OFFICE OF RESEARCH OVERSIGHT

FOCUSED REVIEW REPORT

Feline Research
VA Northeast Ohio Healthcare System
Cleveland, Ohio

July 7, 2021

Veterans Health Administration

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ORO FOCUSED REVIEW REPORT

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Remote Review March – April 2021
Date of Report: July 7, 2021

EXECUTIVE SUMMARY

The Office of Research Oversight (ORO), Veterans Health Administration (VHA), conducted a remote Focused Review of feline research, including the local Institutional Animal Care and Use Committee (IACUC) oversight of such research, at VA Northeast Ohio Healthcare System (VANEOHS) in March – April 2021. 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: research personnel did not ensure cats maintained normal body temperatures when anesthetized for research procedures; research personnel deviated from study protocols prior to securing approval to implement such deviations; the Heating, Ventilation, and Air Conditioning (HVAC) system did not provide adequate humidity to rooms housing cats; rabies vaccines were not consistently administered to cats as described in the facility's written Program of Veterinary Care and were not in accordance with standard veterinary practice; and the IACUC did not ensure appropriate oversight of off-site feline research by regularly receiving and reviewing the semi-annual self-assessments of the affiliate institution where VA feline research activities were conducted. ORO also provided facility personnel with several non-mandatory recommendations to consider for enhancing the research oversight program and sustaining research compliance. Of note, ORO identified two active feline research protocols that could reasonably be construed as requiring additional reviews and approvals beyond those already received (*see* Section V, Observation #1 in this report). As such, ORO recommended that VANEOSH personnel refrain from proceeding with acquiring cats for one of the protocols, and refrain from engaging in further training activities involving cats for the other protocol, until consulting with both the VHA Office of Research & Development and the Office of General Counsel as to whether additional reviews and approvals of the protocols are required. All identified noncompliance must be addressed in a Remedial Action Plan that will be monitored by ORO until satisfied.

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 conducts Focused Reviews to assist facilities in complying with VA and other Federal requirements for research, especially in areas that may be of special concern at individual facilities or across the VHA research system as a whole. ORO's decision to conduct a Focused Review, and the scope of said review, are guided by: the size and/or complexity of a facility's research portfolio; specific issues of concern identified by ORO in an earlier Combined Program Review (CPR) or through other mechanisms (e.g., Facility Director's Certification, reports of noncompliance, etc.); known VHA-wide research compliance issues that might also be of relevance at a given facility; and/or other factors. ORO conducts Focused Reviews in fulfillment of the requirement set forth in 38 U.S.C. §7307(d)(1) that ORO conduct periodic inspections and reviews of VA facility research programs.

ORO conducted a remote, focused compliance review of the Animal Care and Use Program (ACUP) at VA Northeast Ohio Healthcare System (VANEOHS) in March – April 2021. ORO's review focused on VANEOHS' feline research program, related Institutional Animal Care and Use Committee (IACUC) operations, and whether research activities were compliant with applicable Federal regulations and policies.

II. METHOD OF REVIEW

ORO's review of VANEOHS included individual and group interviews of facility leadership, research administrative staff, research oversight committee members and staff, researchers, and/or other personnel associated with the facility's research program (Appendix A). ORO's review evaluated facility research policies, procedures, protocols,[1] memoranda of understanding (MOUs), and related documentation. ORO also conducted a remote video inspection of select areas within the Veterinary Medical Unit (VMU). Therefore, the findings and observations are based on information that ORO could acquire remotely.

III. FACILITY RESEARCH PROGRAM OVERVIEW

VANEOHS is a complexity level 1a facility affiliated with Case Western Reserve University (CWRU), the Cleveland Clinic Foundation (CCF) Lerner School of Medicine, and other healthcare entities in the Cleveland area. It operates a research program involving human subjects, laboratory animals, and hazardous agents, with a research project (direct cost) budget of $17,694,560 in FY20,[2] of which $13,791,274 was provided by the VHA Office of Research and

[1] The corresponding titles for protocols referenced by numerical identifiers in the Findings and Observations in this report are provided in Appendix B.

[2] Data from the facility's filed Research and Development Information System (RDIS) report.

Development (ORD). The Cleveland VA Medical Research and Education Foundation provides a flexible funding mechanism for non-VA sponsored research at VANEOHS.

At the time of ORO's review, there were 38 active animal care and use protocols conducted by 26 Principal Investigators (PIs). Four protocols, conducted by four PIs, included feline subjects; one of the feline protocols was conducted collaboratively with CCF. The research portfolio included studies on the complications of spinal cord injury, the use of neural control modalities to regain function, and the development of next generation electrical implants.

VANEOHS maintains its own IACUC and has executed a MOU with CCF describing shared oversight responsibilities for collaborative animal research activities, including one feline research project that involves the conduct of animal research activities at both locations.

VANEOHS 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; 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).

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, VANEOHS 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 Directive 1058.01 §5.g(6).

1. **Normal body temperatures were not maintained in some instances when cats were anesthetized for research procedures.**

   Finding:
   A review of anesthetic records for cats on Protocol No. 17-012-CT-014-CC revealed that three cats anesthetized for surgical or other study procedures during 2020 had lower than normal body temperatures even though Section C.2.c. of the Animal Component of Research Protocol (ACORP) had indicated that the body temperature of cats would be maintained at 38.5° Celsius (C) (101.3° Fahrenheit (F)). None of these records documented that the provisions for supplemental heat were adjusted to attempt to return the cat's temperature to the normal range intra-operatively or post-procedurally or that any other veterinary medical treatments were implemented to address the hypothermia. Specifically:

   - Cat 17MM1 had a body temperature of 35.9° - 36.5° C (96.6° - 97.7° F) for approximately 4 hours during a procedure on January 29, 2020, and 33.3° - 35.4° C

(91.9° - 95.7° F) for approximately 3.75 hours during a procedure on January 15, 2020;

- Cat 17ERT4 had a body temperature of 33.1° - 34.5° C (91.6° - 94.1° F) for approximately 3 hours during a procedure on July 22, 2020; and
- Cat 17LSN2 had a body temperature of 32.1° - 35.5° C (89.8° - 95.9° F) for approximately 3.75 hours during a procedure on December 7, 2020.

Reference(s):

Guide for the Care and Use of Laboratory Animals, Eighth Edition (The Guide),[3] ***p. 119.*** "**Intraoperative Monitoring.** Careful monitoring and timely attention to problems increase the likelihood of a successful surgical outcome. Monitoring includes routine evaluation of … physiological functions and conditions, such as body temperature…. Maintenance of normal body temperature minimizes cardiovascular and respiratory disturbances caused by anesthetic agents…."

9 Code of Federal Regulations (CFR) §2.33(b)(5). "Each research facility shall establish and maintain programs of adequate veterinary care that include: … Adequate pre-procedural and post-procedural care in accordance with current established veterinary medical and nursing procedures."

9 CFR §2.38(f)(1). "Handling[4] of all animals shall be done as expeditiously and carefully as possible in a manner that does not cause … excessive cooling…."

Instructions for Completion of the Animal Component of Research Protocol Main Body (ACORP Instructions) (Version 4) §Z.1.[5] "The Principal Investigator(s) must certify the accuracy of the information presented in the ACORP, and the agreement to perform the work as described."

Required Action 1:

All cats must be provided with adequate veterinary care, including maintenance of normal body temperature intra- and post-operatively.

2. **Several instances of protocol noncompliance were identified.**

Finding:

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[3] ***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)…."

[4] ***9 CFR §1.1.*** "***Handling*** means petting, feeding, watering, cleaning, manipulating, loading, crating, shifting, transferring, immobilizing, restraining, treating, training, working and moving, or any similar activity with respect to any animal."

[5] *Accessible at* https://www.research.va.gov/programs/animal_research/documents.cfm#docs-c *(last accessed on April 19, 2021)*

Document review and interviews with key personnel revealed that some animal procedures were not performed as described in the approved protocol, and that these protocol deviations, which constituted significant changes from the protocol, had not been first reviewed and approved by the IACUC nor reviewed administratively in conjunction with a documented consultation with the attending veterinarian. Specifically, ORO noted the following protocol deviations:

- Section C.2.c. of Protocol No. 17-012-CT-19-014-CC indicated that cats would be given buprenorphine, an analgesic, prior to the conduct of a research procedure performed under anesthesia; however, a review of Cat 17MM1's records revealed that this dose was not administered before a procedure on January 29, 2020.[6]
- Protocol No. 15-041-CT-19-001 indicated in Appendix 5, where surgical procedures are described, that cats undergoing a terminal surgical procedure would be premedicated with the analgesic buprenorphine (if fentanyl was not given) and the sedative dexmedetomidine, and that anesthesia would be induced with ketamine. The records for Cats 17ETD3 and 17ETG3 did not document the administration of either fentanyl or buprenorphine preoperatively on October 15, 2019, and August 27, 2019, respectively, and indicated the cats were induced with isoflurane, instead of ketamine. Additionally, the record for Cat 17LQD2 did not document how anesthesia was induced or the administration of dexmedetomidine for a terminal surgical procedure on November 12, 2019.

Reference(s):

NIH-OLAW Frequently Asked Questions (FAQs) B.9.[7] "The PHS Policy, *Guide*, and the USDA Animal Welfare Regulations presume that all ongoing animal activities have received the required prospective review and approval. An activity that has been undertaken without prior approval should be halted and subsequently reported to OLAW because it constitutes serious noncompliance."

The Public Health Service Policy on Humane Care and Use of Laboratory Animals (PHS Policy) §IV.B.7.[8] "***Functions of the Institutional Animal Care and Use Committee***…. [T]he IACUC shall …. review and approve, require modifications in (to secure approval), or withhold approval of proposed significant changes regarding the use of animals in ongoing activities."

[6] NIH-OLAW Notice NOT-OD-14-126 "Guidance on Significant Changes to Animal Activities," dated August 26, 2014, recognizes changes in anesthesia, analgesia, or sedation as significant changes. *See* https://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-126.html (*last accessed June 18, 2021*).

[7] *Accessible at https://olaw.nih.gov/faqs#/guidance/faqs (last accessed May 10, 2021)*

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

9 CFR §2.31(c)(7). *"**IACUC functions.*** [T]he IACUC … shall: … Review and approve, require modifications in (to secure approval), or withhold approval of proposed significant changes regarding the care and use of animals in ongoing activities."

VHA Handbook 1200.07, Appendix E §2.a(2)(j). "The IACCU [sic] is responsible for … Ensuring there are procedures are [sic] in place for review and approval of significant changes to all protocols prior to initiation of changes."

VHA Handbook 1200.07, Appendix D §1.z(1)(g)2. "IACUC approval must be obtained before: … There is a change in procedures in any way that might … be considered a significant departure from the written protocol."

ACORP Instructions (Version 4) §Z.1. "The Principal Investigator(s) must certify the accuracy of the information presented in the ACORP, and the agreement to perform the work as described."

VHA Directive 1200.02(1) §14.a(9). "Specific responsibilities [of VA Investigators] include … [a]ssuming full responsibility for all aspects in conducting the research."

The Guide, pp. 25-26. "[The IACUC] is responsible for oversight and evaluation of the entire [Animal Care and Use] Program and its components … [including] review and approval of proposed animal use (protocol review) and of proposed significant changes to animal use…. The following topics should be considered in the preparation of the protocol by the researcher and its review by the IACUC: … appropriate sedation, analgesia, and anesthesia… [and] postprocedural care and observation…."

The Guide, p. 121. "Preemptive analgesia (the administration of preoperative and intraoperative analgesia) enhances intraoperative patient stability and optimizes postoperative care and well-being by reducing postoperative pain…."

NIH-OLAW NOT-OD-14-126, "Guidance on Significant Changes to Animal Activities" (dated August 26, 2014).[9] "The IACUC has some discretion to use IACUC-reviewed and -approved policies to define what it considers a significant change, or to establish a mechanism for determining significance on a case-by-case basis in accordance with the PHS Policy…. [S]ignificant changes include changes that have, or have the potential to have, a negative impact on animal welfare…. In addition, some activities that may not have a direct impact on animal welfare are also considered to be significant…. Specific significant changes [including changes in anesthesia, analgesia, and sedation] … may be handled administratively according to IACUC-reviewed and -approved policies in consultation with a veterinarian authorized by the IACUC…. Consultation with the veterinarian must be documented…."

[9] *Accessible at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-126.html (last accessed June 18, 2021)*

Required Action 2:
The IACUC and PIs must ensure that research is conducted in accordance with the approved protocol (including the protocols listed in this Finding) and that any proposed significant modifications to animal research protocols are approved prior to implementation.

3. **The Heating, Ventilation, and Air Conditioning (HVAC) system did not maintain adequate humidity in rooms housing cats.**

Finding:
Review of select temperature and humidity records of areas where cats were housed indicated that humidity levels were below the *Guide*-recommended and the *Animal Welfare Act Regulations and Standards (AWA R&S)*-required range of 30-70% for 22 days in February 2020 in one housing room; and for 8 of 13 days recorded in February 2020 and 28 days in February 2019 in another housing room. In addition, during the virtual walkthrough of select areas of the VMU, ORO noted that humidity levels were lower than 30% for 5 of the first 6 days of April 2021 documented on the husbandry record for the room in which the cats were currently housed.

Reference(s):
9 CFR §1.1. "***Indoor housing facility*** means any structure or building with environmental controls housing or intended to house animals and meeting the following … requirement[]: **(1)** It must be capable … of maintaining humidity levels of 30 to 70 percent…."

The Guide, p. 139. "Relative humidity [in animal housing areas] should[10] generally be maintained within a range of 30-70% throughout the year."

The Guide, pp. 44-45. "[T]he acceptable range of relative humidity is considered to be 30% to 70% for most mammalian species…. In climates where it is difficult to provide a sufficient level of environmental relative humidity, animals should be closely monitored for negative effects such as excessively flakey skin…."

VHA Handbook 1200.07 §2.g. "[Animal h]ousing needs to ensure that the general health of animals is safeguarded and that undue stress is avoided, with appropriate attention paid to environmental factors such as … humidity."

VHA Handbook 1200.07 Appendix E §3.b(18). "Temperature and humidity in the animal rooms [must] stay within normal ranges."

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[10] ***NIH-OLAW NOT-OD-12-148 "Guidance on Departures from the Provisions of the Guide for the Care and Use of Laboratory Animals" (dated September 10, 2012).*** "Deviation from a should statement [in the *Guide*] without IACUC approval is a noncompliance that must be reported to OLAW through the [Institutional Official (IO)]."

Required Action 3:
The facility must ensure that relative humidity levels in animal housing areas are consistently maintained within an acceptable range.[11]

4. **Rabies vaccines were not consistently administered to cats as described in the facility's written Program of Veterinary Care or in accordance with standard veterinary practice.**

Finding:
The facility's written Program of Veterinary Care developed by the part-time Veterinary [redacted] indicated that cats would be vaccinated for rabies upon arrival to the VMU, if not already vaccinated by the vendor, and then again within 1 year of administration of the initial vaccine. A review of veterinary medical records revealed that this did not consistently occur. Specific examples included:

- Cat 16CIZ2 was acquired by VANEOHS on October 10, 2017. Administration of a rabies vaccines was not documented at any point within its veterinary medical record prior to being adopted out on January 28, 2019.
- Eight cats that had been vaccinated for rabies by the vendor on July 24, 2018, and acquired by VANEOHS on August 2, 2018, were due to receive another rabies vaccine by July 24, 2019. One cat did not receive another rabies vaccine prior to being euthanized on August 27, 2019, and the seven other cats were not subsequently vaccinated for rabies until October 2019.

Reference(s):
VHA Handbook 1200.07 §7.f(3). "**Veterinary Care.** Adequate veterinary medical care must be provided for all animals maintained for research, testing, training, or educational purposes. The program of veterinary medical care must be planned and monitored by a laboratory animal veterinarian qualified by training and experience for this responsibility. The program must include: … Application of currently accepted measures of prophylaxis…."

Louis Stokes Cleveland Department of Veterans Affairs Medical Center (LSCDVAMC)[12] ***PROGRAM OF VETERINARY CARE (undated).***[13] "LSCDVAMC uses only purpose-bred

[11] Although NIH-OLAW has described procedures for IACUCs to review and approve departures from the *Guide* under certain circumstances, the *AWA R&S* only allow exceptions from the *AWA R&S* when such exceptions are specified and justified in the animal research proposal and are approved by the IACUC.

[12] VANEOHS was previously referred to as the Louis Stokes Cleveland Department of Veterans Affairs Medical Center (LSCDVAMC).

[13] According to facility staff, this Program of Veterinary Care (PVC) was in place during the timeframes referenced in the Finding; the current PVC, *VA Northeast Ohio Healthcare System (VANEOHS) PROGRAM OF VETERINARY CARE*

cats. The following vaccinations … are performed for dogs [sic] on arrival (if not performed by the vendor) and annually thereafter: … Rabies vaccination."

LSCDVAMC Adoption Policy for Research Animals (dated June 21, 2018). "**Requirements for Approval of Adoption**…. [A]ll requisite vaccinations will be given."

ORD Guidance Document AR2018-001, "Adoption of Research Animals Covered by the USDA Animal Welfare Act Regulations" (dated June 27, 2018), §4.d.[14] "Regarding dog and cat adoptions, to promote responsible pet ownership, VA generally considers as eligible for adoption … animals of any species that are up-do-date on vaccinations according to current veterinary standards."[15]

9 CFR §§2.33(a)(1)&(b)(2). "Each research facility shall have an attending veterinarian who shall provide adequate veterinary care to its animals in compliance with this section: … In the case of a part-time attending veterinarian or consultant arrangements, the formal arrangements shall include a written program of veterinary care…. Each research facility shall establish and maintain programs of adequate veterinary care that include: … The use of appropriate methods to prevent … diseases…."

Required Action 4:
Rabies vaccines must be consistently administered to cats as described in the facility's written Program of Veterinary Care and in accordance with standard veterinary practice.

5. **The IACUC did not regularly receive and review the semi-annual self-assessments of the affiliate where VA feline research activities were conducted.**

Finding:
Some cats for on-going VA research were housed longer than 12 hours (and, in other cases, for more than 24 hours) at CCF. An MOU, dated March 30, 2015 (which was in place until the current MOU was executed on December 16, 2020), included provisions for the VA IACUC to review CCF semi-annual self-assessments in lieu of conducting an independent assessment of the affiliate's animal care and use program. However, review of IACUC meeting minutes and interviews with committee members confirmed that semi-annual self-assessments from CCF were not received and reviewed by the VA

(dated October 26, 2020), also requires rabies vaccines to be given to cats within 1 year of the initial vaccination by the vendor.

[14] *Accessible at https://www.research.va.gov/programs/animal_research/guidance.cfm (last accessed April 21, 2021)*

[15] *See,* ***Compendium of Animal Rabies Prevention and Control, 2016, Part I §B.1.b.*** "**Prevention and control methods in domestic and confined animals. Preexposure vaccination and management**…. Regardless of the age of the animal at initial vaccination, a booster vaccination should be administered 1 year later…. All … cats … should be vaccinated against rabies and revaccinated in accordance with recommendations in this compendium…." Journal of the American Veterinary Medical Association, March 1, 2016, Vol. 248, No. 5, Pages 505-517. *Accessible at https://avmajournals.avma.org/doi/pdf/10.2460/javma.248.5.505 (last accessed May 5, 2021)*

IACUC as a business item in the past 2 years nor had the VA IACUC conducted any independent assessments of CCF's animal care and use program.

Reference(s):
PHS Policy §§IV.B.1&2. "***Functions of the Institutional Animal Care and Use Committee***. As an agent of the institution, the IACUC shall … review at least once every six months the institution's program for humane care and use of animals … [and] inspect at least once every six months all of the institution's animal facilities (including satellite facilities[16])…."

9 CFR §§2.31(c)(1)&(2). "With respect to activities involving animals, the IACUC, as an agent of the research facility, shall: Review, at least once every six months, the research facility's program for humane care and use of animals, using title 9, chapter I, subchapter A – Animal Welfare, as a basis for evaluation; [and] Inspect, at least once every six months, all of the research facility's animal facilities, including animal study areas[17]."

Animal Care and Use Agreement Between Louis Stokes Cleveland Department of Veterans Affairs Medical Center and The Cleveland Clinic Foundation (dated March 30, 2015) §3. "**Semi-annual Inspection.** Neither IACUC is required to perform duplicate inspections of the alternate institution's facilities. Instead, the semi-annual program review and facility inspection reports prepared by each IACUC will be provided to the alternate IACUC for review and may be accepted by the alternate IACUC in lieu of conducting an independent review and inspection."

Required Action 5:
The IACUC must receive and review the affiliate semi-annual self-assessments or, alternatively, the IACUC itself must conduct a semi-annual review of the affiliate's animal care and use program.

6. **The IACUC did not ensure that all protocols included complete, clear, congruent, and accurate descriptions of research activities.**

Finding:
A review of IACUC-approved protocols revealed various sections that contained conflicting information and, in some instances, contained incomplete or inaccurate information regarding experimental procedures thereby calling into question what

[16] ***PHS Policy §III.B.*** "A satellite facility is any containment outside of a core facility or centrally designated or managed area in which animals are housed for more than 24 hours."

[17] ***9 CFR §1.1.*** "***Study area*** means any building room, area, enclosure, or other containment outside of a core facility or centrally designated or managed area in which animals are housed for more than 12 hours."

procedures were actually approved and/or how the investigator actually intended to carry out the procedures. Specific examples included:

- Protocol No. 15-041-CT-19-001 indicated in Section J that cats would be monitored after the electrode implant surgery by research staff daily for 3 days then weekly; however, Appendix 5 Section 7.e. indicated that after this surgery the cats would be monitored twice daily by protocol personnel until the cats reached the protocol's endpoints. Section C.2.c. and Appendix 5 Section 2 indicated that cats would be given lactated ringers solution (LRS) during the surgical procedures; however, Appendix 5 Section 6.b. indicated cats would be given LRS or sodium chloride with dextrose and sodium bicarbonate. Section C.2.c. indicated that sutures would be removed 7-10 days after the electrode implant surgery; however, Appendix 5 Section 2 indicated that sutures would be removed at 7 days after this surgery.
- Protocol No. 20-010-CT-19-019 did not contain clear and accurate information regarding how cats would be used for training purposes and specific information about the actual types of procedures research personnel would be trained to conduct. Interviews with protocol personnel revealed that no training involving procedures requiring cats to be sedated or anesthetized would be performed under this protocol and that training sessions using cats would be limited to only handling and noninvasive demonstrations of techniques for injections (without the use of actual needles or injection of any substances); however, the protocol itself stated, "Cat procedures will be performed as described in the IACUC approved reference document James G. Fox, Lynn C. Anderson, Franklin M. Loew, and Fred W Quimby, eds.: Laboratory Animal Medicine, second edition, 2002" without describing specifically which procedures would be taught using live animals or how the procedures would be performed. Although VANEOHS personnel indicated cats would not be anesthetized, sedated, or administered any compounds during training sessions, the protocol stated that "Cat drug dosages are consistent with guidance provided in the IACUC approved reference documents James G. Fox, Lynn C. Anderson, Franklin M. Loew, and Fred W Quimby, eds.: Laboratory Animal Medicine, current edition, 2002, and Donald C Plumb, Plumb's Veterinary Drug Handbook, current edition." The protocol also indicated that after being used for training sessions, cats would not be used again for 3 weeks. Review of records revealed that the identification of cats used during training sessions was not recorded or tracked, and interviews revealed that protocol personnel did not maintain this information in another manner.
- Protocol No. 18-065-CT-19-003 indicated in Appendix 3 that ketamine would be given at a dose of 10 mg/kg intravenously (IV); however, Appendix 5 Section 2 indicated that a dose of 3-5 mg/kg intramuscularly (IM) would be given. In Appendix 3 the buprenorphine dose was listed as 0.02-0.03 mg/kg buccally or sublingually; however, Appendix 5 Section 2 listed a dose of 0.01 mg/kg buccally or 0.01-0.03 mg/kg IM, and Appendix 5 Sections 7.b. and 7.c. listed a dose of 0.01-0.03 mg/kg or 0.01 mg/kg buccally, IM, or subcutaneously (SQ). Appendix 3 listed the acepromazine dose as 0.05-0.1 mg/kg IM; however, Appendix 5 Section 2 and

Section 5.b. listed a dose of 0.0250-0.1 mg/kg SQ or IM. Additionally, the protocol indicated in Appendix 3 that "Buprenorphine and Meloxicam and/or Onsior will be given postoperatively…." The protocol language, as written, indicated that meloxicam and Onsior®, both of which are nonsteroidal anti-inflammatory drugs (NSAIDs), could be given together; however, the concurrent use of NSAIDs in cats is contraindicated due to the potential for adverse side effects.

Reference(s):

PHS Policy §IV.C.1. "In order to approve proposed research projects or proposed significant changes in ongoing research projects, the IACUC shall conduct a review of those components related to the care and use of animals and determine that the proposed research projects are in accordance with [PHS] Policy. In making this determination, the IACUC shall confirm that the research project will be conducted in accordance with the Animal Welfare Act … [and] is consistent with the *Guide* unless acceptable justification for a departure is presented."

The Guide, pp. 25-26. "The animal use protocol is a detailed description of the proposed use of laboratory animals. The following topics should be considered in the preparation of the protocol by the researcher and its review by the IACUC: … a clear and concise sequential description of the procedures involving the use of animals…; … appropriate sedation, analgesia, and anesthesia…; … [and] postprocedural care and observation…."

9 CFR §2.31(e)(3). "A proposal to conduct an activity involving animals, or to make a significant change in an ongoing activity involving animals, must contain the following: … A complete description of the proposed use of the animals."

VHA Directive 1200.02(1) §14.a(3)(c). "Specific responsibilities [of VA Investigators] include but are not limited to … [d]eveloping a protocol that … [c]ontains a sufficient description of the research to allow the [Research and Development (R&D)] Committee and/or its subcommittees to fully review the Research Protocol, including all procedures…."

VHA Handbook 1200.07 Appendix D §1.z(1)(e). "The information provided in this [Animal Component of Research Protocol (ACORP)] must be complete and accurate."

USDA Animal Welfare Inspection Guide (USDA AWIG) (dated January 26, 2021) §7.2.4.6.[18] "**Teaching Protocols**. When reviewing teaching protocols, some areas to pay special attention to include: … There is a complete description of the procedures to

[18] *Accessible at https://www.aphis.usda.gov/aphis/ourfocus/animalwelfare/sa_publications/ct_publications_and_guidance_documents (last accessed April 26, 2021)*

be used; [and t]he number of procedures to be performed on each animal is clearly stated…."

Required Action 6:
The IACUC and PIs must ensure that approved protocols contain complete, clear, congruent, and accurate descriptions of research activities, including the protocols identified in this Finding.

7. A significant change to an ongoing animal protocol was approved via a noncompliant method.

Finding:
On October 28, 2020, veterinary verification and consultation (VVC),[19] rather than full committee review (FCR) or designated member review (DMR), was used to approve an amendment to Protocol No. 17-012-CT-19-014-CC that changed the device removal surgery from nonsurvival to survival, to allow adoption of the cats after completion of the research.

Reference(s):
NIH-OLAW NOT-OD-14-126, "Guidance on Significant Changes to Animal Activities" (dated August 26, 2014).[20] "Significant changes described … below, must be approved by one of the valid IACUC approval methods described in the PHS Policy IV.C.2., that is FCR or DMR, including changes: from nonsurvival to survival surgery."

PHS Policy §§IV.C.1.&2. "In order to approve … proposed significant changes in ongoing research projects, the IACUC shall conduct a review of those components related to the care and use of animals…. Prior to the review, each IACUC member shall be provided with a list of proposed research projects to be reviewed … and any member of the IACUC may obtain, upon request, full committee review of those research projects. If full committee review is not requested, at least one member of the IACUC, designated by the chairperson and qualified to conduct the review, shall review those research projects and have the authority to approve, require modifications in (to secure approval), or request full committee review of those research projects."

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[19] NIH-OLAW NOT-OD-14-126 described VVC, or veterinary verification and consultation, as an acceptable route of IACUC approval of certain types of significant changes. Per the notice, certain significant changes "may be handled administratively according to IACUC-reviewed and -approved policies in consultation with a veterinarian authorized by the IACUC. The veterinarian is not conducting [Designated Member Review], but is serving as a subject matter expert to verify that compliance with the IACUC-reviewed and -approved policy is appropriate for the animals in this circumstance…. The veterinarian may refer any request to the IACUC for review for any reason and must refer any request that does not meet the parameters of the IACUC-reviewed and -approved policies." *Accessible at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-126.html (last accessed April 22, 2021)*

[20] *Accessible at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-126.html (last accessed April 22, 2021)*

9 CFR §§2.31(d)(1)&(2). "In order to approve … proposed significant changes in ongoing activities, the IACUC shall conduct a review of those components of the activities related to the care and use of animals…. Prior to IACUC review, each member of the Committee shall be provided with a list of proposed activities to be reviewed … and any member of the IACUC may obtain, upon request, full Committee review of those activities. If full Committee review is not requested, at least one member of the IACUC, designated by the chairman and qualified to conduct the review, shall review those activities, and shall have the authority to approve, require modifications in (to secure approval), or request full Committee review of any of those activities."

Required Action 7:
The IACUC must ensure that proposed significant changes to ongoing animal protocols, including the one in this Finding, are reviewed and approved by compliant methods.

8. **The IACUC was not appropriately constituted between March 2 and December 7, 2020, due to lapses in the appointments of both the nonaffiliated and nonscientific members.**

Finding:
Review of IACUC member appointment letters revealed lapses in the appointments of two required members. The (b)(6) member, who is affiliated with the facility, was appointed to the committee in a letter dated March 7, 2017, for a 3-year term beginning March 2, 2017. The committee's (b)(6) member, who is a (b)(6) who has not been involved with animal research, was appointed to the committee in a letter dated June 1, 2017, for a 3-year term beginning that day. Neither of these individuals was reappointed to the committee by the facility Director until December 7, 2020, resulting in approximately 9- and 6-month lapses in their appointments, respectively, nor were other individuals meeting the (b)(6) and (b)(6) membership qualifications appointed during the lapse, resulting in the IACUC being improperly constituted from March 2 through December 7, 2020.

Reference(s):
VHA Handbook 1200.07 §3.g. "As the highest ranking administrative official at the local VA medical facility, the Director must serve as the [Chief Executive Officer (CEO)], and appoint IACUC members in writing to the VA (or joint VA affiliate) IACUC as required by the Animal Welfare Act … and the Health Research Extension Act…."

VHA Handbook 1200.07 §8.a(1). "Only a properly constituted IACUC may conduct official business. The required voting members include a Chairperson, the Attending Veterinarian, one scientist with animal research experience, a non-affiliated member (must meet the criteria in subpar. 8a(3), this Handbook), and a lay member (who must not be involved in animal research)."

9 CFR §§2.31(b)(1)&(3)(ii). *"**IACUC membership.*** The members of each Committee shall be appointed by the Chief Executive Officer of the research facility; … Of the members of the Committee: … At least one shall not be affiliated in any way with the facility other than as a member of the Committee, and shall not be a member of the immediate family of a person who is affiliated with the facility. The Secretary intends that such person will provide representation for general community interests in the proper care and treatment of animals."

PHS Policy §§IV.A.3.b(3)&(4). "The [IACUC] shall consist of no fewer than five members, and shall include at least: … one member whose primary concerns are in a nonscientific area (e.g., ethicist, lawyer, and member of the clergy); and one individual who is not affiliated with the institution in any way other than as a member of the IACUC, and is not a member of the immediate family of a person who is affiliated with the institution."

NIH-OLAW FAQ B.1, "What are the IACUC membership criteria?"[21] "If an appointed member who fulfills one of the required specified positions (i.e., scientist, nonscientist, veterinarian, or unaffiliated) leaves the committee so that that position is no longer filled, the IACUC is not properly constituted and may not conduct official business until a member who fulfills the required position is appointed by the CEO…."

Required Action 8:
The Research Service must ensure that the IACUC is properly constituted when conducting official business and that all required voting members are appropriately appointed by the facility Director.

9. One alternate IACUC member did not serve on the committee in a compliant manner.

Finding:
An IACUC member was appointed by the facility Director to serve a 3-year term as an "Alternate [redacted] Voting Member" in a letter dated November 1, 2018. Beginning in January 2020, IACUC minutes revealed that this individual began functioning as a regular/primary IACUC member, rather than only participating in the absence of the regular/primary member for whom the individual was appointed to serve as an alternate. At the December 16, 2019, meeting the IACUC had approved a motion to change this individual from an alternate to "a primary voting member;" however, this proposed change was not subsequently forwarded through the R&D Committee to the facility Director, and the facility Director never appointed this individual in writing to serve as a regular/primary IACUC member, rather than as an alternate.

Reference(s):

[21] *Accessible at https://olaw.nih.gov/faqs#/guidance/faqs (last accessed May 10, 2021)*

VHA Handbook 1200.07 §3.g. "As the highest ranking administrative official at the local VA medical facility, the Director must serve as the CEO, and appoint IACUC members in writing to the VA (or joint VA affiliate) IACUC as required by the Animal Welfare Act (title 7 United States Code (U.S.C.) 2143(b)(1)) and the Health Research Extension Act (42 U.S.C. §289d)."

VHA Handbook 1200.07 §8.a. "IACUC members in consultation with the R&D Committee must forward the name(s) of nominees for the IACUC to the medical facility Director. The medical facility Director must officially appoint members in writing…."

NIH-OLAW NOT-OD-11-053, "Guidance to Reduce Regulatory Burden for IACUC Administration Regarding Alternate Members and Approval Dates" (dated March 18, 2011).[22] "The Chief Executive Officer, or designee, must appoint alternates to the IACUC in writing…. Alternates may only serve as an alternate in the membership category(s) for which they are qualified…. An IACUC member and his/her alternate may not contribute to a quorum at the same time or act in an official IACUC capacity at the same time. An alternate may only contribute to a quorum and function as an IACUC member if the regular member for whom they serve as alternate is unavailable to participate in IACUC business…."

Required Action 9:
The Research Service must ensure that all alternate IACUC members serve in that capacity only, unless subsequently appointed by the facility Director to serve in a different capacity.

10. For several protocols, the IACUC did not weigh potential animal welfare concerns against the benefits to be gained.

Finding:
Despite providing an adequate description of the benefits to be gained from the proposed work, two ACORPs failed to describe the potential animal welfare concerns in Section B of the ACORP where the investigator was instructed to explain how the benefits outweigh potential animal welfare concerns (e.g., pain or distress) that may be caused in the animals that are to be used. Specifically:

- Protocol No. 18-065-CT-19-003 did not address any potential animal welfare concerns for the cats during the course of the research in Section B of the ACORP.
- Protocol No. 17-012-CT-19-014-CC stated in Section B of the ACORP that the benefits of the research outweighed the potential distress to the animals involved but did not provide any specific information regarding the actual nature of the potential animal welfare concerns.

[22] *Accessible at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-11-053.html (last accessed April 27, 2021)*

Reference(s):
ACORP Instructions (Version 4) §B. "**Description of Relevance and Harm/Benefit Analysis**…. The IACUC is obligated to weigh the benefits to be gained from the work against potential concerns about animal welfare … so it is important for the protocol to provide the information that the IACUC needs to assess this."

ACORP Main Body (Version 4) §B.[23] "**Description of Relevance and Harm/Benefit Analysis.** Using non-technical (lay) language that a senior high school student would understand, briefly describe how this research project is intended to improve the health of people and/or other animals, or otherwise to serve the good of society, and explain how these benefits outweigh the pain or distress that may be caused in the animals that are to be used for this protocol" (emphases in original).

The Guide, p. 27. "[T]he IACUC is obliged to weigh the objectives of the study against potential animal welfare concerns."

AAALAC FAQ C.3, "Harm-benefit analysis."[24] "[Harm-benefit] analysis should be performed prior to the [IACUC's] final approval of the protocol, and should be a primary consideration in the review process."

Required Action 10:
The IACUC must ensure that the benefits of the study are weighed against potential animal welfare concerns for each ACORP under review.

11. In one instance, a PI did not consider alternatives to procedures involving more than momentary or slight pain or distress when requesting a significant change to an on-going protocol.

Finding:
On October 28, 2020, VVC was used to approve a significant change to Protocol No. 17-012-CT-19-014-CC which included adding a spay or neuter procedure to be performed either at the same time as the device removal surgery or as a separate surgery to facilitate adoption. Neither the amendment form nor the revised ACORP contained a written narrative description of the methods and sources used to determine that alternatives[25] to the spay or neuter surgery, procedures that involve more than momentary or slight pain or distress, were not available.

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[23] *Accessible at* https://www.research.va.gov/programs/animal_research/documents.cfm#docs-c *(last accessed on April 19, 2021)*

[24] VHA Handbook 1200.07 §7.e. indicates that "All VA animal facilities … must be accredited by AAALAC." This FAQ is accessible at https://www.aaalac.org/accreditation-program/faqs/ (*last accessed June 17, 2021*).

[25] The consideration of alternatives in animal research includes the concept of the three R's: Refinements to research (to avoid or minimize discomfort, distress, and pain), Reduction of animal numbers, and Replacement

Reference(s):

9 CFR §2.31(d)(1)(ii). *"**IACUC review of activities involving animals.*** In order to approve … significant changes in ongoing activities … the IACUC shall determine that the … significant changes in ongoing activities meet the following requirements: … The principal investigator has considered alternatives to procedures that may cause more than momentary or slight pain or distress to the animals, and has provided a written narrative description of the methods and sources, e.g., the Animal Welfare Information Center, used to determine that alternatives were not available."

The Guide, p. 25. "The animal use protocol is a detailed description of the proposed use of laboratory animals. The following topics should be considered in the preparation of the protocol by the researcher and its review by the IACUC: … availability or appropriateness of the use of less invasive procedures…."

The Guide, p. 27. "By considering opportunities for refinement, … both the institution and the principal investigator (PI) can begin to address their shared obligations for humane animal care and use."

VHA Handbook 1200.07 Appendix D §1.v(1). "**Consideration of Alternatives and the Prevention of Unnecessary Duplication**. Complete the following items [in the ACORP] and retain copies of computer database search results to demonstrate compliance with the law, if regulatory authorities or the IACUC choose to audit the project. Investigators must consider less painful or less stressful alternatives to procedures…. Perform one or more database searches to meet these mandates, unless compelling justifications can be made without doing so."

ACORP Instructions (Version 4) §§W.1.&4. "**Consideration of Alternatives….** This item addresses minimizing the harm/benefit (*AAALAC FAQs*, C.3; *Guide*, p. 27) to be derived from this work by decreasing the potential for causing pain or distress in the research animals…. VA Policy (*1200.07,* par. 8.f(2)(a)3) requires that the IACUC review documentation that alternatives have been considered for each of the potentially painful or distressing animal procedures proposed…. [Keep] copies of computer database search results in your files to demonstrate your compliance with the law if regulatory authorities or the IACUC should choose to audit your project. 1. The [*AWA R&S*] (§2.31(d)(1)(ii-iii)) require investigators to consider less painful or less stressful alternatives to each potentially painful or distressing procedure, and provide assurance that proposed research does not unnecessarily duplicate previous work. Perform one or more database searches to meet these mandates unless compelling justifications can be

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with non-animal models (if possible). *See also* ***NIH-OLAW FAQ D.7. "Should the IACUC consider the three 'Rs' of alternatives when reviewing protocols? (Refinements to research, Reduction of animal numbers, and Replacement with non-animal models),"*** *which is available at https://olaw.nih.gov/faqs#/guidance/faqs (last accessed May 10, 2021).*

made without doing so…. 4. Refinement refers to use of approaches that lessen or eliminate pain or distress in the animals that are used. This includes (1) choosing procedures that prevent or relieve pain or distress likely to be associated with the experimental design, … (3) appropriate use of analgesics, anesthetics, and tranquilizers, including selection of better agents (more effective, with fewer or less severe potential side effects) as they become available, (4) improving post-surgical care with new technology as it becomes available, and (5) special husbandry such as providing softened food after procedures likely to cause discomfort with swallowing, soft bedding, easier access to food, or environmental enrichment, as appropriate."

ACORP Main Body (Version 4) §W.1. "**Consideration of Alternatives….** These are important to minimizing the harm/benefit to be derived from the work. Document the database searches conducted. List each of the potentially painful or distressing procedures included in this protocol. Then complete the table below to document how the database search(es) you conduct … address(es) each of the potentially painful or distressing procedures."

Required Action 11:
When requesting a significant change to ongoing animal research activities, the PI must consider alternatives to procedures that may cause more than momentary or slight pain or distress to the animals and provide a written narrative description of the methods and sources used to determine that alternatives were not available.

12. The adequacy of annual overheat tests of the VMU was not determined in accordance with VHA Policy.

Finding:
Interviews with key personnel indicated that the determination of a timely and adequate response from facilities management personnel to the required annual overheat test in the VMU was made at the time of the test by VMU personnel, rather than through IACUC deliberation at the committee's next convened meeting. In addition, IACUC minutes did not document conduct of the test, response by facilities management, nor committee discussion as a business item.

Reference(s):
VHA Handbook 1200.07 §§7.a(2)(c)1.&2. "To test the ability of facilities management personnel to properly detect and respond to elevations in animal room temperatures, at least once every fiscal year research personnel must purposely overheat a temperature sensor (e.g., with a hair dryer, with input from facilities management personnel) in at least one animal room in each animal research facility without notifying engineering or facilities management personnel in advance. The response must be carefully noted, and reported to the IACUC by VMU staff at the next convened IACUC meeting. The IACUC must decide if the response to the excessive temperature was timely and adequate…. The IACUC minutes must reflect all reviews of testing."

Required Action 12:
The adequacy of overheat tests of the animal research facility must be determined and documented according to VHA policy.

13. An IACUC-approved exception/departure was not included in IACUC semi-annual reports or USDA Annual Reports.

Finding:
Protocol No. 15-041-CT-19-001 indicated that cats will be housed without elevated resting surfaces post-operatively. This exception to 9 CFR §3.6(b)(4), which requires that housing facilities for cats contain elevated resting surfaces, was specifically justified in the protocol and approved by the IACUC; however, none of the semi-annual reports or USDA Annual Reports from 2019 or 2020 documented this IACUC-approved exception/departure.

Reference(s):
9 CFR §3.6(b)(4) [Part 3 Standards]. "Each primary enclosure housing cats must contain a resting surface or surfaces that, in the aggregate, are large enough to hold all the occupants of the primary enclosure at the same time comfortably. The resting surfaces must be elevated…."

9 CFR §2.38(k)(1). "[E]xceptions to the standards in part 3 and the provisions of subpart C of this part may be made only when such exceptions are specified and justified in the proposal to conduct the activity and are approved by the IACUC."

9 CFR §2.31(c)(3). "IACUC functions. With respect to activities involving animals, the IACUC, as an agent of the research facility, shall: … Prepare reports of its [semi-annual] evaluations conducted … and submit the reports to the Institutional Official of the research facility…. The reports must contain a description of the nature and extent of the research facility's adherence to this subchapter, must identify specifically any departures from the provisions of [the *AWA R&S*], and must state the reasons for each departure."

USDA AWIG §7.5.1.1. "Semi-annual reports of the review of humane care and use program **and** the facility inspection … must: … Identify specifically any departures from the Regulations and Standards [and] State the reason for each departure…."

9 CFR §2.36(b)(3). "The [USDA] annual report shall: … Assure that the facility is adhering to the standards and regulations under the Act, and that it has required that exceptions to the standards and regulations be specified and explained by the principal investigator and approved by the IACUC. A summary of all such exceptions must be attached to the facility's annual report. In addition to identifying the IACUC-approved

exceptions, this summary must include a brief explanation of the exceptions, as well as the species and number of animals affected."

USDA AWIG §7.5.3.1. "Exceptions or exemptions to a particular AWA Regulation or Standard **approved by the IACUC must be** [2.36(b)(3)]: Specified, and Explained by the principal investigator. If a Regulation or Standard provides specific parameters for an exemption, those parameters must be followed.
Exceptions that **should** be reported on the Annual Report: Exceptions approved by the IACUC under 2.38(k) that are not provided for under the Regulations and Standards, including but not limited to: Removal of resting platforms from cat enclosures…."

See also ***PHS Policy §IV.B.3.c.***

Required Action 13:
The IACUC must ensure that all IACUC-approved exceptions/departures are included in IACUC semi-annual reports and USDA Annual Reports.

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:**
VA animal research involving cats is subject to additional review and approval, beyond that provided at the VA facility level, under specific circumstances described in Public Law (PL) 116-94 §249 (December 20, 2019), PL 116-260 §247 (December 21, 2020), and *ORD Guidance Document AR2017-001, "Canine, Feline and Non-Human Primate (Sensitive Species) Research Protocols"* (hereafter, "*ORD AR2017-001*").[26] The PLs, both of which were appropriation acts, prohibited funds (appropriated or otherwise made available through the acts) from being used to conduct feline research commencing on or after October 1, 2019, unless the VA Secretary specifically approved the research in writing.[27] *ORD AR2017-001 Revision 1*, effective May 3, 2018,

[26] The PLs incorporate by reference both the initial version of the ORD guidance document as well as subsequently revised versions of that document. *ORD AR2017-001* was first released on December 15, 2017, and originally only applied to canine research. Five subsequent revisions have been released. The first revision, dated May 3, 2018, expanded the applicability of the guidance document to research involving felines and non-human primates. The current version of this document, dated July 16, 2020, is accessible at https://www.research.va.gov/programs/animal_research/guidance.cfm (*last accessed June 2, 2021*).

[27] The PLs do not specify when feline research is considered to have commenced (e.g., when the local facility's Research Service notifies the investigator that a research project can be initiated; when funds are first made available to the investigator for use; when funds are first spent for those aspects of the research that directly

stipulated that feline research that is VA-funded or conducted on VA property could only commence after certain actions had been completed beyond those required at the local VA facility level, including: (i) completion of a VA Central Office (VACO) ethics review; (ii) review and approval by the ORD Office of the Chief Veterinary Medical Officer (CVMO); and (iii) review and approval by the Chief Research and Development Officer (CRADO).

At the time of ORO's review, VANEOHS had four feline research protocols with current approvals from the local IACUC and Research and Development (R&D) Committee. Two of the four protocols – Protocol #15-041-CT-19-001[28] and Protocol # 17-012-CT-19-014-CC[29] – were already approved and research activities were underway when the above referenced ORD guidance and PLs were first issued. Therefore, at the time of approval, the research conducted under these protocols was not required to, and did not, undergo the additional review and approval processes described in ORD AR2017-001 Revision 1, effective May 3, 2018, and the PLs. [30]

A third protocol – Protocol No. 20-010-CT-19-019 – described the training of research personnel using cats and also served as a holding protocol, providing for the routine husbandry and care of cats held, but not currently being used for studies involving experimental procedures (e.g., cats being quarantined upon arrival or awaiting adoption after the conclusion of a research protocol). With regard to the training aspects of the protocol, VHA policy considers the use of animals for training to be a *research* activity.[31] With regard to the "holding" aspects of the protocol, it is noted that such activities are part of the institutional research program and directly support research activities.[32] This protocol was approved by the VANEOHS IACUC and R&D Committee on March 15, 2020, and April 28, 2020, respectively. The first training

involve the cats, for example purchasing, housing, or experimental manipulation of cats; or under other circumstances).

[28] Protocol No. 15-041-CT-19-001 was approved by the VANEOHS IACUC and R&D Committee on September 17, 2015, and November 5, 2015, respectively.

[29] Protocol No. 17-012-CT-19-014-CC was approved by the VANEOHS IACUC and R&D Committee on April 3, 2017, and May 4, 2017, respectively.

[30] Based on the current version of ORD AR2017-001 (Revision 5), effective July 16, 2020, these protocols are required to undergo the additional review set forth in the ORD guidance by March 27, 2022, or earlier if there is a significant change in scope of the research.

[31] ***VHA Handbook 1200.07, "Use of Animals in Research,"*** defines animal research in §3.d as "any use of laboratory animals in research, testing, or training." The Handbook's approach, which applies a single set of requirements to activities involving animals used in research, testing, or training, is similar to that taken in policies issued by other federal entities, including: the *Public Health Service Policy on Humane Care and Use of Laboratory Animals (PHS Policy)*; the *Animal Welfare Act Regulations and Standards (AWA R&S); and the U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training.*

[32] Per ***NIH-OLAW FAQ D.16,*** "[Use of animals] as sentinels, breeding stock, blood and blood product donors, or for other similar purposes … is part of the institutional research program and directly supports research activities." *Accessible at https://olaw.nih.gov/faqs#/guidance/faqs (last accessed June 2, 2021).*

session using a live cat, which facility personnel indicated only included non-invasive handling and sham procedures, was conducted on July 16, 2020. VANEOHS administrative research personnel informed ORO that this protocol, which commenced after October 1, 2019, was neither reviewed nor approved by the VA Secretary, the ORD Office of the CVMO, or the CRADO, and did not undergo a VACO ethics review.

In light of the activities conducted under this protocol, including training activities which under VHA policy are considered research activities, ORO strongly recommends VANEOSH personnel consult with both the ORD Office of the CVMO and the Office of General Counsel Specialty Team Advising Research (OGC-STAR) to determine whether this protocol must undergo a VACO ethics review and receive approval from the ORD Office of the CVMO, CRADO, and VA Secretary prior to conducting any further activities under this protocol. ORO further recommends that the outcome of that consultation be documented. If it is determined that the activities conducted under this protocol were *not* intended to be subject to the additional approvals specified in ORD Guidance and the PLs, ORO strongly recommends that the ORD Office of the CVMO revise ORD AR2017-001 to clarify its narrower scope.

The fourth protocol – Protocol No. 18-065-CT-19-003 – was approved by the VANEOHS IACUC and R&D Committee on February 12, 2019, and February 21, 2019, respectively, and involved research funded by VA. On August 27, 2020, the VANEOHS Research Service was notified by the ORD Office of the CVMO that the protocol had cleared the ORD Just-in-time[33] (JIT) review process and funding was released to begin the animal research. At the time of ORO's review, none of the funds had been spent to obtain, house, or manipulate any cats for this protocol.

ORD AR2017-001 Revision 2, effective October 25, 2018, which was in place when the protocol was approved by the IACUC and R&D Committee, indicated in §3.a. that any new, proposed VA-funded feline study could commence only after undergoing the described additional review process, including a VACO ethics review, and review and approval by the ORD Office of the CVMO and the CRADO. Although this VA-funded protocol did undergo JIT review by the ORD Office of the CVMO, VANEOHS personnel indicated neither of the additional reviews had been conducted at the time of ORO's review.

Representatives from the ORD Office of the CVMO indicated in a conversation with ORO on April 20, 2021, that there had been funding provided for similar research at the facility in 2013, and Protocol No. 18-065-CT-19-003 was considered to be "grandfathered in" as a continuation of this previously approved feline research

[33] ***VHA Handbook 1200.07 §3.l.*** "**Just-in-Time (JIT).** JIT refers to the ORD review system (for VA applications involving animals) that requires proof of IACUC approval and a copy of an ACORP, only if an application has received favorable scientific review and is likely to receive funding."

project, rather than *new* feline research subject to the relevant *ORD AR2017-001* requirements for additional review outside of the facility (beyond the JIT review, which is required for all VA-funded animal research).

Protocol No. 18-065-CT-19-003 listed Protocol No. 013-016-CT-005 in Section A.6.c. as relevant to the proposed research described in Protocol No. 18-065-CT-19-003. However, in Section A.6.b.(1) of the protocol, the PI indicated that the research proposed in Protocol No. 18-065-CT-19-003 constituted a new ("de novo") study.[34, 35] Further, at the time that the purported precursor Protocol No. 013-016-CT-005 was closed on September 30, 2018, due to reaching the end of its funding, feline research was subject to ORD *AR2017-001 Revision 1*, effective May 3, 2018; this document indicated that "[a]ll animal protocols already underway at the release of this guidance will be subject to this guidance whenever the sponsor renews funding." As such, even if Protocol No. 18-065-CT-19-003 were to somehow be construed as a continuation of research activities from Protocol No. 013-016-CT-005, that research did not undergo the additional reviews upon renewal of funding.

Regardless of whether Protocol No. 18-065-CT-19-003 is considered to be a de novo protocol subject to ORD AR2017-001 (Revision 2), or a continuation of a previous protocol with renewed funding subject to ORD AR2017-001 (Revision 1), VANEOSH research personnel should ensure that a VACO ethics review is conducted, and CRADO approval secured, prior to acquiring any cats for this protocol.

It is further noted that although Protocol No. 18-065-CT-19-003 was approved by the local IACUC and R&D Committee *prior* to October 1, 2019, the date on and after which new VA research involving cats would have been required to also secure written VA Secretary approval per applicable PLs, the JIT review process authorizing release of funds to begin work on the protocol was not completed until after this date; additionally, as of the time of ORO's review, no cats had yet been obtained for this protocol. Given that the ORD Office of the CVMO JIT review process for this study was completed *after* October 1, 2019, and activities directly involving the cats, including their acquisition, will occur *after* October 1, 2019, **ORO recommends that VANEOSH personnel consult with both the ORD Office of the CVMO and OGC-STAR to determine whether these post-October 1, 2019, activities would be subject to the public law requirement for VA Secretary approval. ORO further recommends that the outcome of that consultation be documented. If such a consultation were to**

[34] Specifically, the PI indicated in Protocol No. 18-065-CT-19-003 that "[a]lthough this study is de novo, it bears great similarity to a recently completed, approved study … in feline subjects…" (emphases added).

[35] Protocol No. 18-065-CT-19-003 indicated it involved implanted hardware similar to Protocol No. 013-016-CT-005 and had overlapping personnel. However, the aims of Protocol No. 18-065-CT-19-003 focused primarily on development of new connectors, evaluation of their biocompatibility, and the resistance in the leads without stimulation studies, while the aims of Protocol No. 013-016-CT-005 focused primarily on creating automated tuning methods for functional neuromuscular stimulation (FNS).

result in a determination that VA Secretary approval is *not* legally required under applicable PLs, it would nonetheless be prudent to ensure that VHA leadership and the VA Secretary are aware of the research activities to be conducted under this protocol and the determination that additional approvals are not legally required.

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."

ORD AR2017-001 Revision 5 (dated July 16, 2020). *"Note: … Work with sensitive species, regardless of funding source, is not permitted to begin until Secretarial approval has been documented in writing. It is illegal to spend VA funds on any studies involving sensitive species until written Secretarial approval has been granted….*

2. **Issue:** This guidance applies to protocols for research with … felines … as follows:
a. Each local program must ensure that work on any new proposed research with … felines … to be conducted on VA property (with any funding source) or funded by VA (at any performance site), commences only after:

- The project associated with the protocol has local Research and Development Committee approval;
- The protocol has been reviewed, revised as needed, and approved by the local IACUC, and the Office of the CVMO;
- A veterinary ethics review has been completed, with results provided to the Chief Research and Development Officer;
- The protocol has been approved by the Chief Research and Development Officer, after review of the protocol and the results of the veterinary ethics review;
- Additional review and approval required by senior VHA managers, at their discretion, has been completed.
- Written Secretarial approval of the work has been documented in writing….

d. All animal protocols already underway at the release of this guidance will be subject to re-review by March 27, 2022, or earlier if the scope of the research changes significantly….

4. **FY2020 Legislative Update.** Consistent with earlier legislative mandates, no new research studies involving sensitive species may begin after October 1, 2019 until reviewed and approved by the VA Secretary per the FY2020 VA funding legislation ('Further Consolidated Appropriations Act, 2020', PL 116-94, 12/20/2019, Section 249). Section 249 has additional restrictions placed upon sensitive species research that must be met, such as a requirement that studies address a combat-related condition or illness."

ORD AR2017-001 Revision 2 (dated October 25, 2018). "3. **Issue:** This guidance applies to … feline … protocols as follows:

a. Each local program must ensure that work on any new proposed … feline …study to be conducted on VA property (any funding source) or funded by VA (any performance site), commences only after:

- The project associated with the protocol has local Research and Development Committee approval.
- The protocol has been reviewed and approved by the local IACUC, and the Office of the CVMO
- A VA Central Office ethics review has been completed.
- The protocol has been reviewed and approved by the Chief Research and Development Officer….
- Additional review and approval required by senior VHA managers, at their discretion, has been completed….

d. All animal protocols already underway at the release of this guidance will be subject to re-review by March 27, 2022 or earlier if the scope of the research will change significantly."

ORD AR2017-001 Revision 1 (dated May 3, 2018). "3. **Issue**. This guidance applies as follows:

a. Each local program must ensure that work on any new proposed … feline … study to be conducted on VA property (any funding source) or funded by VA (any performance site), commences only after:

- The project associated with the protocol has local Research and Development committee approval
- The protocol has been reviewed and approved by the local IACUC, the Office of the CVMO, and the Chief Research and Development Officer
- A VACO ethics review has been completed.
- Additional review and approval required by senior VHA managers, at their discretion, has been completed….

d. All animal protocols already underway at the release of this guidance will be subject to this guidance whenever the sponsor renews funding."

PL 116-260 §247, December 21, 2020. "(a) None of the funds appropriated or otherwise made available by this Act may be used to conduct research commencing on or after October 1, 2019, that uses any … feline … unless the Secretary of Veterans Affairs approves such research specifically and in writing pursuant to subsection (b). (b)(1) The Secretary of Veterans Affairs may approve the conduct of research commencing on or after October 1, 2019, using … felines … if the Secretary determines that— (A) the scientific objectives of the research can only be met by using such … felines …; (B) such scientific objectives are directly related to an illness or injury that is combat-related; and (C) the research is consistent with the revised Department of Veterans Affairs canine research policy document dated December 15, 2017, including any subsequent revisions to such document."

PL 116-94 §249, December 20, 2019. "(a) None of the funds appropriated or otherwise made available by this Act may be used to conduct research commencing on or after October 1, 2019, that uses any … feline … unless the Secretary of Veterans Affairs approves such research specifically and in writing pursuant to subsection (b). (b)(1) The Secretary of Veterans Affairs may approve the conduct of research commencing on or after October 1, 2019, using … felines … if the Secretary determines that— (A) the scientific objectives of the research can only be met by using such … felines …; (B) such scientific objectives are directly related to an illness or injury that is combat-related; and (C) the research is consistent with the revised Department of Veterans Affairs canine research policy document dated December 15, 2017, including any subsequent revisions to such document."

2. Observation:

ORO noted that the VMU was set to undergo some significant staffing changes immediately after ORO's review. At the time of the review, VMU staffing consisted of a VMU (b)(6) and two (b)(6), both of whom held (b)(6) credentials, and an animal caretaker. ORO was informed that subsequent to the retirement of the current (b)(6), the (b)(6) had been selected to fill the (b)(6) position and a new (b)(6) had been hired; however, the new (b)(6) was not credentialed as an (b)(6). Due to the significant level of administrative responsibilities of the (b)(6) position (including, but not limited to, supervisory tasks, management of the facility, ordering, contracting, rounds, and coordination of safety) and the fact that the (b)(6) also serves as the IACUC (b)(6) (with responsibilities including, but not limited to, management of the IACUC; drafting minutes, agendas, and committee communication; administrative review of certain protocol amendments; drafting regulatory and accreditation documents; and communication with regulatory and accreditation entities), the amount of (b)(6) time available to support animal research, veterinary, and husbandry activities at VANEOHS will be greatly reduced. In consideration of the reduction in (b)(6) time dedicated to direct animal care activities, the Research Service, in consultation with the (b)(6) and (b)(6) should consider carefully monitoring the efficiency of husbandry, veterinary, and research activities within the facility once these new staffing arrangements are fully implemented to ensure animal welfare and compliance are not negatively impacted.

Reference(s):

9 CFR §2.33(b)(1). "Each research facility shall establish and maintain programs of adequate veterinary care that include: The availability of appropriate … personnel … to comply with the provisions of [the AWA R&S]."

VHA Handbook 1200.07 §6.b(5)(c). "Primary duties of VMOs and VMCs include, but are not limited to: … Ensuring adequate caretaker staffing and proper support of animal research projects at the facility."

3. **Observation:**
Cats on Protocol No. 17-012-CT-19-014-CC, which was conducted collaboratively with CCF, were routinely housed at the VA VMU. Various aspects of the research activities were conducted at both the VA VMU and CCF, with some (but not all) cats housed overnight at CCF after procedures involving anesthesia. During interviews, a representative from the Research Service indicated that VANEOHS had reported the animal usage associated with this protocol on its USDA Annual Reports. Interviews with other personnel and review of additional documents revealed that, in fact, both VANEOHS and CCF had reported the cats involved in this collaborative research during FY2019 and FY2020 on each of their individual USDA Annual Reports, even though animals are only to be reported in a single Annual Report during any given reporting period. Although the previous MOU between VANEOHS and CCF, which was executed in March 2015 and active during this time period, did not specify which facility was responsible for reporting animal usage to the USDA, ORO notes that the current MOU, executed in December 2020, specified that only CCF would include the cats used for this collaborative research in its Annual Report; if this does not accurately reflect the intended annual reporting practices moving forward, the Research Service should work with the affiliate to amend the MOU as necessary.

Additionally, ORO noted that VANEOHS did not consistently complete the USDA Annual Report as instructed on the form; specifically in 2018 and 2019, column F of the Annual Report included the total of all animals present in the facility during the reporting period rather than only reporting the total number of animals used in research activities.[36]

ORO recommends that the Research Service review its procedures for tracking and reporting animal research activities to USDA to ensure it complies with the requirements found in 9 CFR §2.36 and additional guidance available from the USDA Animal Care program including, but not limited to, the USDA Animal Welfare Inspection Guide (AWIG).

Reference(s):
USDA AWIG (dated January 26, 2021), §7.5.3. "**Annual Report**…. If an animal was moved to another [Research Facility (RF)] during the reporting year, the animal should only be reported once by either: The RF with the highest pain category for the animal, or [i]f the pain categories are the same, then by the last RF to possess the animal."

USDA AWIG §7.4. "… **Projects that Involve Multiple Registrants**…. [I]t is the responsibility of the registrants to determine which party is responsible for the … reporting of the animals on the Annual Report."

[36] *See Animal Plant and Health Inspection Service (APHIS) Form 7023 for additional information. Accessible at https://www.aphis.usda.gov/library/forms/pdf/APHIS_7023.pdf (last accessed April 26, 2021)*

USDA AWIG §7.4.1. "**No Delegation of Responsibilities.** If the research facilities have not delegated responsibilities [f]or projects involving multiple registrants…, then: … Only one of the RFs should report the animals on the Annual Report…."

USDA AWIG §7.4.2. "**Specific Responsibilities.** If the contract designates specific responsibilities to each partner, the facility is a site of both registrants. The inspector should inspect only the designated institution for the specific responsibility agreed upon in the contract. For example: … The contract specifies that both RF A and RF B are responsible for the IACUC functions, but only RF B is responsible for … reporting on the Annual Report, then: The inspector inspects: … the [USDA Annual Report] reporting of the animals under the contract at RF B."

4. **Observation:**
ORO noted that when the IACUC's (b)(6) member, a (b)(6) who has not conducted animal research, was re-appointed to the committee by the facility Director on December 7, 2020, the appointment memorandum reappointed him as a (b)(6) member, rather than as a (b)(6) member, which facility personnel indicated occurred due to an inadvertent typographical error. The IACUC should work with the facility Director, through the R&D Committee, to ensure that this member's appointment letter is modified to accurately reflect the member's role on the committee.

Reference(s):
VHA Handbook 1200.07 §8.a(1). "Only a properly constituted IACUC may conduct official business. The required voting members [of the IACUC] include a Chairperson, the Attending Veterinarian, one scientist with animal research experience, a non-affiliated member … and a lay member (who must not be involved in animal research)."

5. **Observation:**
ORO noted that prior to October 2020, the IACUC's report documenting the outcome of the semi-annual facility inspection and review of the facility's program for humane care and use of animals did not consistently provide specific plans for each deficiency identified. Although it appears that this noncompliance was subsequently remediated, as all deficiencies identified in the October 2020 semi-annual evaluation report included such plans, ORO encourages the IACUC to review its procedures and practices to ensure future semi-annual evaluations continue to include reasonable and specific plans for the correction of each deficiency identified.

Reference(s):
PHS Policy §IV.B.3.d. "If program or facility deficiencies are noted, the [semi-annual] reports must contain a reasonable and specific plan and schedule for correcting each deficiency."

9 CFR §2.31(c)(3). "If program or facility deficiencies are noted, the [semi-annual] reports must contain a reasonable and specific plan and schedule with dates for correcting each deficiency."

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: research personnel did not ensure cats maintained normal body temperatures when anesthetized for research procedures; research personnel deviated from study protocols prior to securing approval to implement such deviations; the HVAC system did not provide adequate humidity to rooms housing cats; rabies vaccines were not consistently administered to cats as described in the facility's written Program of Veterinary Care and were not in accordance with standard veterinary practice; and the IACUC did not ensure appropriate oversight of off-site feline research by regularly receiving and reviewing the semi-annual self-assessments of the affiliate institution where VA feline research activities were conducted. ORO also provided facility personnel with several non-mandatory recommendations to consider for enhancing the research oversight program and sustaining research compliance. Of note, ORO identified two active feline research protocols that could reasonably be construed as requiring additional reviews and approvals beyond those already received. As such, ORO recommended that VANEOSH personnel refrain from proceeding with acquiring cats for one of the protocols, and refrain from engaging in further training activities involving cats for the other protocol, until consulting with both the VHA Office of Research & Development and the Office of General Counsel as to whether additional reviews and approvals of the protocols are required. All identified noncompliance must be addressed in a Remedial Action Plan that will be monitored by ORO until satisfied.

OFFICE OF RESEARCH OVERSIGHT

(b)(6)

(b)(6)

(b)(6) Research Safety and Animal Welfare (RSAW), ORO

APPENDIX A
ORO REVIEW TEAM and FACILITY REPRESENTATIVES

ORO Remote Review Team:

[redacted]

Animal Care and Use Program (ACUP) Team [redacted]
ACUP Team [redacted]

Facility Representatives:

Andrew Pacyna, FACHE — Acting Executive Director

[redacted] Patient Care Services; [redacted]

[redacted] Research & Development (R&D)
[redacted] R&D

[redacted] Institutional Animal Care and Use Committee (IACUC) [redacted]
Veterinary Medical Consultant, [redacted]
[redacted] IACUC [redacted]

IACUC [redacted]
IACUC [redacted]
IACUC [redacted]
IACUC [redacted]

Dennis Bourbeau, PhD — Principal Investigator (PI)

[redacted] IACUC [redacted] PI

APPENDIX B
TITLES OF RESEARCH PROTOCOLS CITED IN FINDINGS AND OBSERVATIONS*

* This appendix captures information for *only* those protocols that are referenced in a Finding or Observation in this report. The protocols listed below were reviewed either in their entirety or for select section(s) applicable to a specific issue/concern.

- 013-016-CT-005 Exploiting Selective Recruitment to Delay Fatigue during Electrical Stimulation
- 15-041-CT-19-001 Afferent Stimulation to Evoke Recto-colonic Reflex for Colonic Motility
- 17-012-CT-19-014-CC Conscious Ambulatory Bladder Monitoring to Understand Neural Control of Urinary Tract Function
- 18-065-CT-19-003 Optimization & Pre-clinical Testing of Implantable, In-Line High Density 23-Channel Connector
- 20-010-CT-19-019 Holding and Training Protocol (cat)

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 Directive 1058.01 §5.g(6):

> *Each VA medical facility Director whose VA medical facility has a research program is responsible for: … Ensuring timely implementation of remedial actions to address research noncompliance identified by VA medical facility personnel, ORO, and other entities.*
>
> *(a) Remedial actions to correct noncompliance identified by ORO or that is otherwise required to be reported to ORO **must be completed within 180 calendar days** after any determination of noncompliance, except where extenuating circumstances exist (e.g., remediation requires substantial renovation or fiscal expenditure, hiring, or legal negotiations).*
>
> *(b) Where remedial actions cannot be completed in 180 calendar days, the VA medical facility Director must provide the appropriate ORO workgroup(s) with written justification and a reasonable timeline for completion.*

Deadline for completion of Required Actions: **January 3, 2022**

Animal Care and Use. ORO Case Number: **541-0073-A**

Required Action 1: All cats must be provided with adequate veterinary care, including maintenance of normal body temperature intra- and post-operatively.	
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 and PIs must ensure that research is conducted in accordance with the approved protocol (including the protocols listed in this Finding) and that any proposed significant modifications to animal research protocols are approved prior to implementation.	
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: The facility must ensure that relative humidity levels in animal housing areas are consistently maintained within an acceptable range.	

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: Rabies vaccines must be consistently administered to cats as described in the facility's written Program of Veterinary Care and in accordance with standard veterinary practice.	
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 5: The IACUC must receive and review the affiliate semi-annual self-assessments or, alternatively, the IACUC itself must conduct a semi-annual review of the affiliate's animal care and use program.	
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 6: The IACUC and PIs must ensure that approved protocols contain complete, clear, congruent, and accurate descriptions of research activities, including the protocols identified in this Finding.	
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 7: The IACUC must ensure that proposed significant changes to ongoing animal protocols, including the one in this Finding, are reviewed and approved by compliant methods.	
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 8: The Research Service must ensure that the IACUC is properly constituted when conducting official business and that all required voting members are appropriately appointed by the facility Director.	
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 9: The Research Service must ensure that all alternate IACUC members serve in that capacity only, unless subsequently appointed by the facility Director to serve in a different capacity.	
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 10: The IACUC must ensure that the benefits of the study are weighed against potential animal welfare concerns for each ACORP under review.	
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 11: When requesting a significant change to ongoing animal research activities, the PI must consider alternatives to procedures that may cause more than momentary or slight pain or distress to the animals and provide a written narrative description of the methods and sources used to determine that alternatives were not available.	
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 12: The adequacy of overheat tests of the animal research facility must be determined and documented according to VHA policy.	
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 13: The IACUC must ensure that all IACUC-approved exceptions/departures are included in IACUC semi-annual reports and USDA Annual Reports.	
Facility Response	***ORO Comments***
Response #1 ([DATE of response submission]) **Facility Action:** [TEXT] **Proposed Completion Date:** [DATE]	[ORO comments will be inserted here]