

I. INTRODUCTION and REVIEW FOCUS

The Office of Research Oversight (ORO), Veterans Health Administration (VHA), reports to the Under Secretary for Health and oversees Department of Veterans Affairs (VA) research program compliance with respect to human subject protections, laboratory animal welfare, research safety and laboratory security, research information security, and research misconduct. ORO is also responsible for conducting education programs for facility Research Compliance Officers (RCOs). ORO performs periodic prospective and for-cause reviews, as needed, at facilities engaged in VHA research, to ensure compliance with the laws, regulations, and policies applicable to VHA research.

On August 29, 2019, ORO was notified by VA Northeast Ohio Healthcare System (VANOHS) personnel that a cat housed in the facility's Animal Research Facility (ARF) for research purposes had died unexpectedly under anesthesia on July 30, 2019, during a training session with a new computed tomography (CT) scanner in the ARF. ORO responded to the facility on September 4, 2019, and requested additional information. Based on the information provided by VANOHS personnel and a remaining need by ORO for additional clarification on aspects of the incident, ORO conducted an on-site For-Cause Review at VANOHS on October 22-24, 2019.

II. METHOD OF REVIEW

ORO's review included individual and group interviews with facility leadership, research administrative staff, research oversight committee members and staff, investigators, and/or other personnel associated with the facility's research compliance program as well as the trainers and all personnel who were both present during the anesthesia of the cat and who were available for interview[1] (Appendix A). ORO's review evaluated select facility research policies, procedures, and related documentation; ORO also reviewed the operating and instructional manuals associated with the CT and anesthesia equipment. In addition, ORO conducted a limited physical inspection of the ARF, including the CT and anesthesia equipment.

III. BACKGROUND INFORMATION

VANOHS Programmatic Information

Primary oversight of the VANOHS Animal Care and Use Program (ACUP) is provided by the facility's Institutional Animal Care and Use Committee (IACUC). VANOHS has a current Public Health Service (PHS) Animal Welfare Assurance D16-00535 (A3928-01) expiring March 31, 2023, on file with the National Institutes of Health – Office of Laboratory Animal Welfare (NIH-OLAW); holds full accreditation with the Association for the Assessment and Accreditation of Laboratory Animal Care, International (AAALAC; Unit No. VA-019); and is registered with the U.S. Department of Agriculture – Animal and Plant Health Inspection Service (USDA-APHIS; Registration No. 31-V-0004).

[1] ORO requested to speak with all individuals who were present during the incident but not all were available for interview.

The VANOHS research program was supported by two Veterinary Medical Consultants (VMCs), one of whom served as the Attending Veterinarian[2] (AV) with programmatic authority and provided the majority of veterinary care. The AV typically visited the facility three to four times weekly for 1 to 3 hours per visit or as needed; the alternate VMC, who began serving in January 2019, provided veterinary coverage for the facility in the absence of the AV and typically visited the ARF once weekly. ARF staffing included a full-time ARF supervisor (who also served as the IACUC Coordinator), two full-time Veterinary Technicians, and one full-time animal husbandry staff member supporting the ACUP.

In recent years, the VANOHS research portfolio has involved animal research with a variety of species, including nonhuman primates, canines, felines, rabbits, and rodents. VANOHS feline research has focused on bladder control and spinal cord injuries.

Circumstances Surrounding the Feline Death during a July 2019 Research Equipment Training Demonstration in the VANOHS ARF[3]

An VANOHS Principal Investigator (PI) acquired a PerkinElmer Quantum GX2 microCT Imaging System (microCT; s*ee Figure 1*) and RAS-4 Rodent Anesthesia System (Rodent Anesthesia Machine; *see Figure 2*) for *in vivo* research imaging of rodents that was installed in the ARF in May 2019. The vendor's website[4] indicated the microCT was designed for use with mice, rats, and rabbits. Although the microCT had originally been purchased for use in rodent research imaging, the facility had hoped to utilize this microCT for on-site research imaging of cats currently taking place at the affiliate. The vendor's website[5] indicated that the Rodent Anesthesia Machine was for use with mice and rats; during interviews, a trainer from the vendor informed ORO that she had never seen this anesthesia machine used with cats or with intubation.[6]

Vendor training for VANOHS personnel on the imaging system was scheduled for July 30-31, 2019. Email correspondence and interviews revealed that a cat housed in the ARF for research purposes and that had a history of bladder stones was designated by the AV to be imaged, purportedly, to assess its clinical condition (i.e., as part of the cat's on-going veterinary medical care). In conjunction, VA staff would be concurrently trained regarding appropriate use of the

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[2] The regulatory frameworks in *The Animal Welfare Act Regulations and Standards (9 CFR)* and *The Public Health Service Policy on Humane Care and Use of Laboratory Animals (PHS Policy)* establish that the Attending Veterinarian has direct or delegated authority and responsibility for activities involving animals at a facility. *For additional information see 9 CFR §1.1 definition of Attending Veterinarian, §2.31(b)(3)(i), §2.33 Attending Veterinarian and Veterinary Care as well as PHS Policy §IV.A.3.b(1).*

[3] Information ascertained through on-site interviews (*see Appendix A*) and review of select documentation (*see Appendix B*).

[4] *Accessible at* https://www.perkinelmer.com/product/quantum-gx2-instrument-cls149276 (*site visited November 6, 2019*)

[5] *Accessible at* https://www.perkinelmer.com/product/rodent-anesthesia-system-ras-4-cls146737 (*site visited November 6, 2019*)

[6] Intubation mean inserting an endotracheal tube into the animal's trachea for delivery of gas anesthesia.

imaging system and anesthesia machine. However, the decision to image the cat for *veterinary diagnostic purposes* was not documented in the cat's veterinary medical record.

On July 30, 2019, two vendor trainers were on-site for the scheduled 2-day training session. On the morning of the first day, the trainers provided classroom instruction to research personnel and ARF staff on the operation and capabilities of the microCT machine.

The vendor trainers and the ARF Supervisor had conferred via email and telephone prior to the visit to plan the anesthesia of the cat. Based on review of these emails and interviews with key personnel, the initial plan was to anesthetize the cat with the Rodent Anesthesia Machine, with anesthetic gas delivery via a nose cone. When the lead Veterinary Technician and trainers went to the ARF during the lunch break to look at the anesthesia equipment together, it was determined that the available nose cone was incompatible with the Rodent Anesthesia Machine due to the lack of an exhaust port; as a result, the lead Veterinary Technician indicated he would not proceed with anesthesia unless the AV was present and called the AV to request that she come to the ARF.

On the afternoon of July 30, 2019, approximately 10 individuals were present for the imaging demonstration including the two vendor trainers, the Veterinary Technician, a newly rehired Veterinary Technician who was scheduled to start in August, and at least 6 observers (including research staff and students). When the AV arrived, she evaluated the waste anesthesia gas line setup of the Rodent Anesthesia Machine, which was what she thought had been requested of her. The Veterinary Technicians were in the back of the crowded L-shaped room, not within close proximity of the AV, and could not hear the conversations between the trainers and AV. The Veterinary Technicians induced anesthesia using the VA "large animal" anesthesia machine

***Figure 1**: PerkinElmer Quantum GX2 microCT Imaging System.[4] Red arrow indicates opening through which anesthesia tubing enters/exits CT machine.*

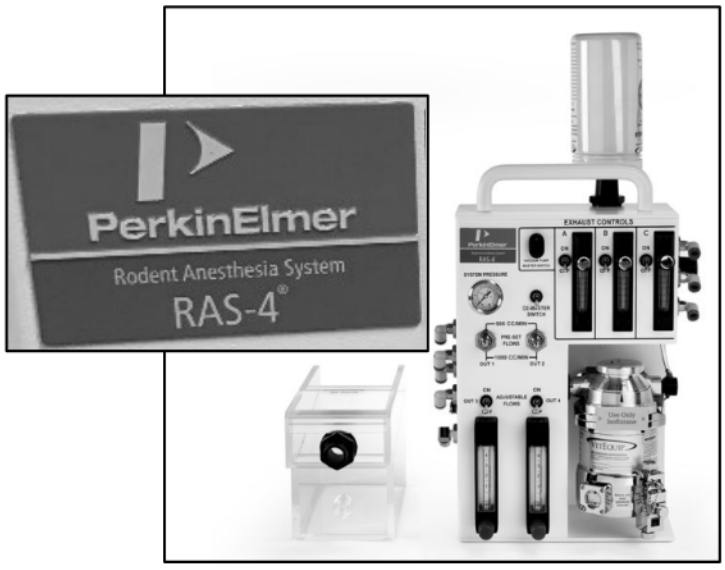

***Figure 2**: RAS-4 Rodent Anesthesia System.[5] Inset: Close-up of nameplate on machine at VANOHS.*

after believing they had received confirmation from the AV that they could proceed with induction, intubation, and imaging of the cat; however, the AV indicated in an email to ORO dated October 13, 2019, that she only provided recommendations to the trainers regarding evacuation of waste anesthesia gas from the chamber of the microCT.

Upon moving the fully anesthetized and intubated cat from the back of the room to the area with the microCT, personnel recognized that the tubing of the VA "large animal" anesthesia machine was not compatible with the microCT machine, as it was too large to fit through the aperture on the side of the CT machine once its door was closed (*see area indicated by red arrow in Figure 1*). Subsequently, the cat's endotracheal tube was connected directly to the inspiratory tube of the Rodent Anesthesia Machine.

The Rodent Anesthesia Machine was equipped with a non-rebreathing circuit requiring separate inhalation and exhalation tubes, rather than a single tube like the VA "large animal" anesthesia machine. With the cat's endotracheal tube connected only to the inhalation tube of the Rodent Anesthesia Machine, no outlet was provided for exhaled gases. Within seconds of making this connection, it was noted that the body of the cat became acutely distended. The breathing tube was disconnected from the anesthesia machine, the cat was taken to a treatment room, and emergency procedures were initiated. Ultimately, however, the cat did not respond to the treatments and euthanasia solution was administered.

Post-mortem examination revealed that the cat had an accumulation of air under the skin, inside the ribcage, outside of the lungs, and within the abdominal cavity as well as tearing of the lungs and diaphragm – a result of excessive inspiratory pressure due to the configuration of the anesthesia machine.

Planning for the training demonstration and the anesthesia of the cat had taken place primarily via email between the ARF Supervisor, research personnel, and the two vendor trainers beginning in May 2019. Although the AV was included as a recipient on some of the emails to plan the training, ORO was not provided with any documentation that demonstrated the active participation of the AV in the planning process. IACUC meeting minutes reflected that although the IACUC was aware of the upcoming training, the committee was not actively involved in the planning.

During interviews with ORO, vendor trainers (who were both PhD-level scientists) and VANOHS ARF personnel indicated that they were depending on the AV to provide guidance regarding appropriate anesthesia for the cat. Conversely, the AV indicated in an email to ORO dated October 13, 2019, as well as during on-site interviews, that although she prescribed the CT procedure that required anesthesia, she did not provide guidance to personnel during the planning of anesthesia for the cat's CT scan or, despite being present, during the actual administration of anesthesia on July 30th. She indicated she had thought the trainers were familiar with the operation, capabilities, and limitations of the Rodent Anesthesia Machine and depended on them rather than evaluating its use and providing guidance.

Through interviews with key personnel and the review of IACUC minutes, information submitted to ORO via email, and other documents provided both remotely and onsite, ORO identified several root causes that contributed to the death of the cat including, but not limited to:

- Communication break-downs among VA personnel as well as between VA personnel and the vendor trainers;
- Failure to provide veterinary guidance to personnel anesthetizing the cat; and
- Lack of appropriate planning in advance of the anesthesia and imaging of the cat.

Corrective actions implemented by the VANOHS IACUC at the August 15, 2019, IACUC meeting included:

- Acceptance of the training provided to the ARF Supervisor and Veterinary Technician by vendor trainers at the time of and immediately after the event as adequate;
- Acceptance of the use of the "large animal" anesthesia machine as a replacement for the Rodent Anesthesia Machine when imaging large animals with the microCT; the tubing was altered subsequent to the event to allow compatibility with the imaging equipment.

Corrective actions implemented by the VANOHS IACUC at the September 19, 2019, IACUC meeting included:

- The IACUC Chair, ARF Supervisor, Veterinary Technician, and AV should receive training on improving interpersonal communications.
- The IACUC Chair and AV must register for an upcoming IACUC 101/201 training session and, within one month of completion, give a review of the materials. (The Veterinary Technician involved in the incident had attended an IACUC 101/201 training session in August 2019).
- The Veterinary Technicians and AV will be required to attend training, to be conducted by an outside consultant, regarding use of the Rodent Anesthesia Machine; the training session will be open to all potential users.
- The IACUC Chair must draft a letter to be sent to PerkinElmer regarding the incident.
- An SOP will be developed regarding the process for verifying the safe use of any new "life support equipment" and any "off-label" use of existing "life support equipment."
- No non-rodent animals will be used with the microCT until an SOP is developed, reviewed, and approved.

In response to ORO's November 5, 2019, request for an interim update, VANOHS notified ORO on November 27, 2019, that additional corrective actions were implemented subsequent to the For-Cause Review; these and all previous corrective actions will be remotely monitored by ORO via the attached Remedial Action Plan through completion.

IV. FINDINGS, REFERENCES, and REQUIRED ACTIONS

The following items describe findings of noncompliance identified in ORO's review. Within 30 days after receipt of this report, VANOHS must complete the applicable sections of the attached Remedial Action Plan and submit it to ORO as instructed. The plan must include specific remedial actions and timely completion dates for each Finding, as indicated at VHA Handbook 1058.01 §5.c.

1. **The AV did not provide adequate guidance and direction to personnel anesthetizing a cat.**

   Finding:
   A cat housed in the ARF for research purposes and that had a history of bladder stones was selected by the AV to be imaged with the microCT in order to assess its clinical condition (i.e., as part of the cat's on-going veterinary medical care). Although this imaging procedure, which must be conducted under anesthesia, was prescribed by the AV, no veterinary guidance was provided to ARF staff regarding the proper administration of anesthesia to the cat to successfully conduct the imaging prior to or on the day of the procedure.

   Based upon review of emails and interviews with key personnel, the initial plan for anesthesia, developed by the ARF Supervisor and PerkinElmer trainers, was to administer gas anesthesia to the cat via a nose cone using the Rodent Anesthesia Machine. Instead, the cat was induced with the VA "large animal" anesthesia machine and intubated because it was recognized on the day of the procedure that the VA nose cone was not compatible with the Rodent Anesthesia Machine. After inducing anesthesia, personnel noted that the tubing of the VA "large animal" anesthesia machine was not compatible with the new CT machine. The cat's endotracheal tube was then connected to the non-rebreathing Rodent Anesthesia Machine that came with the CT; however, the configuration of this anesthesia machine did not provide an outlet for expired gases, resulting in the death of the animal.

   The AV indicated in an email to ORO dated October 13, 2019, as well as during on-site interviews, that she did not provide guidance to personnel either for the planning of anesthesia for the cat's CT scan or, despite being present, for the actual management of anesthesia on July 30th. Furthermore, the AV indicated she thought the trainers were familiar with the operation, capabilities, and limitations of the Rodent Anesthesia Machine and therefore had relied on their knowledge rather than evaluating its use and providing guidance.

   Reference(s):
   9 Code of Federal Regulations (CFR) §1.1. *"Attending veterinarian* means a person who … has direct or delegated authority for activities involving animals…."

The Guide for the Care and Use of Laboratory Animals, Eighth Edition (The Guide), p. 106.[7] "The veterinary care program is the responsibility of the attending veterinarian (AV)…. The AV should provide guidance to investigators and all personnel involved in the care and use of animals to ensure appropriate … handling … [and] anesthesia…."

VHA Handbook 1200.07 §7.f(4). "**Veterinary Care.** Adequate veterinary medical care must be provided for all animals…. The program of veterinary medical care must be planned and monitored by a laboratory animal veterinarian…. The program must include … the proper use of anesthetics … as directed by the responsible veterinarian…."

9 CFR §§2.33(a)(1)&(b)(4). "**Attending veterinarian and adequate veterinary care.** Each research facility shall have an attending veterinarian who shall provide adequate veterinary care to its animals … [and] shall establish and maintain programs of adequate veterinary care that include … [g]uidance to … personnel involved in the care and use of animals regarding handling … [and] anesthesia [of animals]…."

9 CFR §2.38(f)(1). "Handling of all animals shall be done as expeditiously and carefully as possible in a manner that does not cause … physical harm…."

Health Research Extension Act of 1985, Public Law 99-158 §§495(a)2(A)&(B). "Guidelines under this paragraph shall require the appropriate use of … anesthetics … for animals in [biomedical] research; and appropriate pre-surgical and post-surgical veterinary medical and nursing care for animals in such research."

Required Action 1:
As part of the research facility's programs of adequate veterinary care, the AV must provide direction and guidance regarding appropriate anesthesia and handling of all animals.

2. OLAW and AAALAC were not provided timely written notification of a reportable event.

Finding:
At the August 15, 2019, IACUC meeting, the committee determined that the cat's death was an event reportable to ORO, OLAW, and AAALAC. Although facility personnel notified ORO of the reportable event on August 29, 2019, facility personnel inadvertently failed to promptly notify OLAW and AAALAC. Once it was recognized

[7] ***VHA Handbook 1200.07 §4.b(4).*** "[A]ll VA facilities conducting animal research must comply with … the PHS Policy. The PHS Policy includes the … Guide for the Care and Use of Laboratory Animals (prepared by the National Research Council; henceforth called the Guide)…."

that the required notifications to OLAW and AAALAC had not been sent, a preliminary verbal notification was made to OLAW on November 19, 2019, and a formal written notification was sent to OLAW and AAALAC on November 27, 2019.[8]

Reference(s):

VHA Handbook 1200.07 §§8.i(5)(b)&(d). "Deficiencies meeting any of the criteria in subparagraph 8i(1) **must be reported in writing within 15 business days** through the [Associate Chief of Staff (ACOS) for Research and Development (R&D)] and the medical facility Director to the following agencies and offices: … OLAW, as required by PHS Policy … [and] AAALAC, as required by AAALAC rules of accreditation" (emphasis added).

VHA Handbook 1200.07 §8.i(1)(a). "As a condition of extending the privilege of conducting animal research to individual medical facilities, VA Central Office expects that the IACUC and institutional administrators will avoid any appearance of hiding or suppressing deficiencies…. The main categories of deficiencies that must be reported to outside authorities … are as follows: Any serious or continuing non-compliance with PHS Policy (including any serious deviation or continuing non-compliance with the provisions of the Guide, as required by the PHS Policy) or USDA [Animal Welfare Act (AWA)]."

VHA Handbook 1200.07 §8.k(1). "If preliminary findings suggest that an allegation does indeed represent a reportable deficiency as defined in subparagraph 8i, the agencies and/or groups listed in subparagraph 8i(5) must be contacted as indicated in paragraph 8i(4)."

The Public Health Service Policy on Humane Care and Use of Laboratory Animals (PHS Policy) §§IV.F.3.a.&b. [9] "The IACUC, through the Institutional Official, shall promptly provide OLAW with a full explanation of the circumstances and actions taken with respect to: any serious or continuing noncompliance with this Policy [and] any serious deviation from the provisions of the *Guide*."

NIH-OLAW NOT-OD-05-034, "Guidance on Prompt Reporting to OLAW under the PHS Policy on Humane Care and Use of Laboratory Animals" (dated February 24, 2005). "Institutions should notify OLAW of matters falling under IV.F.3 promptly, i.e., without delay…. A comprehensive list of definitive examples of reportable situations is impractical. Therefore, the examples below do not cover all instances but demonstrate the threshold at which OLAW expects to receive a report…. Examples of

[8] Due to encryption problems with the initial email transmissions, this formal notification was retransmitted to OLAW and AAALAC on December 2, 2019.

[9] ***VHA Handbook 1200.07 §4.b(4).*** "[A]ll VA facilities conducting animal research must comply with … the PHS Policy."

reportable situations [include]: 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…."

See also *NIH-OLAW's website "Reporting Noncompliance"* for additional information.[10]

Required Action 2:
The IACUC must ensure that notifications regarding reportable events are submitted in writing within 15 business days through the ACOS for R&D and the medical facility Director to OLAW and AAALAC.

3. **Training activities involving live animals were conducted without an IACUC approved protocol.**

Finding:
ORO was unable to definitively establish if the principle underlying rationale for selecting the cat was for training and demonstration purposes, which would have necessitated an IACUC-approved protocol, or to meet the veterinary medical needs of the animal, since the documented veterinary diagnostic plan in the cat's medical record indicated radiographs, rather than a CT, would be used to evaluate dissolution of the bladder stones. Additionally, the user manual for the micro CT included the following statement: "**CAUTION: Do not use this Quantum GX2 microCT Imaging System for medical purposes such as diagnosis or treatment.**"

ORO, however, did identify other training activities involving live animals conducted without an IACUC-approved protocol. Specific examples included:

- At least two rabbits and one cat were utilized for non-invasive, hands-on animal handling and restraint training since the beginning of 2018 without an IACUC-approved protocol.
- At least 22 mice and rats were utilized for hands-on animal handling, subcutaneous injection, and intraperitoneal injection training since the beginning of 2018 without an IACUC-approved protocol.

Reference(s):
VHA Handbook §1200.07 §3.d. "Animal research, as used in this Handbook, refers to any use of laboratory animals in research, testing, or training."

VHA Handbook §1200.07 §8.f(2). "All research projects involving animals must be approved by the IACUC and then by the R&D Committee prior to commencement."

[10] *Accessible at* https://olaw.nih.gov/guidance/reporting-noncompliance.htm

9 CFR §1.1. *"Activity* means … those elements of … teaching procedures that involve the care and use of animals."

9 CFR §2.31(c)(6). "With respect to activities involving animals, the IACUC, as an agent of the research facility, shall: … Review and approve, require modifications in (to secure approval), or withhold approval of those components of proposed activities related to the care and use of animals…."

PHS Policy §I. "It is the Policy of the Public Health Service (PHS) to require institutions to establish and maintain proper measures to ensure the appropriate care and use of all animals involved in research, research training, and biological testing activities (hereinafter referred to as 'activities')…."

PHS Policy §IV.B.6. "As an agent of the institution, the IACUC shall … review and approve, require modifications in (to secure approval), or withhold approval of those components of PHS-conducted or supported activities related to the care and use of animals…."

Required Action 3:
All animal research, including training and demonstration activities utilizing live animals, must be approved by the IACUC prior to commencement.

4. **The ARF fire alarm system was not configured in a manner that permitted all employees working in the ARF to perceive the alarm.**

Finding:
Fire alarms that produced both an audible and a visual strobe alert were located only in the hallways of the ARF. An employee, who was deaf and had worked in the ARF for many years, routinely worked alone both in animal rooms and other locations where the strobe light from the hallway alarms would not be visible, thus preventing him from perceiving the alert in the event the fire alarm system was activated.

Reference(s):
29 CFR §§1910.165(b)(2)&(3). "The employee alarm shall be capable of being perceived … by all employees in the affected portions of the workplace. *Tactile devices may be used to alert those employees who would not otherwise be able to recognize the audible or visual alarm. The employee alarm shall be distinctive and recognizable as a signal to evacuate the work area…*" (emphasis added).

Required Action 4:
VANOHS must ensure that alerts from the fire alarm system in the ARF can be perceived by all employees in the workplace and provide a distinctive and recognizable signal.

NOTE: *While on-site, ORO requested that VANOHS personnel develop an interim action plan to address the incidental safety finding rather than waiting until issuance of this report. On November 5, 2019, ORO requested an interim update. VANOHS reported that a line-drop from the facility's fire alarm system to a transmitter located on the employee's desk with the capability to communicate with the fire alert system for the ARF and the first and second floors of research. Once programming of the system is complete, a fire drill will be completed.*

V. ADDITIONAL OBSERVATIONS

ORO provides the following observations to assist the facility in further enhancing its research oversight program. The facility should evaluate the potential value of each relative to the particular needs of its own program.

1. **Observation:**
   The human-animal bond improves animal welfare by reducing animal stress through gentle handling practices, enhancing the animal's sense of safety and security, and fostering trust. This bond improves job satisfaction but also has the potential to lead to stress and/or emotional distress in animal handlers and research facility staff, particularly when research activities may include the euthanasia of animals. Since the VANOHS research program involves the use of companion animals, the Research Service is strongly encouraged to consider the potential value of developing an employee wellness program tailored to the special emotional needs of individuals involved directly and indirectly in the VA animal research program. Additional information can be found on the American Association of Laboratory Animal Science (AALAS) website.[11]

2. **Observation:**
   The Research Service should consider posting the policy for reporting animal welfare concerns more prominently and in additional locations where animal research takes place. Currently, the majority of the VANOHS Animal Incident Report sheets were posted on one bulletin board in the ARF and was obscured by a manila folder; the exposed text did not clearly indicate that the document provided information related to reporting potential animal welfare concerns.

   Reference(s):
   The Guide, p. 24. "Mechanisms for reporting [animal welfare] concerns should be posted in prominent locations in the facility…."

3. **Observation:**

[11] *Accessible at* https://www.aalas.org/education/educational-resources/cost-of-caring

Interviews with key personnel revealed that some practices (i.e., documentation of personnel training by Principal Investigators) were not being carried out as expected by the IACUC and that some animal activities (i.e., use of live animals for training) were taking place without the knowledge of the IACUC. The IACUC should consider evaluating current practices and methods utilized to conduct post-approval monitoring and semi-annual evaluations to ensure these practices and methods efficiently and effectively evaluate the compliance of the animal care and use program.

4. **Observation:**
Interviews with individual members as well as the full IACUC revealed apparent gaps in knowledge regarding appropriate IACUC function and policies regarding animal reporting and investigating animal welfare concerns. The Research Service should consider the potential value of providing additional opportunities for continuing education for its IACUC members regarding IACUC responsibilities, Federal regulations/policies, VHA policies, and the investigation and reporting of potential animal welfare concerns. Additional educational opportunities would help ensure that all members have a shared understanding regarding appropriate IACUC function and member roles.

Reference(s):
VHA Handbook 1200.07 §6. "The facility Director is responsible for ensuring … that IACUC members, IACUC support staff, veterinarians, and animal care staff have adequate opportunities to receive continuing education."

VHA Handbook 1200.07 §6.c(4). "**Continuing Education**. Training is mandated for all personnel who work with laboratory animals, including laboratory animal veterinarians, the supervisor, and husbandry care staff…. [I]t is critical that local funds be allocated for continuing education on an annual basis."

VI. CONCLUSIONS

ORO identified issues that will need to be remediated to come into compliance with applicable laws, regulations, and/or policies pertaining to the review, conduct and/or oversight of research. Identified noncompliance included, but was not limited to: inadequate veterinary guidance to personnel anesthetizing a cat, resulting in the cat's death; inadvertently neglecting to provide timely written notification of this reportable event to NIH-OLAW and AAALAC; the conduct of training activities with live animals without IACUC approval; and not ensuring that the fire alarm system was configured so that an ARF employee, who was deaf, could perceive alerts from it in all areas where he routinely worked. The Research Service was instructed to immediately begin remediating the finding related to the fire alarm system to ensure the on-going safety of this employee. All identified noncompliance must be addressed in a Remedial Action Plan that will be monitored by ORO until satisfied.

OFFICE OF RESEARCH OVERSIGHT

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Director, Research Safety and Animal Welfare, ORO

APPENDIX A
ORO REVIEW TEAM and FACILITY REPRESENTATIVES

ORO On-Site Review Team:

(b)(6)

Facility Representatives:

Jill Dietrich, JD, MBA, FACHE Medical Center Director

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APPENDIX B
SELECT DOCUMENTS REVIEWED

1. "Veterans Affairs Medical Center – Cleveland, OH (541) FWA#: 00004231 Research Initial Report" dated August 28, 2019, and associated attachment "Reportable Adverse Event Occurring July 30, 2019" (undated); submitted to ORO via email August 29, 2019
2. "Trainer 1: (Excerpts from CV)" (undated)
3. "Trainer 2: (CV excerpts)" (undated)
4. "Copies of all correspondence with the vendor related to setting up the training session" (undated)
5. Veterinary Medical Record, animal identification 17LM13
6. "ANIMAL RESEARCH FACILITY LSCDVAMC ANIMAL NECROPSY PROTOCOL" dated July 30, 2019; signed August 4, 2019
7. "RAS-4 Rodent Anesthesia System™ User Manual" P/N CLS147579 Rev. B
8. "Site Visit Preparation for the RAS-4 Rodent Anesthesia System" P/N CLS148054 Rev. A
9. "RAS-4 Quick Start Guide" P/N CLS14281 Rev. A
10. "System Manual Quantum GX2 microCT Imaging System" dated April 2018
11. "DOCUMENTS REQUIRED FOR THE ORO SITE VISIT" (undated)
12. "Timeline of Events 7/20/2019 from Intubation through Euthanasia" (undated)
13. "Updated Review of Reportable Adverse Event from Research and Development Committee: Minutes of September 5, 2019 Meeting" (undated)
14. "Email Verification of CT Scanner Anesthesia Training" email sent from Institutional Animal Care and Use Coordinator to various research facility personnel (including the Attending Veterinarian, Veterinary Technicians, the Associate Chief of Staff for Research and Development, the research Administrative Officer, investigators, and other research personnel on October 8, 2019
15. Correspondence from LSCVAMC to PerkinElmer dated October 16, 2019 (unsigned)
16. Various training records
17. LSVAMC Report of the Semiannual Evaluation dated April 19, 2019
18. "LSDVAMC PROGRAM OF VETERINARY CARE" (undated)
19. "LSDVAMC VMU VETERINARY SIGN IN SHEET" various dates 2018-19
20. "Inventory of Cats on Premises as of October 15, 2019"
21. Cat acquisition and transportation documentation, various dates
22. "Louis Stokes Cleveland Department of Veterans Affairs Medical Center Institutional Animal Care and Use Committee Policies & Procedures" Version 0.01, approved May 18, 2017
23. LSCVAMC Standard Operating Procedures (SOPs):
    a) SOP No. 14 (Version .01) "Cat Enrichment" dated March 16, 2019
    b) SOP No. 13 (Version .01) "Cat Husbandry" dated March 16, 2019
    c) SOP No. 15 (Version .01) "Cat Medical Care" dated March 16, 2019
    d) SOP No. 53 (Version 0.01) "ClearVet X-ray Machine Preparation and Usage" dated June 17, 2019
    e) SOP No. 38 (Version .01) "Euthanasia" dated February 21, 2019
    f) SOP No. 46 (Version .02) "Veterinary X-ray Safe Operating Procedure" dated February 21, 2019
    g) SOP No. 58 (Version .01) "Isoflurane Induction Box Usage" dated August 15, 2019

h) SOP "Perkin Elmer Quantum GX Micro CT Operating Procedure for Non-Living Specimens" dated October 9, 2019

24. IACUC Minutes, April through October 2019 Meetings
25. R&D Committee Minutes, August and September 2019 Meetings
26. LSCVAMC Local Forms:
    a) "Micro-CT Scheduling" (undated)
    b) "Micro-CT User Training Log" Version 1, dated September 18, 2019
    c) "MicroCT Sign-In/Out Sheet" (undated)
    d) "LSCDVAMC INVESTIGATOR TRAINING SHEET" (undated)
27. "Program Description Animal Care and Use Program Animal Research Facility Louis Stokes Cleveland Department of Veterans Affairs Medical Center" and cover memo dated December 1, 2017
28. Various emails, including but not limited to:
    a) October 13, 2019, Subject "[EXTERNAL] Response to IACUC for October meeting, Forwarded: Comments on IACUC minutes and other packet materials" from (b)(6) (b)(6) to ORORSAW with attachments
    b) October 22, 2019, Subject "FW: [EXTERNAL] Here is the post mortem report for [cat]" from (b)(6) with an attachment
    c) October 22, 2019, Subject "Documents" from (b)(6) (b)(6) with attachments
    d) October 23, 2019, Subject "FW: [EXTERNAL] Fwd: [External] Re: Email chain and CVs" from (b)(6)

REMEDIAL ACTION PLAN

ORO is providing a separate MSWord version of the Table below for the Facility to record proposed remedial steps for each Required Action specified in ORO's Report, with projected dates of completion. Please return to ORO the MSWord version of the table with the Facility portion completed, by the method and date specified in ORO's communication transmitting this Report. For completion of a Required Action, please provide relevant **supporting documents** (e.g., meeting minutes, work orders) to verify completion. For document revision submissions, please highlight the revisions.

Please provide a **specific justification** for any remedial action completion date projected to extend beyond the timeline set forth in VHA Handbook 1058.01 §5.c:

> *The VA facility Director must ensure timely implementation of remedial actions in response to identified noncompliance or as otherwise found warranted by ORO.*
>
> *(1) Except where remediation requires substantial renovation or fiscal expenditure, hiring, legal negotiations, or other extenuating circumstances**, remedial actions must be completed within 120 calendar days** after any determination of noncompliance.*
>
> *(2) Where remedial actions cannot be completed in 120 calendar days, the VA facility Director must provide ORO with an acceptable written justification and an acceptable timeline for completion.*

Deadline for completion of Required Actions: **May 14, 2020**

Animal Care and Use. ORO Case Number: **541-0064-A**

Required Action 1: As part of the research facility's programs of adequate veterinary care, the AV must provide direction and guidance regarding appropriate anesthesia and handling of all animals.	
Facility Response	***ORO Comments***
Response #1 ([DATE of response submission]) **Facility Action:** [TEXT] **Proposed Completion Date:** [DATE]	[ORO comments will be inserted here]
Required Action 2: The IACUC must ensure that notifications regarding reportable events are submitted in writing within 15 business days through the ACOS for R&D and the medical facility Director to OLAW and AAALAC.	
Facility Response	***ORO Comments***
Response #1 ([DATE of response submission]) **Facility Action:** [TEXT] **Proposed Completion Date:** [DATE]	[ORO comments will be inserted here]
Required Action 3: All animal research, including training and demonstration activities utilizing live animals, must be approved by the IACUC prior to commencement.	
Facility Response	***ORO Comments***

Response #1 ([DATE of response submission]) **Facility Action:** [TEXT] **Proposed Completion Date:** [DATE]	[ORO comments will be inserted here]
Required Action 4: VANOHS must ensure that alerts from the fire alarm system in the ARF can be perceived by all employees in the workplace and provide a distinctive and recognizable signal.	
Facility Response	***ORO Comments***
Response #1 ([DATE of response submission]) **Facility Action:** [TEXT] **Proposed Completion Date:** [DATE]	[ORO comments will be inserted here]