OFFICE OF RESEARCH OVERSIGHT

FOCUSED REVIEW REPORT

Animal Care and Use Program

VA Greater Los Angeles Healthcare System
Los Angeles, CA

June 26, 2020

Veterans Health Administration

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ORO FOCUSED REVIEW REPORT

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Remote Review March/April 2020
Date of Report: June 26, 2020

EXECUTIVE SUMMARY

The Office of Research Oversight (ORO), Veterans Health Administration (VHA), conducted a remote Focused Review of the Animal Care and Use Program (ACUP) at VA Greater Los Angeles Healthcare System (VAGLAHS) in March/April 2020. Specifically, the review evaluated the facility's use of United States Department of Agriculture (USDA) covered species in VA research and Institutional Animal Care and Use Committee (IACUC) operations. 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 communicate with the Attending Veterinarian (AV) in a timely manner regarding a cat with a veterinary medical problem; veterinary care procedures for one cat were not performed as directed by the AV; VAGLAHS did not establish adequate mechanisms to accurately document and monitor animal use; research personnel did not follow IACUC approved protocols; VAGLAHS did not report to the National Institutes of Health-Office of Laboratory Animal Welfare (NIH-OLAW) and ORO deficiencies that constituted reportable noncompliance; some animal research protocols did not contain an adequate rationale for the appropriateness of the numbers of animals requested for use; and the IACUC did not consistently ensure that approved protocols included complete, clear, internally congruent, and accurate descriptions of research activities. 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 Greater Los Angeles Healthcare System (VAGLAHS) in March/April 2020. ORO's review at VAGLAHS focused on VAGLAHS's animal research involving United States Department of Agriculture (USDA) covered species[1] and Institutional Animal Care and Use Committee (IACUC) operations.

II. METHOD OF REVIEW

ORO's review of VAGLAHS 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,[2] memoranda of understanding (MOUs), and related documentation.

ORO's review did not involve a physical inspection of the facility's research areas. Therefore, the findings and observations described in this report are based on information that ORO could acquire remotely.

III. FACILITY RESEARCH PROGRAM OVERVIEW

VAGLAHS is a complexity level 1a care facility academically affiliated with the University of California, Los Angeles (UCLA) and the University of Southern California (USC). It operates a research program involving human subjects, laboratory animals, and hazardous agents, with a

[1] ***9 Code of Federal Regulations (CFR) §1.1.*** "***Animal*** means any live or dead dog, cat, nonhuman primate, guinea pig, hamster, rabbit, or any other warm-blooded animal, which is being used, or is intended for use for research, teaching, testing, experimentation, or exhibition purposes, or as a pet. This term excludes birds, rats of the genus *Rattus*, and mice of the genus *Mus*, bred for use in research; horses not used for research purposes; and other farm animals, such as, but not limited to, livestock or poultry used or intended for use as food or fiber, or livestock or poultry used or intended for use for improving animal nutrition, breeding, management, or production efficiency, or for improving the quality of food or fiber. With respect to a dog, the term means all dogs, including those used for hunting, security, or breeding purposes."

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

research project (direct cost) budget of $36,462,567 in FY2019,[3] of which $16,678,112 was provided by the VHA Office of Research and Development (ORD). The Greater Los Angeles Veterans Research and Education Foundation (GLAVREF) provides a flexible funding mechanism for non-VA sponsored research at VAGLAHS.

At the time of ORO's review, there were 102 animal care and use protocols, 17 of which involved USDA species including cats, rabbits, hamsters, gerbils, and pigs. The research portfolio included studies on Alzheimer's disease, cancer, traumatic brain injury, epilepsy, bone healing, pain, diabetes, infectious disease, drug addiction, sleep disorders, and gastrointestinal disorders. Veterinary Medical Units (VMUs) are maintained at both the West Los Angeles (WLA) and Sepulveda campuses.

VAGLAHS maintains its own IACUC. VAGLAHS has a current Public Health Service (PHS) Animal Welfare Assurance D16-00002 (A3002-01) expiring September 30, 2021, on file with the National Institutes of Health – Office of Laboratory Animal Welfare (NIH-OLAW) as well as three Interinstitutional Assurances establishing VAGLAHS as the IACUC of record and performance site for animal research funded by NIH grants awarded to two outside entities: WebSciences, for research involving cats (Assurances A8806-01 effective June 14, 2018, and A8806-02 effective July 13, 2018) and Sentia Medical Sciences, Inc., for research involving rodents (Assurance A8765-02 effective May 16, 2018). VAGLAHS holds full accreditation with the Association for the Assessment and Accreditation of Laboratory Animal Care, International (AAALAC; Unit No. VA-068); and is registered with the U.S. Department of Agriculture – Animal and Plant Health Inspection Service (USDA-APHIS; Registration No. 93-V-0006). VAGLAHS has executed MOUs regarding collaborative animal research with academic affiliates UCLA and USC.

VAGLAHS maintains its own Subcommittee on Research Safety (SRS), which is also constituted as an Institutional Biosafety Committee (IBC) and registered with the NIH-Office of Science Policy (NIH-OSP).

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, VAGLAHS must complete the applicable sections of the attached Remedial Action Plan and submit it to ORO as instructed. The plan must include specific remedial actions and timely completion dates for each Finding, as indicated at VHA Handbook 1058.01 §5.c.

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

1. **Medical care of a cat with a veterinary medical problem was not provided by or in consultation with a qualified veterinarian.**

Finding:
Document review and interviews with key personnel revealed that laboratory personnel treated a veterinary medical condition without first consulting the Attending Veterinarian (AV). On March 11, 2019, research laboratory personnel conducted a minor surgical procedure on cat 17LFC4 involving administration of anesthesia and re-suturing of a research-related surgical incision that had not healed appropriately. Laboratory personnel did not consult the AV prior to performing this procedure; therefore, the AV did not have the opportunity to evaluate the cat and prescribe treatment for this veterinary medical concern. Neither Protocol No. 05005-18 nor No. 05006-18 for cats included provisions for laboratory personnel to perform incision repairs. Thus, laboratory personnel provided veterinary care outside the scope of their positions and without direction from the AV.

Reference(s):
9 CFR §2.31(d)(1)(vii). "Medical care for animals will be … provided as necessary by a qualified veterinarian."

Guide for the Care and Use of Laboratory Animals, Eighth Edition (The Guide),[4] ***p. 114***.
"There should be a timely and accurate method for communication of any abnormalities in or concerns about animal health, behavior, and well-being to the veterinarian or the veterinarian's designee. The responsibility for communicating these concerns rests with all those involved with animal care and use. Reports should be triaged to ensure that animals most in need receive priority attention, and the veterinarian or veterinarian's designee should perform an objective assessment of the animal(s) to determine an appropriate course of action."

9 CFR §§2.33(b)(2)&(3). "Each research facility shall establish and maintain programs of adequate veterinary care that include … [t]he use of appropriate methods to prevent, control, diagnose, and treat diseases and injuries … [and d]aily observation of all animals to assess their health and well-being; *Provided, however*, That daily observation of animals may be accomplished by someone other than the attending veterinarian; and *Provided, further,* That a mechanism of direct and frequent communication is required so that timely and accurate information on problems of animal health, behavior, and well-being is conveyed to the attending veterinarian…."

Required Action 1:
VAGLAHS must ensure that medical care for animals with veterinary medical problems is provided by or in consultation with a qualified veterinarian.

[4] ***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)…."

2. Veterinary care procedures for one cat were not performed as directed by the AV.

Finding:
Protocols No. 05005-18 and No. 05006-18[5] involved the placement of headcaps on cats. The protocols specified that "[t]he marginal surgical areas [of the cat's headcap] will be cleaned **according to procedures requested by [the AV]**…" (emphasis added). Review of clinical and headcap treatment records (i.e., "VMU Daily Treatment Record" and the "VMU Post Procedure Record") for cats assigned to these protocols, as well as interviews with key personnel, revealed that one cat's cleaning procedures did not consistently occur as directed by the AV. During a period of time when cat 15ESX4 was prescribed twice weekly headcap cleanings, no treatments were provided from January 8 to 15, 2019.

NOTE: *ORO identified additional instances when treatments for some cats did not occur at the documented prescribed interval. During VAGLAHS' factual review of ORO's draft report, the facility indicated that for these other instances the AV had verbally communicated modifications to written treatment plans; however, documentation of these oral instructions, which contradicted written instructions, was not identified by ORO in the animals' records. For example, during periods of time when twice weekly headcap cleanings were recorded as the prescribed interval, no treatments were recorded and no change in prescribed frequency had been documented. Specifically, cat 17LFE1 had an 11-day gap in documented treatments from November 21 to December 2, 2019, and a 12-day gap in documented treatments from September 26 to October 8, 2019. Additionally, cat 17LFC4 had a 15-day gap in documented treatments from April 8 to 23, 2019. In other instances, the documented treatments were increased from the interval that records indicated had been prescribed by the AV. Examples included daily treatment for cat 15ESX4 between December 19, 2019, and January 4, 2020, despite a recorded prescribed interval of every other day cleanings and approximately every other day treatment for this cat from January 6 through 17, 2020, resulting in a frequency of three- to four-times per week despite a recorded prescribed interval of twice weekly cleanings.*

Reference(s):
VHA Handbook 1200.07 §6.b(5)(b). "Primary duties of [Veterinary Medical Officers (VMOs)] … include … [p]roviding professional guidance and technical support to the health care facility's investigators in planning, executing, and directing [Research and Development (R&D)] activities using animals."

9 CFR §2.33(a)(2). "Each research facility shall assure that the attending veterinarian has appropriate authority to ensure the provision of adequate veterinary care and to oversee the adequacy of other aspects of animal care and use."

[5] VAGLAHS personnel could not determine with certainty which of these two protocols the cat was assigned to during the time period mentioned in the Finding due to deficiencies related to tracking of animal use at the facility (*See Finding No. 3*); however, the content of both protocols with regards to instructions for headcap cleanings was identical.

The Guide, p. 14. "The *attending veterinarian* (AV) is responsible for the health and well-being of all laboratory animals used at the institution. The institution must provide the AV with sufficient authority … to manage the program of veterinary care."

Required Action 2:
The Research Service and investigators must ensure veterinary care procedures are performed as directed by the AV.

3. **VAGLAHS did not implement adequate mechanisms to accurately document and monitor animal use.**

Finding:
Interviews with key personnel and document review revealed that inadequate mechanisms to document and monitor animal use, complicated by limitations of the vivarium management software, resulted in the inability to determine protocol assignments for cats and the inability to submit accurate annual reports to USDA.

Facility representatives indicated that protocol transfer requests were submitted via an "Animal Transfer Form." The form specified that it was to "be used for all transfers of animals between protocols" and referenced "prepar[ing] a memo in accordance with the [Standard Operating Procedure (SOP)] 'Transferring Animals Between Protocols' and submit[ting] both the memo and this form…." However, facility personnel were not able to provide the referenced SOP or any examples of completed transfer forms or memos.

Interviews with key personnel associated with Protocols No. 05005-18 and No. 05006-18 revealed that some cats had been used on both protocols. Laboratory personnel were unable to identify which protocol each cat was assigned to over time, and no records (e.g., "Animal Transfer Form" and "Transferring Animals Between Protocols" SOP memo) provided to ORO documented these transfers or clearly indicated which protocol was followed when research-related procedures were conducted. Additionally, VMU personnel and the IACUC were unaware cats were being transferred between protocols; the inability to identify protocol assignment for a cat during a given animal research procedure could prevent the veterinarian and the IACUC from fulfilling oversight responsibilities such as postapproval monitoring and ensuring individual animals do not undergo multiple major survival surgeries on separate protocols without appropriate justification, review, and approval.

Furthermore, inadequate practices for monitoring animal use resulted in the submission of inaccurate USDA Annual Reports. For the past two reporting periods, not all animals utilized in VA research were reported and, in one instance, animals were inappropriately categorized. The USDA Annual Reports in FY2018 and FY2019 did not report the use of any gerbils even though nine and six gerbils, respectively, were used during those reporting periods. The FY2019 VAGLAHS USDA Annual Report indicated that three cats were used in animal research and one cat was held (not used in research) between October 1, 2018, and September 30,

2019; however, document review revealed that all four cats were used for research during this time.

ORO notes that a previous ORO focused review of animal research conducted at the facility identified the same noncompliance issue. [6]

Reference(s):
NIH-OLAW Frequently Asked Question (FAQ) F.2, "Is the IACUC responsible for tracking animal usage?"[7] "[PHS Policy] implicitly requires that institutions establish mechanisms to document and monitor numbers of animals acquired and used, including any animals that are euthanized because they are not needed…. Institutions have adopted a variety of administrative, electronic, and manual mechanisms to meet institutional needs and PHS Policy requirements."

The Guide, p. 115. "Medical records are a key element of the veterinary care program and are considered critical for documenting animal well-being as well as tracking animal care and use at a facility. A veterinarian should be involved in establishing, reviewing, and overseeing medical and animal use records."

9 CFR §§2.36(b)(5)&(6). "The annual report [to USDA] shall … State the common names and the numbers of animals upon which teaching, research, experiments, or tests were conducted involving no pain, distress, or use of pain-relieving drugs. Routine procedures (e.g., injections, tattooing, blood sampling) should be reported with this group; [and] State the common names and the numbers of animals upon which experiments, teaching, research, surgery, or tests were conducted involving accompanying pain or distress to the animals and for which appropriate anesthetic, analgesic, or tranquilizing drugs were used."

VHA Handbook 1200.07 §8.l(1). "**USDA Annual Report of Research Facility.** This report (required by the USDA Animal Welfare Act Regulations and Standards, see 9 CFR 2.36) must be completed and submitted to ORD…. The forms are collected by ORD and sent to the appropriate USDA sector office. A copy of each form is also sent to the [Central Veterinary Medical Officer (CVMO)]'s office by ORD."

Required Action 3:
VAGLAHS, in cooperation with the IACUC and the veterinarian, must implement mechanisms to accurately document and monitor animal use. In addition, the facility must conduct a root cause analysis to determine why the previous remediation efforts to address this issue were not sustained.

[6] See Finding III.5 of ORO Report, dated August 31, 2017, Focused Review: Canine Research and Associated Facility Oversight of the Greater Los Angeles VA Health Care System, Los Angeles, CA.

[7] *Accessible at:* https://olaw.nih.gov/guidance/faqs *(last accessed April 21, 2020)*

4. Several instances of protocol noncompliance were identified.

Finding:
Document review and interviews with key personnel revealed that some animal procedures were not performed as described in the approved protocol, and the protocol deviations had not been first reviewed and approved by the IACUC as a significant change to the protocol. Specifically, ORO noted the following protocol deviations:

- Cats on Protocols No. 05005-18 and No. 05006-18 were first assigned to one of the protocols and then would be moved to the other after completing work on the first; however, both IACUC-approved protocols only listed euthanasia as the final disposition of the cats and did not describe the potential of transfer to another protocol as an alternative disposition.
- A postapproval monitoring report for Protocol No. 05005-18 described administration of injections of substances into the hypoglossal nucleus at concentrations and volumes that exceeded the amounts described in the IACUC-approved protocol. Additionally, some cats were administered 100% nitrogen gas to induce a hypoxic state rather than a mixture of 90% nitrogen with 10% oxygen in air as described in the approved protocol.
- Protocol No. 05005-18 included an electrode implantation surgery. A mixture of dexmedetomidine, ketamine, and butorphanol was approved to be given at a dose of 0.2 ml/kg as a premedication before surgery; however, records indicated that this drug mixture was instead given at a dose of 0.05 ml/kg and 0.08 ml/kg to cat 17LFC4 on April 8 and September 27, 2019, respectively. Per the approved protocol, dexamethasone, a steroid, was to be given pre-operatively only; however, records indicated that dexamethasone was instead given the day after a November 22, 2019, surgery to cat 17LFE1. Per the approved protocol, enrofloxacin, an antibiotic, was to be given at a dose of 5 mg/kg; however, enrofloxacin was instead given at a dose of 2.5 mg/kg to cat 17LFC4 on September 27, 2019. Buprenorphine, an analgesic, was to be given pre-operatively per the approved protocol; however, pre-operative buprenorphine was not given to cat 17LFC4 prior to operations on April 8 and September 27, 2019, nor to cat 15EG4 prior to an operation on July 25, 2018.
- Protocols No. 05005-18 and No. 05006-18 included a head implant surgery.[8] A mixture of dexmedetomidine, ketamine, and butorphanol were approved to be given at a dose of 0.2 ml/kg as a premedication before surgery; however, records indicated that this drug mixture was instead given at a dose of 0.1 ml/kg to cat 17LFC4 on February 26, 2019, and at a dose of 0.05 ml/kg to cat 17LFE1 on June 14, 2019. Per the protocol, dexamethasone was to be given at a dose of 0.5 mg/kg pre-operatively only; however, records indicated that dexamethasone was instead given to cat 17LFE1 at a dose of 1 mg/kg on June 14,

[8] As noted in Finding IV.3, VAGLAHS did not implement existing mechanisms to track protocol assignments and transfers between protocols for cats, so it was not always clear which protocol was being followed for any particular cat procedure for Protocols No. 05005-18 and No 05006-18. Deviations related to the head implant surgeries were included in this Finding (IV.4) if personnel did not follow *either* Protocol No. 05005-18 or No. 05006-18, both of which were in place at the time of the surgeries and included this procedure.

2019, and was also given the day *after* cat 17LFC4 underwent surgery on February 26, 2019.

- Protocol No. 04005-15, involving rabbits, described use of 0.25% bupivacaine, a local anesthetic, pre-operatively. Eighteen individual rabbits (T3935 through T3954) were not administered bupivacaine. This protocol also described use of the opioid buprenorphine for post-operative analgesia and did not describe post-operative use of any antibiotics. Post-operative records for 18 individual rabbits (T3935 through T3954) instead documented the use of carprofen, a nonsteroidal anti-inflammatory drug, in addition to buprenorphine, as well as the use of enrofloxacin, an antibiotic.
- Protocols No. 10015-19, involving pigs and rabbits; No. 03003-18, involving pigs; No. 04009-19, involving rabbits; No. 04005-15; and No. 12019-18 were approved to take place at affiliated universities. The protocols stated that enrichment was to be determined by the VA VMO; however, instructions regarding the enrichment of these animals were not provided to the affiliated university.
- Protocols No. 06011-17 and No. 03003-19, involving hamsters, and No. 04011-12, No. 04012-12, No. 09016-13, and No. 12023-13, involving gerbils, stated that enrichment was to be determined by the VA VMO. The VMO indicated instructions for enrichment were communicated to animal husbandry staff via the VMU SOPs; however, none of the VMU SOPs addressed enrichment for hamsters or gerbils.

Reference(s):

NIH-OLAW FAQ B.9.[9] "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[10] ***(PHS Policy) §IV.B.7.*** "***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."

VHA Handbook 1200.07, Appendix E §2.a(2)(j). "The IACCU [sic] is responsible for … [e]nsuring 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: … [t]here is a change in procedures in any way that might … be considered a significant departure from the written protocol."

[9] *Accessible at:* https://olaw.nih.gov/guidance/faqs *(last accessed April 21, 2020)*

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

Instructions for Completion of the Animal Component of Research Protocol (ACORP) (Version 4) §Z.1. [11] "The Principal Investigator(s) must certify the accuracy of the information presented in the ACORP, and the agreement to perform the work as described."

Instructions for Completion of the ACORP (Version 4) §U. "**Termination or removal from the protocol**. The disposition of each animal on this protocol must be specified. Transfer of animals to other protocols, and each method of euthanasia that may be used, must be specifically approved by the IACUC."

VHA Handbook 1200.07, Appendix D §1.z(1)(g)4. **"**IACUC approval must be obtained before: … animals approved on this protocol are used on another of [the Principal Investigator's (PI's)] IACUC-approved protocols."

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: … euthanasia or disposition of animals…."

NIH-OLAW NOT-OD-14-126 "Guidance on Significant Changes to Animal Activities," dated August 26, 2014.[12] "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."

Required Action 4:
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.

[11] *Accessible at:* https://www.research.va.gov/programs/animal_research/documents.cfm#docs-c *(last accessed April 21, 2020)*

[12] *Accessible at: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-126.html (last accessed April 21, 2020)*

5. In some instances, VAGLAHS did not report to NIH-OLAW and ORO deficiencies that constituted reportable noncompliance.

Finding:
In some instances, the VAGLAHS IACUC did not report noncompliance to NIH-OLAW and ORO. Specific examples included:

- At the April 3, 2019, IACUC meeting, the IACUC reviewed a postapproval monitoring report that indicated personnel working on Protocol No. 05005-18 had anesthetized a cat using an induction method not described on the protocol and performed a minor surgical procedure (re-suturing a surgical incision that was not adequately healed) without seeking veterinary evaluation, guidance, and direction; this procedure was not described in the IACUC-approved protocol. Although the committee indicated in the minutes that "the laboratory did not follow proper protocol and performed a procedure that was not described in the approved ACORP," and "[p]rocedures performed that are not described in the ACORP are prohibited and are a protocol violation," the committee indicated that since "the animal was not harmed … reporting of this incident is not necessary or required." The IACUC's conclusion that reporting of the protocol violation was not required was inconsistent with NIH-OLAW's guidance on reporting deficiencies.
- At the February 5, 2020, IACUC meeting, the Chair reported that a review of research records associated with Protocol No. 05005-18 had revealed that the volume and concentration of substances injected in the hypoglossal nucleus was greater than listed in the approved protocol and that 100% nitrogen gas was used to induce hypoxia in cats rather than 90% nitrogen as described in the protocol. Subsequently, the research group submitted a protocol modification request to obtain IACUC approval for these significant changes and an IACUC member conducted an investigation, which did not identify any further issues. At the end of the meeting, the committee unanimously voted that the incident was reportable. A memorandum to notify ORO of this reportable incident was drafted and sent for the facility Director's signature on February 6, 2020. During interviews with ORO, a member of the Research Service revealed she had contacted the CVMO subsequent to the February 5, 2020, meeting regarding this incident. She indicated that the CVMO recommended consulting with NIH-OLAW for guidance and that the facility should follow OLAW's recommendation. OLAW advised that the incident was reportable, and this information was shared with the IACUC during an emergency meeting held February 7, 2020. Minutes indicated that "Some members felt the differences in the amounts used were very small and animals were not harmed … so it was not reported. Others argued it was a deviation from an approved protocol and, regardless of the amount changed, should be reported." A new motion was made that this compliance issue constituted a reportable event; however, the motion failed to pass, which contradicted NIH-OLAW's direct advice and written guidance on reporting deficiencies, and neither OLAW nor ORO were notified of the protocol deviation.

Reference(s):

VHA Handbook 1200.7 §8.i. "**Mandated Reporting of Deficiencies.** As a condition of extending the privilege of conducting animal research to individual medical facilities, VA Central Office expects that the IACUC and institutional administrators will avoid any appearance of hiding or suppressing deficiencies. ***NOTE:*** *This goal is best achieved by prompt reporting of deficiencies before others outside of the program do so. Consistent with NIH Notice NOT-OD-05-034 dated 2/24/05, 'Guidance on Prompt Reporting to OLAW under the PHS Policy on Humane Care and Use of Laboratory Animals,' facilities are to notify appropriate agencies by phone immediately that a full, written account of a reportable deficiency is forthcoming.*"

PHS Policy §IV.F.3.a. "The IACUC, through the Institutional Official, shall promptly provide OLAW with a full explanation of the circumstances and actions taken with respect to any serious or continuing noncompliance with this Policy."

NIH-OLAW NOT-OD-05-034, "Guidance on Prompt Reporting to OLAW under the PHS Policy on Humane Care and Use of Laboratory Animals," dated February 24, 2005.[13] "All institutions with Animal Welfare Assurances are required to comply with the provisions of [PHS Policy §]IV.F.3. The Institutional Official signing the Assurance, in concert with the IACUC, is responsible for this reporting. Reporting promptly to OLAW under IV.F.3 serves dual purposes. Foremost, it ensures that institutions deliberately address and correct situations that affect animal welfare, PHS-supported research, and compliance with the Policy. In addition, it enables OLAW to monitor the institution's animal care and use program oversight under the Policy, evaluate allegations of noncompliance, and assess the effectiveness of PHS policies and procedures. The underlying foundation of the PHS Policy is one of institutional self-evaluation, self-monitoring and self-reporting…. A comprehensive list of definitive examples of reportable situations is impractical. Therefore, the examples below do not cover all instances but demonstrate the threshold at which OLAW expects to receive a report…. Examples of reportable situations: … conduct of animal-related activities without appropriate IACUC review and approval; failure to adhere to IACUC-approved protocols; [and] implementation of any significant change to IACUC-approved protocols without prior IACUC approval as required by IV.B.7…."

VHA Handbook 1058.01 §§ 7.e&f. "**Reportable Incidents Under Applicable Federal Standards.** VA personnel, including [without compensation (WOC)] and [intergovernmental personnel agreement (IPA)] appointees, must ensure written notification of the IACUC within 5 business days after becoming aware of any incident that is reportable under relevant VHA Handbooks or applicable Federal requirements related to laboratory animal welfare or research safety. **IACUC Review of Reported Incidents.** The IACUC must review any incident described at paragraphs 7.a. through 7.e. at its next convened meeting. (2) The IACUC must notify the VA facility Director and the [Associate Chief of Staff for Research and Development

[13] *Accessible at:* https://grants.nih.gov/grants/guide/notice-files/NOT-OD-05-034.html *(last accessed April 21, 2020)*

(ACOS/R&D)] within 5 business days after reaching a determination that a reportable incident has occurred…. (3) The VA facility Director must report the incident to ORO within 5 business days after receiving the IACUC's notification."

Required Action 5:
The IACUC must ensure that NIH-OLAW and ORO are promptly notified of all reportable deficiencies and incidents.

6. **Some animal research protocols did not contain an adequate rationale for the appropriateness of the numbers of animals requested for use.**

Finding:
Document review indicated that some protocols lacked adequate rationale for the numbers of animals requested for use. In some cases, the number requested was inconsistent with the justification provided, the rationale for the specific number was omitted, or the described study design was incongruent with the total number of animals requested. Specific examples included:

- For Protocol No. 05005-18, involving cats, a total of 6 animals was requested in Section I of the ACORP; however, Section C.2.b. (justification of the "total numbers of animals requested") discussed the number of neurons necessary to record statistically significant data without relating this to the number of animals.
- For Protocol No. 05006-18, involving cats, a total of 6 animals was requested in Section I of the ACORP; however, Section C.2.b. provided statistical justification, including use of a power analysis, for the use of only 2 animals.
- For Protocol No. 10016-18, involving rabbits, a total of 108 animals was requested in Section I of the ACORP; however, Section C described the use of 24 rabbits each for Aims 1a and 1b, and 36 or 72 rabbits for Aim 2 (depending on previous results), for a total of 84 or 120 animals.
- Through post-approval monitoring, facility personnel self-identified and subsequently corrected two additional instances when the IACUC approved protocols that lacked adequate rationale for the numbers of animals requested for use. For Protocol No. 07012-16, involving cats, a total of 80 animals was requested in Section I of the ACORP; however, Section C.2.b. included a justification for the use of only 16 animals. For Protocol No. 04006-15, involving cats, a total of 40 animals was requested in Section I of the ACORP; however, Section C.2.b. included a justification for the use of only 8 animals. ORO notes that these incidents pre-dated other examples identified by ORO in this report suggesting that effective procedures to ensure consistent review and evaluation of the rationales for animal numbers in research protocols were not implemented after the facility's previous self-identification of the issue.

Reference(s):
9 CFR §2.31(e)(2). "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

rationale for involving animals, and for the appropriateness of the species and numbers of animals to be used…."

PHS Policy §IV.D.1.b. "[Protocol proposals] shall contain the following information: … rationale for involving animals, and for the appropriateness of the species and numbers used…."

The Guide, p. 25. "The following topics should be considered in the preparation of the protocol by the researcher and its review by the IACUC: … justification of the species and number of animals proposed; whenever possible, the number of animals and experimental group sizes should be statistically justified (e.g., provision of a power analysis; see Appendix A, Experimental Design and Statistics)…."

VHA Handbook 1200.07 §8.f(2)(a)2. "Evaluations. ***NOTE:*** *Evaluations of the animal protocol forms are based on standards promulgated by the USDA [Animal Welfare Act (AWA)] (see 9 CFR §2.31(d), PHS Policy (see Sec. IV. C), the Guide (see 'Monitoring the Care and Use of Animals'), VA policy, and other Federal regulations or guidelines that impact the conduct of IACUC business.* The IACUC needs to consider the following topics in the preparation and review of animal care and use protocols regardless of the funding source or if not funded (see also App. D): … Justification of the species and number of animals requested. Whenever possible, the number of animals requested should be justified statistically."

Instructions for Completion of the ACORP (Version 4) §§C.2.b & I.[14] "**Justify the group sizes and the numbers of animals requested.** *(US Government Principles*, Principle III*)* To show that the proposed work conforms to applicable US and VA requirements regarding numbers of animals used, describe how the number of animals needed for the experiments was estimated. Explain how this estimate is related to the experimental and control groups described in Item C.2.a, above, and how the optimal number of animals to be included in each group was estimated. The *Guide (p. 25)* states that whenever possible, the number of animals requested should be justified statistically. A power analysis is strongly encouraged to justify group sizes when appropriate…. The total in each category, for each species, will be the total number approved by the IACUC for use over the life of the protocol."

Required Action 6:
The IACUC must ensure that adequate justification for the number of animals requested for use is provided in the VA ACORP, including for the protocols identified in this Finding. In addition, the facility must conduct a root cause analysis to determine why previous remediation efforts to address this issue were not effective at preventing recurrence.

[14] *Accessible at:* https://www.research.va.gov/programs/animal_research/documents.cfm#docs-c *(last accessed April 21, 2020)*

7. The IACUC did not consistently ensure that approved protocols included complete, clear, internally congruent, and accurate descriptions of research activities.

Finding:
Review of IACUC-approved protocols revealed that some protocols contained incomplete, unclear, or inaccurate information regarding experimental procedures, humane endpoints, enrichment, and personnel training requirements. In other instances, various sections within a protocol contained conflicting information regarding the same procedure, thereby calling into question what procedures the IACUC had actually approved. Specific examples included:

- Protocol No. 05005-18, involving cats, indicated in Appendix 6 that a training procedure involved pain and/or distress that would not be relieved; however, interviews with key personnel revealed that, in fact, the training procedures *did not* involve any pain or distress, nor was such pain or distress anticipated.
- Protocol No. 10016-18, involving rabbits, indicated in Section T that the animals would be anesthetized with isoflurane and propofol prior to euthanasia; however, no further information was provided anywhere in the ACORP or its appendices regarding the dose, route, or source of these anesthetic agents. Additionally, Appendix 3 Section 2 listed the topical use of oxymetazoline for laryngeal biopsies; however, this compound was not listed in Section 1 where information was to be provided (but was not) regarding the source or nature of the compound.
- Some protocols described use of compounds in animals that were not included in Appendix 3 which is intended to (but did not) include information regarding the source, dosing rate/frequency of drugs, and the toxicity of potentially hazardous materials to be administered to the animals. Specific examples included:
    - Protocol No. 06012-17, involving rabbits, that included Emla Cream, a topical local anesthetic, as a refinement for venipuncture;
    - Protocol No. 09014-18, involving pigs, that included intravenous phenylephrine to be administered during cardiac stress testing; and
    - Protocol No. 12019-18, involving pigs, that described use of flumazenil or atipamezole to reverse anesthesia.
- The main body of the ACORP for Protocol No. 12019-18 briefly mentioned use of flumazenil or atipamezole to reverse anesthesia in association with a research surgery, but no information on the use of these drugs was included in Appendix 5 where surgical procedures are described.
- Protocol No. 10016-18 contained inconsistent information about the dosing of two drugs. Appendix 3 indicated that dexamethasone would be given at a dose of 0.5-2 mg/kg intravenously (IV) every 8 hours for three doses; Appendix 5 Section 5.b. indicated that it would be given before surgery at a dose of 5-6 mg/kg IV or subcutaneously (SQ) and then be given every 6-12 hours post-operatively for 48 hours; Appendix 5 Section 7.d. indicated it would be given post-operatively at a dose of 1 mg/kg IV or SQ every 8 hours for three doses; and Appendix 5 Section 7.f. indicated three doses would be administered post-operatively. The main body of the ACORP in Section I indicated that buprenorphine would be given at a dose of 0.02-0.04 mg/kg three times a day as necessary for pain not

controlled by meloxicam for up to 6 days; Appendix 5 Section 2 indicated it would be given twice a day for 3 days; and Appendix 5 Section 7.c. indicated it would be given at a dose of 0.2-0.4 mg/kg three times a day for 6 days as needed.

- Protocol No. 09014-18 included the administration of two controlled drugs, ketamine and buprenorphine; however, neither drug was listed in ACORP Section X where information was to be provided (but was not) regarding how the drugs would be stored, who would be provided access, or where the drugs would be obtained.
- Protocol No. 04005-15, involving rabbits, indicated use of bone marrow biopsy from the iliac crest for cell harvest. No descriptions of the biopsy method or use of anesthesia or analgesia were provided.
- Protocol No. 10015-19, involving pigs and rabbits, did not define required humane endpoint criteria in Section U of the ACORP instead, Section U stated that veterinarians would monitor various diagnostic tests, but did not provide any additional details of the veterinarians' assessment.

ORO notes that a previous ORO focused review of specific animal research conducted at the facility identified the same noncompliance issue.[15]

Reference(s):
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…."

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 this [PHS] Policy. In making this determination, the IACUC shall confirm that the research project … is consistent with the *Guide* unless acceptable justification for a departure is presented."

The Guide, pp. 25-26. "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…; conduct of surgical procedures…; … criteria and process for timely intervention, removal of animals from a study, or euthanasia if painful or stressful outcomes are anticipated; … adequacy of training and experience of personnel in the procedures used…;[and] use of hazardous materials…."

VHA Directive 1200.02 §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

[15] See Finding III.2 of ORO Report, dated August 31, 2017, Focused Review: Canine Research and Associated Facility Oversight of the Greater Los Angeles VA Health Care System, Los Angeles, CA.

research to allow the R&D Committee and/or its subcommittees to fully review the Research Protocol, including all procedures…."

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

VHA Handbook 1200.07, Appendix D (Animal Component of Research Protocol (ACORP)), §1.s. "**Endpoint Criteria**. Provide specific endpoint criteria that will be used for determining when sick animals, both on and off study, will be euthanatized or otherwise removed from a study. Examples of appropriate criteria that need to be considered include: a weight loss limit as a percentage of initial or expected body weight…."

INSTRUCTIONS FOR COMPLETION OF THE ACORP APPENDIX 3 – BIOSAFETY (VERSION 4) §1.[16] "**Summary of All Materials Administered to Animals on this Protocol.** Include ALL materials administered to animals on this protocol, such as, but not limited to, radioisotopes, chemicals, drugs (standard clinical agents as well as test agents, and all controlled substances listed in Item X.1 of the main body of the ACORP), infectious agents, biomaterials, prosthetic devices, and cells, tissues, or body fluids."

Required Action 7:
The IACUC must ensure that approved protocols contain complete, clear and accurate information, and that various sections within a protocol have congruent descriptions, including the protocols identified in this Finding. In addition, the facility must conduct a root cause analysis to determine why the previous remedial action was not maintained.

8. The IACUC did not notify the VA facility Director and ACOS/R&D of determinations of non-reportability for animal research incidents in at least two instances.

Finding:
In at least two instances, the IACUC did not notify the VA facility Director or ACOS/R&D within 5 business days of making a determination that an incident brought to its attention was not reportable. Specific examples included:

- At a convened meeting on April 3, 2019, the IACUC reviewed a notification related to postapproval monitoring of Protocol No. 05005-18 and found it to be not reportable. No notifications were made to the ACOS/R&D or the facility Director regarding this determination.
- At a convened meeting on February 7, 2020, the IACUC re-reviewed postapproval monitoring of Protocol No. 05005-18, and a motion that this incident be deemed reportable failed. The ACOS/R&D had received an earlier email notification with a preliminary report indicating the incident was reportable, with a request for a signature

[16] *Accessible at:* https://www.research.va.gov/programs/animal_research/documents.cfm#docs-c *(last accessed April 21, 2020)*

from the facility Director. However, the IACUC did not provide the ACOS/R&D updated information after the committee reassessed the initial determination at the February 7, 2020, convened meeting, and determined that the incident was not reportable.

Reference(s):
VHA Handbook 1058.01 §7.f(4). "The IACUC must ... notify the VA facility Director and the ACOS/R&D within 5 business days after any determination that an incident brought to its attention under paragraphs 7.a. through 7.e. [related to animal research] was not reportable."

Required Action 8:
The IACUC must ensure that the VA facility Director and the ACOS/R&D are notified within 5 business days after any determination that an incident brought to its attention was not reportable.

9. VAGLAHS did not establish or maintain MOUs or other formal written agreements with four outside institutions to describe all respective responsibilities associated with collaborative animal research.

Finding:
VAGLAHS established an MOU describing shared responsibilities for collaborative animal research with the USC in 2009; however, the agreement expired on November 1, 2019. Interviews with key personnel revealed that although VAGLAHS had initiated procedures to re-establish an MOU, no further actions to complete this process had taken place since December 2019.

In 2018, VAGLAHS approved Protocol No. 05009-18, a VA-funded animal research protocol that involved the use of mice and a collaboration with Augusta University's Medical College of Georgia; no MOU or other formal written understanding was established between VAGLAHS and this university to define their respective responsibilities.

Three Interinstitutional Assurances[17] were negotiated with NIH-OLAW to establish VAGLAHS as the IACUC of record and the performance site for animal research funded by NIH grants awarded to two institutions that did not maintain their own independent Assurances, IACUCs, or animal facilities: WebSciences for research involving cats (Assurances A8806-01 effective June 14, 2018, and A8806-02 effective July 13, 2018) and Sentia Medical Sciences, Inc., for research involving rodents (Assurance A8765-02 effective May 16, 2018). These assurances established the oversight relationship between these outside institutions and VAGLAHS with

[17] During VAGLAHS' factual review of ORO's draft report, VAGLAHS personnel indicated it was their understanding that NIH-OLAW considered the need for an additional written agreement to be a recommendation, not a requirement, when an Interinstitutional Assurance had been established. ORO independently contacted the NIH-OLAW Division of Assurances which confirmed that the Interinstitutional Assurance, in and of itself, was not sufficient to meet the expectations of the *Guide*, page 15, that indicates, "In cases of such collaboration involving animal use (beyond animal transport), participating institutions should have a formal written understanding (e.g., a contract, memorandum of understanding, or agreement) that addresses the responsibility for…."

NIH-OLAW but did not address all respective responsibilities and expectations of each institution regarding the collaborative research (e.g., animal ownership).

Reference(s):
The Guide, p. 15. "Interinstitutional collaboration has the potential to create ambiguities about responsibility for animal care and use. In cases of such collaboration involving animal use (beyond animal transport), the participating institutions should have a formal written understanding (e.g., a contract, memorandum of understanding, or agreement) that addresses the responsibility for offsite animal care and use, animal ownership, and IACUC review and oversight."

NIH-OLAW NOT-OD-01-017 "OFFICE OF EXTRAMURAL RESEARCH GUIDANCE REGARDING ADMINISTRATIVE IACUC ISSUES AND EFFORTS TO REDUCE REGULATORY BURDEN," dated February 12, 2001.[18] "There are many circumstances that involve partnerships between collaborating institutions or relationships between institutional animal care programs…. It is imperative that institutions define their respective responsibilities."

Required Action 9:
VAGLAHS must establish and maintain formal written agreements (e.g., a contract, memorandum of understanding, other agreement, etc.) regarding all respective institutional responsibilities for all ongoing collaborative animal research, including for the collaborations described in this Finding.

10. The VAGLAHS IACUC did not receive copies of the approved protocol and approval notices, as required by the MOU, when VA research was concurrently approved by the UCLA IACUC.

Finding:
Although the MOU between VAGLAHS and UCLA regarding responsibilities for shared oversight of collaborative research, signed January 2, 2018, stated that copies of the approved protocol and approval notices would be provided to the VAGLAHS IACUC when the UCLA IACUC concurrently reviewed VA research, interviews with key personnel indicated that the VAGLAHS IACUC did not receive this information and had not implemented any alternate procedures to maintain awareness of the content of VA protocols approved by the UCLA IACUC.

Reference(s):
Memorandum of Understanding (MOU) Between VA Greater Los Angeles Healthcare System and University of California Los Angeles With Regard to Collaboration on the Use of Animals in Research (signed January 2, 2018), §F.3. "In the case of VA-funded research, regardless of where the study is performed, the VA form must be used and must be approved by the GLA IACUC. The sponsoring Party may, at its discretion, impose additional requirements for review

[18] Accessible at *https://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-017.html (last accessed April 21, 2020)*

of activities conducted at the other Party's facility. In cases where the UCLA IACUC reviews VA research, UCLA shall submit to GLA a copy of the approved protocol and approval notice for GLA approval."

Required Action 10:
When VA research is reviewed and approved by the UCLA IACUC, the Research Service must ensure that the VAGLAHS IACUC is provided with copies of the UCLA IACUC-approved protocol and approval notice.

11. One protocol included single housing of rabbits without an appropriate scientific justification.

Finding:
Document review indicated that Protocol No. 10016-18, involving rabbits, contained inadequate justifications for single housing of a social species. Specifically, the protocol described single housing as the default housing method without providing a scientific justification related to the experiment even though rabbits can successfully be socially housed. The rationale provided in the approved ACORP stated, "Per normal vivarium protocol, rabbits are housed singly per cage. All animals are jointly housed in a room, within vision of each other" and "To prevent aggression between adult animals, rabbits are routinely housed singly per cage. All animals are jointly housed in a room, within vision of each other." Although the ACORP contains this explanation requesting single housing based on vivarium procedure, neither the IACUC minutes nor the ACORP documented consideration of specific scientific justifications related to this protocol requiring single housing to prevent compromise of animal welfare or research data. Furthermore, rabbits are social species that can be successfully group housed with appropriate behavioral management.

Reference(s):
Instructions for Completion of the ACORP (Version 4) §M.1.c.[19] "The *Guide* recommends that social animals be housed in stable pairs or groups unless they must be housed alone for experimental reasons … (*Guide*, p. 51 and 64). Provide the justification if any animals are to be housed singly (if species is not considered 'social', then so note)."

The Guide, p. 51. "Social animals should be housed in stable pairs or groups of compatible individuals unless they must be housed alone for experimental reasons…."

The Guide, p. 64. "Single housing of social species should be the exception and justified based on experimental requirements…."

[19] *Accessible at:* https://www.research.va.gov/programs/animal_research/documents.cfm#docs-c *(last accessed April 21, 2020)*

AAALAC Position Statement on Social Housing.[20] "Social housing will be considered by AAALAC International as the default method of housing unless otherwise justified based on social incompatibility resulting from inappropriate behavior, veterinary concerns regarding animal well-being, or scientific necessity approved by the IACUC (or comparable oversight body)."

Required Action 11:
The IACUC must ensure that protocols involving the single housing of social species, including the one mentioned in this Finding, document appropriate scientific justifications based on experimental requirements.

12. Two animal protocols did not have an investigator who could assume full responsibilities for all aspects of the research.

Finding:
Interviews with key personnel revealed that the PI for Protocols No. 12013-13, involving gerbils, and No. 06012-17, involving rabbits, died in November 2019. No actions were taken to amend (including assignment of the two protocols to a new PI), suspend, or terminate these protocols, and three gerbils assigned to Protocol No. 12013-13 were still present in the VMU at the time of this focused review.

Reference(s):
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. If responsibility for all aspects of the research cannot be fulfilled the research may need to be amended, suspended, or terminated."

VHA Directive 1200.01 §12.a(1)(g). "Reviews by the R&D Committee and its subcommittees must ensure: … Availability of qualified research team members, including investigators, who can conduct the approved research…."

Required Action 12:
The Research Service, in consultation with the ACOS/R&D, IACUC, and other key components of the ACUP, must ensure that when investigators can no longer assume full responsibilities for all aspects of animal research, protocols, including the ones mentioned in this Finding, are amended, suspended, or terminated and, when necessary, that a responsible party is identified for any remaining animals.

[20] ***VHA Handbook 1200.07 §7.e*** indicates that "All VA animal facilities … must be accredited by AAALAC." AAALAC has developed position statements that are used by the Council on Accreditation to evaluate and accredit animal research programs. Additional information, and this position statement, are available at: https://www.aaalac.org/accreditation-program/position-statements/#social *(last accessed April 21, 2020)*

13. Two individuals involved in VA animal research had expired VA appointments.

Finding:
Two individuals on Protocol No. 05005-18, involving cats, did not have current VA WOC appointments. The appointment for one of these individuals expired December 28, 2018; the appointment for the other individual expired in January 2020. The first individual whose VA appointment expired in 2018 was also the PI for Protocol No. 05006-18.

Reference(s):
VHA Directive 1200.02(1) §12.a(4)(a). "[S]pecific responsibilities of the ACOS/R&D include … [e]nsuring that all research personnel hold an official VA appointment from [Human Resources Management Service (HRMS)] (as a compensated, full-time or part time employee, a WOC, or under an IPA) prior to conducting or being involved in any way in VA research activities, and that the individuals maintain their appointment while conducting or being involved in any way in any VA research activities."

VHA Directive1200.02(1) §12.a(4)(b). "[S]pecific responsibilities of the ACOS/R&D include … [e]nsuring that all requests for WOC appointments for research have been appropriately justified and the appointments are in compliance with all applicable research, HRMS, and other VA policies."

Required Action 13:
The ACOS/R&D must ensure that all research personnel involved in animal research activities maintain VA appointments.

14. The IACUC did not consistently ensure that the use of non-pharmaceutical grade compounds (NPGCs) was identified, scientifically justified and adequately described in approved protocols.

Finding:
Document review of select IACUC-approved protocols revealed that, in some cases, scientific justifications and specific information for the assurance of animal welfare (e.g., provisions for sterility, pH, osmolality, and stability) regarding the use of NPGCs[21] in live animals were not provided or were inadequate/inaccurate. Therefore, the IACUC could not conduct an informed review and assessment of potential adverse consequences involving administration of NPGCs. Additionally, in several instances, NPGCs used in animals were not identified as such. Specific examples included:

[21] A pharmaceutical grade compound is any active or inactive drug, biologic, reagent, etc., manufactured under Good Manufacturing Practices (GMP) which is approved, conditionally approved, or indexed by the Food and Drug Administration (FDA) or for which a chemical purity standard has been written or established by a recognized compendium (e.g., United States Pharmacopeia-National Formulary).

- Protocol No. 09016-13, involving gerbils, described the oral administration of amoxicillin and identified the source of this antibiotic drug as a company that does not provide pharmaceutical grade compounds. Amoxicillin was not identified as a NPGC in Appendix 3 of the ACORP; thus, information for the assurance of animal welfare was not provided.
- Protocol No. 05006-18, involving cats, identified the use of several NPGCs, including baclofen, pindolol, and acetylcholine, and indicated as justification for such use that FDA-approved formulations were unavailable; however, these compounds were, in fact, available as FDA-approved compounds.
- Protocol No. 12019-18, involving pigs, described the use of streptozocin and indicated it was being purchased from a source that does not provide pharmaceutical grade compounds; however, the protocol did not identify this compound as an NPGC in Appendix 3, acknowledge the availability of a pharmaceutical grade preparation, nor provide appropriate justifications for its use or assurance of animal welfare in its preparation.

Reference(s):

The Guide, p. 31. "The use of non-pharmaceutical-grade chemicals or substances should be described and justified in the animal use protocol and be approved by the IACUC…. In such instances, consideration should be given to the grade, purity, sterility, pH, pyrogenicity, osmolality, stability, site and route of administration, formulation, compatibility, and pharmacokinetics of the chemical or substance to be administered, as well as animal welfare and scientific issues relating to its use…."

VHA Handbook 1200.07, Appendix D, §1.z(1)(e). "The information provided in this ACORP must be complete and accurate."

INSTRUCTIONS FOR COMPLETION OF THE ACORP APPENDIX 3 – BIOSAFETY (VERSION 4) §2.[22] "OLAW requires that only pharmaceutical grade compounds be administered to animals unless the use of non-pharmaceutical grade compounds is justified by scientific necessity and the lack of availability of an acceptable veterinary or human pharmaceutical grade compound (*OLAW FAQs*, F.4)…. Mark with a * each material, diluent, or vehicle to be administered to the animals on this protocol that is not pharmaceutical grade. For each of these, provide the justification for using a non-pharmaceutical grade compound, and describe how it will be ensured that the grade, purity, sterility, pH, pyrogenicity, osmolality, stability, formulation, and pharmacokinetics of the material will be suitable for use in the animals (*Guide*, p. 31). Note that OLAW specifically advises that cost-savings alone do not adequately justify the use of non-pharmaceutical grade compounds in animals."

[22] *Accessible at:* https://www.research.va.gov/programs/animal_research/documents.cfm#docs-c *(last accessed April 21, 2020)*

NIH-OLAW FAQ F.4, "May investigators use non-pharmaceutical-grade substances in animals?"[23] "OLAW and USDA agree that pharmaceutical-grade substances, when available, must be used to avoid toxicity or side effects that may threaten the health and welfare of vertebrate animals and / or interfere with the interpretation of research results. However, it is frequently necessary to use non-pharmaceutical-grade substances … to meet scientific and research goals. The IACUC is responsible for evaluating the potential adverse consequences of non-pharmaceutical-grade substances when used for research."

See also *AAALAC FAQ C.9, "Non-Pharmaceutical-Grade Compounds."*[24]

Required Action 14:
The IACUC must ensure that any proposed use of NPGCs is identified, adequately described and scientifically justified in approved protocols, including in the protocols identified in this Finding.

15. Some personnel involved in the animal research program did not complete all required training.

Finding:
Interviews with key personnel and review of select records revealed that not all individuals involved in the animal research program had completed all required training. Specific examples included:

- For Protocol No. 09014-18, the only person approved to conduct a surgery to induce cardiac ischemia in pigs had never completed the "Working with the VA IACUC" training.
- The alternate nonscientific member on the IACUC had never completed the mandatory training "Essentials for IACUC Members."
- The PIs for Protocols No. 05005-18 and No. 05006-18, involving cats, as well as another individual involved with Protocol No. 05005-18, had not completed the training "Waste Anesthesia Gases Training for Research Staff," which the Research Service indicated was required on an annual basis for individuals involved in research including use of anesthetic gases.
- One individual on Protocol No. 05005-18 had not completed the training "Laboratory Hazard Communication and Research Safety/Biosafety Annual Refresher," which the Research Service indicated was required on an annual basis.

Reference(s):
VHA Handbook 1200.07 §8.m. "**Mandatory Training.** Through IACUC oversight, each VA medical facility must ensure that all personnel involved with animal research receive training to competently and humanely perform their duties related to animal research. This mandate

[23] *Accessible at*: https://olaw.nih.gov/guidance/faqs *(last accessed April 21, 2020)*

[24] *Accessible at:* https://www.aaalac.org/accreditation-program/faqs *(last accessed April 21, 2020)*

extends to IACUC members, veterinarians, veterinary technicians, husbandry staff, research technicians, investigators, and all others that perform procedures or manipulations on laboratory animals. ***NOTE:*** *It includes investigators responsible for supervising animal research that they themselves do not perform.* (1) Prior to approving any protocol, the IACUC must ensure that all staff listed on the protocol have been adequately trained (see: USDA AWA, 9 CFR 2.32(a); Principle VIII, U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, And Training). As a minimum, the training utilized must cover all topics listed in USDA AWA, 2.32(c). IACUC members must be trained on topics pertinent to their committee tasks."

ORD Website, "Required training for staff involved in the use of animals in research."[25] "All personnel who participate in or supervise research that involves laboratory animals must complete 'Working with the IACUC' at least every three years…. Personnel that serve on or provide support to … any VA Institutional Animal Care and Use Committee (IACUC) of record … must take the following web-based training at least every three years: Essentials for IACUC Members."

9 CFR §§2.32(a)-(b). "It shall be the responsibility of the research facility to ensure that all scientists, research technicians, animal technicians, and other personnel involved in animal care, treatment, and use are qualified to perform their duties. This responsibility shall be fulfilled in part through the provision of training and instruction to those personnel…. [T]he qualifications of personnel [shall be] reviewed, with sufficient frequency to fulfill the research facility's responsibilities under this section and § 2.31."

U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training, Principle VIII. "Investigators and other personnel shall be appropriately qualified and experienced for conducting procedures on living animals. Adequate arrangements shall be made for their in-service training, including the proper and humane care and use of laboratory animals."

Department of Veterans Affairs, Greater Los Angeles Healthcare System Animal Welfare Assurance Number D16-00002 (effective date September 20, 2018) §III.G. "All research staff working with animals (Principal Investigators, students, laboratory staff, visiting scholars, etc.) are required to pass and be current on the test for the general on-line course 'Working with the IACUC'…. All IACUC members are required to take and be current on 'Essentials for IACUC Members.'"

Required Action 15:
VAGLAHS must ensure that all personnel involved in the animal research program, including those mentioned in this Finding, complete all required training.

[25] *Accessible at:* https://www.research.va.gov/programs/animal_research/required_training.cfm *(last accessed May 4, 2020)*

16. The Occupational Health and Safety Program (OHSP) did not provide an opportunity for participation to all at-risk personnel within the ACUP.

Finding:
Interviews with key personnel revealed that three members of the IACUC (i.e., one non-affiliated member, the non-scientific member, and the alternate non-scientific member) were never offered enrollment in the animal research occupational health and safety Preventative Medicine Program (PMP) in relationship to their IACUC duties, even though the non-affiliated member had entered the VMU during semiannual facility inspections. Additionally, the written policy describing the facility's OHSP, dated July 2008, did not provide an opportunity for participation to all personnel who are at risk of exposure to animals, such as IACUC members exposed to animals during semiannual facility inspections or during the course of other activities related to their committee duties.

Reference(s):
VHA Handbook 1200.07 §10.a(1). "Each VA facility with an animal research program must develop a written policy establishing an occupational health and safety program (OHSP) to protect the personnel who are involved in animal research, or who are otherwise at risk of exposure to animals or their (unfixed) tissues or fluids…. **Opportunity to Participate.** All Federal employees, without compensations (WOC), and other non-Federal personnel who work with animals or unfixed tissues used in VA research must be given the opportunity to participate in the OHSP at the VA facility at no charge. In addition, the following individuals who have intermittent contact with animals or the animal facility must also have the opportunity to enroll at no charge: IACUC voting members (including the non-affiliated and non-scientist member) and non-voting participants who enter the animal facility as part of the IACUC semi-annual evaluation of the animal care and use program and facilities."

VHA Handbook 1200.07 Appendix C §4.a(1). "All personnel who are involved in animal research, or who are otherwise at risk of exposure to animals or their (unfixed) tissues or fluids must be given the opportunity to either participate in PMP, participate in a similar PMP provided by an affiliate or other institution, or sign a waiver declining to participate.... The Institutional Animal Care and Use Committees (IACUC), with input from health care professionals, must decide the level of PMP services needed for each person or group based upon a risk assessment."

NIH-OLAW FAQ G.2., "What is required for an occupational health and safety program?"[26]
"An effective occupational health and safety program must encompass all personnel that have contact with animals."

[26] *Accessible at*: https://olaw.nih.gov/guidance/faqs *(last accessed April 21, 2020)*

Required Action 16:
VAGLAHS must ensure that all at-risk personnel involved in the ACUP are included in the PMP and OHSP.

17. Some individuals involved in the animal research program had not completed an annual occupational health medical review and/or obtained a clearance.

Finding:
Document review and interviews with key personnel identified individuals involved in the animal research program who had not been provided an annual medical review and/or clearance. Examples included:

- One individual on Protocol No. 05005-18, involving cats, whose occupational health review/clearance was last completed January 12, 2018;
- A nonaffiliated IACUC member, who had entered the VMU during semi-annual facility inspections, indicated she had been enrolled in the facility's OHSP in approximately October 2011 but had not subsequently been evaluated or provided on-going services; and
- Three individuals on Protocol No. 05009-18, involving rabbits, who were listed as enrolled in the affiliate's occupational health and safety PMP but had not obtained an annual occupational health medical review and/or clearance.

Interviews with key personnel revealed that the IACUC did not currently have a mechanism for ensuring all individuals involved in the animal research program were up-to-date on their annual occupational health medical review/clearance. The IACUC had previously relied on a database to verify initial enrollment and track on-going status of animal research personnel in the OHSP; however, this database became corrupt in approximately November 2019. No interim measures had been implemented to track this information, and the IACUC did not request that individuals provide proof of enrollment (or declination thereof).

Reference(s):
VHA Handbook 1200.07 Appendix C §4.a(2)(b). "Medical Follow-up. At least annually after employment begins, an occupational health and safety physician, or other qualified medical professional, needs to review each employee's medical history [for employees with animal contact or exposure to animal allergens]."

VHA Handbook 1200.07 Appendix C §4.a(2)(c). "Access to Animals and IACUC Approvals. Because VA must ensure that a safe workplace is provided, all employees covered in subparagraph 4a(1) must provide proof to the IACUC that they have enrolled in PMP or have declined enrollment before they enter the animal research facility and before they begin work with animals."

VHA Directive 1200.01 §12.a(1)(a). "Reviews by the R&D Committee and its subcommittees must ensure … the implementation of adequate safety measures for research … personnel."

The Guide, p. 22. "A preemployment health evaluation and/or a health history evaluation before work assignment is advisable to assess potential risks for individual employees. Periodic medical evaluations are advisable for personnel in specific risk categories."

VAGLAHS RESEARCH AND DEVELOPMENT INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE STANDARD OPERATING PROCEDURE 151-CA-01.02 (S) "OCCUPATIONAL HEALTH PROGRAM FOR RESEARCH PERSONNEL WITH ANIMAL CONTACT," dated July 2008, §§4.A. & 5.A(5). "Research Service will maintain a database of employees with animal contact, and will track whether they have had their initial and annual health evaluations…. An annual review of workers with animal contact is required to detect problems in the early stage and ensure that required immunizations are current. The Research Office will send employees an e-mail notification when their annual health evaluation is due along with an attached [Research Medical Questionnaire (RMQ)]. Administrative Medicine will provide a written notice to the Research Office that the employee is fit for duty."

Department of Veterans Affairs, Greater Los Angeles Healthcare System Animal Welfare Assurance Number D16-00002 (effective date September 20, 2018) §III.E. "**The risk-based occupational health and safety program for personnel working in laboratory animal facilities and personnel who have frequent contact with animals….** *New employees* are given a health questionnaire (the Research Medical Questionnaire) and an appointment at one of our Administrative Medicine facilities…. *Continuing employees* are screened once each fiscal year using the same procedure. *Compliance* is monitored by Research Administration…. If someone's medical clearance is not current, they must bring it up to date…."

Required Action 17:
The Research Service, in coordination with the IACUC, must ensure all individuals involved in animal research receive annual occupational health evaluations.

18. IACUC minutes did not contain sufficient details regarding the activities of the committee.

Finding:
Document review and interviews with key personnel revealed that IACUC meeting minutes did not consistently capture the activities and deliberations of the committee in sufficient detail to document the activities of the committee and demonstrate compliance with regulatory requirements. Specific examples included:

- June 13, 2018, IACUC meeting minutes indicated that Protocol No. 05005-18, involving rabbits, required modifications to secure approval that would be evaluated via Designated Member Review (DMR). Correspondence dated July 12, 2018, issued to the PI indicated that approval was granted. Minutes for the August 1, 2018, IACUC meeting included an entry in section *XIV. Unfinished Business A. Final Approvals 1. New* that only contained the protocol number, PI name, and protocol title; the method used to complete the triennial review were not provided.

- May 2, 2018, IACUC meeting minutes indicated that Protocol No. 05005-18, involving rabbits, underwent triennial review and required modifications to secure approval that would be evaluated via DMR. Correspondence dated May 25, 2018, issued to the PI indicated that approval was granted with an effective date of May 27, 2018. Minutes for the June 13, 2018, IACUC meeting include an entry in section *XIV. Unfinished Business A. Final Approvals 4. Triennials* that only contains the protocol number, PI names, and protocol title; the method used to complete the triennial review were not provided.
- ORD Central Office comments and suggested changes for Protocol No. 12019-18, involving pigs, were reviewed by the IACUC at the March 6, 2019, IACUC meeting. Minutes indicated that the committee approved a motion requiring the PI to submit a modification to address the comments. This item was not tracked in the IACUC minutes, and no further entries were found in subsequent IACUC minutes documenting the resolution of this request.
- ORD Central Office comments and suggested changes for Protocol No. 05009-18, involving rabbits, were reviewed by the IACUC at the March 1, 2018, IACUC meeting. Minutes indicated that the committee approved a motion requiring the PI to submit a modification to address the comments. This item was not tracked in the IACUC minutes, and no further entries were found in subsequent IACUC minutes documenting the resolution of this request.
- Neither the presence nor absence of the alternate nonscientific member was documented in IACUC minutes between September 4, 2019, and February 7, 2020.
- The IACUC euthanasia SOP was sent to DMR for review and approval at the March and April 2018 IACUC meetings. No further entries were made in IACUC meeting minutes to document or track the completion of this business item.
- A report out from the affiliate was regularly listed as an item at the beginning of the IACUC agenda and minutes. However, an affiliate report-out had not been provided since September 2019 despite successive minutes listing the item on the agenda. When affiliate reports were given, details of the report were not consistently documented in the minutes, and the minutes did not distinguish whether or not a report was provided.

Reference(s):

9 CFR §2.35(a)(1). "**Recordkeeping requirements.** The research facility shall maintain the following IACUC records: Minutes of IACUC meetings, including records of attendance, activities of the Committee, and Committee deliberations."

PHS Policy §IV.E.1.b. "***Recordkeeping Requirements.*** The awardee institution shall maintain … minutes of IACUC meetings, including records of attendance, activities of the committee, and committee deliberations…."

NIH-OLAW NOT-OD-09-035 "Guidance to IACUCs Regarding Use of Designated Member Review (DMR) for Animal Study Proposal Review Subsequent to Full Committee Review

(FCR)," dated March 28, 2014.[27] "The specific method of review for each protocol should be documented, along with the outcome of the review in the IACUC meeting minutes."

NIH-OLAW FAQ D.3, "What are the possible methods of IACUC approval?"[28] "There are only two valid methods of IACUC review allowed by the PHS Policy: (1) full-committee review by a convened quorum of the members of the IACUC, or (2) designated member review by one or more members, employed only after all voting members have been provided an opportunity to call for full-committee review…. The specific method of review for a given protocol must be documented, along with the outcome of the review."

NIH-OLAW FAQ B.7, "What information should be in IACUC minutes?"[29] "PHS Policy requires that minutes of IACUC meetings, records of attendance, activities of the Committee, and Committee deliberations, be maintained by the institution. Accordingly there should be documentation of major issues discussed by the IACUC and the outcome of the discussions in sufficient detail for an outsider to ascertain the nature of the discussion and the conclusions reached. Written transcripts or tape recordings of meetings are not required."

VHA Handbook 1200.07 §8.h(1)(e). "Business items need to be retained under old business in subsequent minutes until the final approval is given by the IACUC, the project is disapproved by the IACUC, or the project is withdrawn from consideration by the investigator. The final disposition of each project needs to be clearly stated in the minutes."

Required Action 18:
The IACUC must ensure that meeting minutes contain sufficient detail of the activities and deliberations of the committee.

19. Significant protocol changes, including requests to change the PI and increase animal numbers by >10%, were made via a noncompliant approval process.

Finding:
Review of IACUC minutes and protocol approval documentation revealed that the administrative review process (effective date of action April 18, 2018), rather than DMR or FCR, was used to approve significant changes to Protocols No. 04006-15 and No. 07012-16. Specifically, the administrative review process was used for each of these protocols to assign new PIs and approve the use of four additional cats beyond the originally requested two animals.[30]

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[27] *Accessible at:* https://grants.nih.gov/grants/guide/notice-files/NOT-OD-09-035.html *(last accessed June 3, 2020)*

[28] *Accessible at:* https://olaw.nih.gov/guidance/faqs *(last accessed April 21, 2020)*

[29] *Accessible at:* https://olaw.nih.gov/guidance/faqs *(last accessed April 21, 2020)*

[30] Although the local IACUC SOP allowed for administrative approval of certain animal number increases, the approval of four additional cats exceeded the SOP's threshold of ≤ 10% change for use of this approval method.

Reference(s):

NIH-OLAW NOT-OD-14-126 "Guidance on Significant Changes to Animal Activities," dated August 26, 2014.[31] "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…. Significant changes described in 1.a.-g., 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: … f. in Principal Investigator (PI)…. A significant change that may be handled administratively according to an existing IACUC-reviewed and -approved policy without additional consultation or notification is an increase in previously approved animal numbers."

IACUC SOP 1 (IACUC Function) STANDARD OPERATING PROCEDURE; INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (dated December 2016) §C.4.a)vii. "**ADMINISTRATIVE REVIEW OF MODIFICATIONS**…. The IACUC Coordinator will conduct a preliminary review of all modification requests. If it is determined that a modification request meets any of the criteria listed below the IACUC coordinator or designee of the Chair may approve these outright [including the a]ddition of ≤10% more animals of a species/strain already approved on the current ACORP."

PHS Policy §IV.C.2. "Prior to the review, each IACUC member shall be provided with a list of proposed research projects to be reviewed. Written descriptions of research projects that involve the care and use of animals shall be available to all IACUC members, 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. If full committee review is requested, approval of those research projects may be granted only after review at a convened meeting of a quorum of the IACUC and with the approval vote of a majority of the quorum present."

Required Action 19:

The IACUC must ensure that all significant changes, including changes in PI and animal number increases, are approved by an appropriate method.

[31] *Accessible at: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-126.html (last accessed April 21, 2020)*

20. The IACUC did not ensure that the semi-annual evaluation reports were consistently sent to the R&D Committee for review.

Finding:
Interviews and a review of meeting minutes revealed that the IACUC had not consistently been sending the semi-annual evaluation reports (including the program review, facility inspection, and other associated required documentation) to the R&D Committee for review. Furthermore, there was an approximately 21-month gap between consecutive reviews of these semi-annual reports. The May 30, 2018, R&D Committee minutes documented review of a full report of the semi-annual evaluation; however, the October 4, 2018; April 3, 2019; and September 4, 2019, semi-annual evaluations were not sent to the R&D Committee for review. The February 26, 2020, R&D Committee Agenda indicated that the program review, not the full report of the semi-annual evaluation, from the most recent semi-annual evaluation was to be presented to the committee.

References(s):
VHA Handbook 1200.07 §8.f(1)(e)NOTE. *"A copy* [of the report of the semi-annual evaluation] *needs to be sent to the local R&D Committee for review, but R&D Committee approval is not needed before the document is sent to the CVMO."*

Required Action 20:
The IACUC must ensure that the semi-annual evaluation report is routinely sent to the R&D Committee for review.

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:
Interviews with members of the IACUC and research personnel revealed apparent gaps in knowledge regarding appropriate IACUC function, the reporting and investigation of animal welfare concerns, animal stress versus distress,[32] and other areas related to IACUC responsibilities.

[32] *The books "Recognition and Alleviation of Pain in Laboratory Animals" and "Recognition and Alleviation of Distress in Laboratory Animals," are available electronically for free from The National Academies Press online at:* https://www.nap.edu/catalog/12526/recognition-and-alleviation-of-pain-in-laboratory-animals and https://www.nap.edu/catalog/11931/recognition-and-alleviation-of-distress-in-laboratory-animals *(last accessed April 22, 2020).*

The Research Service should consider the potential value of providing additional opportunities for continuing education for IACUC members and research personnel regarding IACUC responsibilities, Federal regulations/policies, VHA policies, and the investigation and reporting of potential animal welfare concerns. Additional educational opportunities would help ensure that research personnel and all committee members have a shared understanding regarding appropriate IACUC function and member roles.

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

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

2. **Observation:**
The human-animal bond improves animal welfare by reducing animal stress through gentle handling practices, enhancing the animal's sense of safety and security, and fostering trust. This bond improves job satisfaction but also has the potential to lead to stress and/or emotional distress in animal handlers and research facility staff, particularly when research activities may include the euthanasia of animals. Since the VAGLAHS research program involves the use of companion animals, the Research Service is strongly encouraged to consider the potential value of developing an employee wellness program tailored to the special emotional needs of individuals involved directly and indirectly in the VA animal research program. Additional information can be found on the American Association of Laboratory Animal Science (AALAS) website.[33]

3. **Observation:**
ORO strongly encourages the IACUC and the AV to work with the PI for Protocol No. 12019-18, involving pigs and conducted at USC, to re-evaluate the interplay between the humane and experimental endpoints of this protocol while giving special consideration to the "3Rs" (replacement, reduction and refinement), particularly the latter two. ORO noted that this protocol may require the euthanasia of some pigs prior to reaching experimental endpoints due to an affiliate policy that appears to preclude housing of pigs that weigh greater than 50 kg. Euthanizing pigs because of a policy-based humane endpoint such as an animal weight limit prior to completion of all planned experimental activities for some of the aims may result in the inability of the

[33] Accessible at https://www.aalas.org/education/educational-resources/cost-of-caring *(last accessed April 22, 2020)*

PI to collect the data described in the approved protocol from those animals and, ultimately, result in the unnecessary use of additional animals.

Specifically, Section T of the protocol, where endpoints were described, indicated that, "[i]f at any time the pig reaches the 50 kg weight limit during the study a [Department of Animal Research (DAR)] veterinarian will be consulted per facility guidelines," and in Section C.2. the protocol indicated that, "**[d]ue to the weight limit (50 kg) for housing the pigs** and the hesitance. [sic] of the USC IACUC to repeat the surgeries, the pigs will be euthanized according to the experiment setup. For a majority of the pigs, this will be long after all treated wounds have closed and a minimum of 28 days after initial surgery. **The exception being pigs who will have treated wounds excised before complete closure to analyze markers throughout the wound healing cycle whose second surgery may not be healed by the time the animals are euthanized"** (emphases added)**.**

Reference(s):

The Guide, pp. 4-5. "The decision to use animals in research requires critical thought, judgment, and analysis. Using animals in research is a privilege granted by society to the research community…. It is a trust that mandates responsible and humane care and use of these animals. The *Guide* endorses the responsibilities of investigators as stated in the *U.S. Government Principles for Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training*…. The Three Rs represent a practical method for implementation of the principles described above. In 1959, W.M.S. Russell and R.L. Burch published a practical strategy of replacement, refinement, and reduction—referred to as the Three Rs—for researchers to apply when considering experimental design in laboratory animal research…. *Refinement* refers to modifications of husbandry or experimental procedures to enhance animal well-being and minimize or eliminate pain and distress…. *Reduction* involves strategies for obtaining comparable levels of information from the use of fewer animals or for maximizing the information obtained from a given number of animals (without increasing pain or distress) so that in the long run fewer animals are needed to acquire the same scientific information."

The Guide, p. 27. "The experimental endpoint of a study occurs when the scientific aims and objectives have been reached. The humane endpoint is the point at which pain or distress in an experimental animal is prevented, terminated, or relieved…. The PI, who has precise knowledge of both the objectives of the study and the proposed model, should identify, explain, and include in the animal use protocol a study endpoint that is both humane and scientifically sound. The identification of humane endpoints is often challenging, however, because multiple factors must be weighed, including the model, species (and sometimes strain or stock), animal health status, study objectives, institutional policy, regulatory requirements, and occasionally conflicting scientific literature. Determination of humane endpoints should involve the PI, the veterinarian, and the IACUC, and should be defined when possible before the start of the study."

VHA Handbook 1200.07 §3.q. "Reduction may include … gathering a maximum amount of data from each animal subject…."

4. **Observation:**
ORO strongly encourages the IACUC and AV to evaluate current practices regarding the establishment, maintenance, and review of SOPs related to the ACUP to ensure they effectively implement the Program while ensuring regulatory compliance and supporting high-quality animal research and humane animal use. ORO identified several SOPs and written procedures describing ACUP recurring research procedures that were not being appropriately maintained, updated, and/or reviewed on a regular basis. Specific examples included:

- The VMU SOP No. 151-VMU-12 "DOG HUSBANDRY," dated February 2020, provided to ORO for review did not incorporate changes related to monthly duties the facility had indicated to NIH-OLAW were made in correspondence dated September 6, 2018, related to its 2018 site visit.
- SOP No. 151-CA-01.02 (S) "OCCUPATIONAL HEALTH PROGRAM FOR RESEARCH PERSONNEL WITH ANIMAL CONTACT," provided to ORO for review and referenced in the facility's Animal Welfare Assurance was dated July 2008. The IACUC indicated that it could not recall when this SOP had last been reviewed.
- The copy of "IACUC SOP 1 (IACUC Function)" provided to ORO for review was dated December 2016 and, during multiple interviews, was verified to be the most recent version; however, an unsigned, apparently more recent copy (dated December 2016 in the document itself but January 2019 in the file name) was provided on the last day of ORO's remote interviews.
- The IACUC Euthanasia Policy provided to ORO for review was dated May 2017 and indicated it was a draft. Interviews with key personnel confirmed that this policy was still a draft and was never finalized despite IACUC minutes documenting that this SOP was sent to DMR for reformatting.

Reference(s):
The Guide, p. 13. "[T]he primary oversight responsibilities in the [Animal Care and Use] Program rest with the [Institutional Official (IO), i.e., the facility Director in the VA system], the AV, and the IACUC…. Together they establish policies and procedures, ensure regulatory compliance, monitor Program performance, and support high-quality science and humane animal use."

NIH-OLAW FAQ D.14. "May standard operating procedures (SOPs) or blanket protocols that cover a number of procedures be utilized in lieu of repeating descriptions of identical procedures in multiple protocols?"[34] "SOPs should be

[34] *Accessible at:* https://olaw.nih.gov/guidance/faqs *(last accessed April 21, 2020)*

reviewed by the IACUC at appropriate intervals (at least once every three years) to ensure they are up-to-date and accurate. (See NOT-OD-14-126)."

5. **Observation:**
The IACUC should consider reviewing its practices to ensure email voting or polling is not utilized to conduct official IACUC business. Review of IACUC minutes revealed some limited instances when email voting or polling was utilized by the IACUC to approve SOPs or vote on the selection of new members. The use of electronic voting or polling does not allow for real time verbal interaction equivalent to that occurring in a physically-convened meeting and, therefore, is not equivalent to convening a quorum of members for a meeting.

Reference(s):
NIH-OLAW NOT-OD-06-052, "Guidance on Use of Telecommunications for IACUC Meetings under the PHS Policy on Humane Care and Use of Laboratory Animals," dated March 24, 2006.[35] "Methods of telecommunications (e.g., telephone or video conferencing) are acceptable for the conduct of official IACUC business requiring a quorum, provided the following criteria are met: … The forum allows for real time verbal interaction equivalent to that occurring in a physically-convened meeting (i.e., members can actively and equally participate and there is simultaneous communication)."

6. **Observation:**
The facility's current animal welfare whistleblower posting did not include a senior point of contact such as the Institutional Official (Director, in the VA System). The Research Service is encouraged to consider adding the facility Director as an additional point of contact for reporting potential animal welfare concerns.

Reference(s):
The Guide, p. 24. "Mechanisms for reporting [animal welfare] concerns should be posted in prominent locations in the facility and on applicable institutional website(s) with instructions on how to report the concern and to whom. Multiple points of contact, including senior management, the IO, IACUC Chair, and AV, are recommended."

7. **Observation:**
As noted in Finding IV.10, the IACUC did not receive copies of UCLA IACUC-approved VA protocols and had not implemented any alternate procedures to maintain awareness of the content of protocols describing VA Research approved by the UCLA IACUC. Failure to maintain this active communication could result in incongruence between the protocols approved by each IACUC, potentially leading to confusion for

[35] *Accessible at:* https://grants.nih.gov/grants/guide/notice-files/NOT-OD-06-052.html *(last accessed April 22, 2020)*

the PI and other personnel regarding what procedures the IACUCs had in fact approved and to protocol noncompliance, particularly if the animal research procedures described in these different versions varied. The Research Service should work with affiliate IACUC(s) to identify a process that facilitates communication and sharing of information between the committees and ensures congruency between VA and university approved protocols in order to prevent inadvertent noncompliance.

8. **Observation:**
The IACUC, under the guidance and direction of the AV, should consider incorporating some flexibility, when appropriate, when reviewing and approving protocols in order to facilitate best practices and minimize potential noncompliance. Specifically, descriptions of surgical anesthetic protocols may incorporate dose ranges (rather than a strict, single dose) to allow appropriately trained personnel to titrate drugs to achieve desired effect using professional judgement in real-time. This practice would improve the quality of anesthesia and veterinary care provided to the animals while also limiting possible protocol deviation. Consultation with the AV and ACUP personnel administering these substances, and development and implementation of appropriate training along with these modifications, if pursued, would be key components to successful implementation of this practice.

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 communicate with the Attending Veterinarian (AV) in a timely manner regarding a cat with a veterinary medical problem; veterinary care procedures for one cat were not performed as directed by the AV; VAGLAHS did not establish adequate mechanisms to accurately document and monitor animal use; research personnel did not follow IACUC approved protocols; VAGLAHS did not report to the National Institutes of Health-Office of Laboratory Animal Welfare (NIH-OLAW) and ORO deficiencies that constituted reportable noncompliance; some animal research protocols did not contain an adequate rationale for the appropriateness of the numbers of animals requested for use; and the IACUC did not consistently ensure that approved protocols included complete, clear, internally congruent, and accurate descriptions of research activities. 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)

Director, Research Safety and Animal Welfare, ORO

APPENDIX A
ORO REVIEW TEAM and FACILITY REPRESENTATIVES

ORO Remote Review Team:

(b)(6)

Facility Representatives:

(b)(6)

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.

***NOTE**: Protocols with the same name but different protocol numbers reflect the facility's practice to change protocol numbers at each triennial review.*

- 03003-18 Vocal Cord Tissue Engineering: Pre-Clinical Scale-Up
- 03003-19 Functions of Leptospira Lig Proteins in the Pathogenesis of Leptospirosis
- 04005-15 Human Bone Engineering and Resorption in a Novel Mineralized Collagen Scaffold
- 04006-15 Resolution of the Mechanisms Responsible for Atonia during REM Sleep
- 04009-19 Preclinical Evaluation of Nanoparticulate Mineralized Collagen Glycosaminoglycan Materials in Calvarial Regeneration
- 04011-12 Adaptive Responses of *Helicobacter Pylori* to Chronic Acid Exposure
- 04012-12 Investigation of H. Pylori-Host Interactions Contributing to Gastric Pathology
- 05005-18 GABAergic Switches Control Wakefulness, NREM Sleep and REM Sleep
- 05006-18 Resolution of the Mechanisms Responsible for Atonia during REM Sleep
- 05009-18 Exercise-Induced Shear Stress Modulates Metabolic Pathways for Vascular Repair and Protection
- 06011-17 Virulence Proteins of Pathogenic Leptospiral Species
- 06012-17 The Pharmacokinetics of the Novel Potassium Competitive Acid Blocker, JCHC-PCAB
- 07012-16 GABAergic Switches Control Wakefulness, NREM Sleep and REM Sleep
- 09014-18 Tailoring Stress Cardiac MRI for Women with Ischemic Heart Disease
- 09016-13 Mechanisms of Gastric Mucosal Response to *H Pylori* Infection at Acidic pH
- 10015-19 3-D Intravascular Sensors for Lipid-Rich Plaques
- 10016-18 Tissue Engineering to Regenerate Functional Vocal Fold after Scarring or Tissue Loss
- 12013-13 Acid Adaptation Targets for Eradication of *Helicobacter pylori*
- 12019-18 The Role of Exogenous Type VII Collagen on the Healing of Skin Wounds
- 12023-13 Acid Adaptation Targets for Eradication of *Helicobacter pylori*

REMEDIAL ACTION PLAN

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

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

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

Deadline for completion of Required Actions: **October 24, 2020**

Animal Care and Use Program. ORO Case Number: **691-0110-A**

Required Action 1: VAGLAHS must ensure that medical care for animals with veterinary medical problems is provided by or in consultation with a qualified veterinarian.	
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 Research Service and investigators must ensure veterinary care procedures are performed as directed by the AV.	
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: VAGLAHS, in cooperation with the IACUC and the veterinarian, must implement mechanisms to accurately document and monitor animal use. In addition, the facility must conduct a root cause analysis to determine why the previous remediation efforts to address this issue were not sustained.	
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: 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 5: The IACUC must ensure that NIH-OLAW and ORO are promptly notified of all reportable deficiencies and incidents.	
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 must ensure that adequate justification for the number of animals requested for use is provided in the VA ACORP, including for the protocols identified in this Finding. In addition, the facility must conduct a root cause analysis to determine why previous remediation efforts to address this issue were not effective at preventing recurrence.	
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 approved protocols contain complete, clear and accurate information, and that various sections within a protocol have congruent descriptions, including the protocols identified in this Finding. In addition, the facility must conduct a root cause analysis to determine why the previous remedial action was not maintained.	
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 IACUC must ensure that the VA facility Director and the ACOS/R&D are notified within 5 business days after any determination that an incident brought to its attention was not reportable.	
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: VAGLAHS must establish and maintain formal written agreements (e.g., a contract, memorandum of understanding, other agreement, etc.) regarding all respective institutional responsibilities for all ongoing collaborative animal research, including for the collaborations described 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 10: When VA research is reviewed and approved by the UCLA IACUC, the Research Service must ensure that the VAGLAHS IACUC is provided with copies of the UCLA IACUC-approved protocol and approval notice.	
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: The IACUC must ensure that protocols involving the single housing of social species, including the one mentioned in this Finding, document appropriate scientific justifications based on experimental requirements.	
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 Research Service, in consultation with the ACOS/R&D, IACUC, and other key components of the ACUP, must ensure that when investigators can no longer assume full responsibilities for all aspects of animal research, protocols, including the ones mentioned in this Finding, are amended, suspended, or terminated and, when necessary, that a responsible party is identified for any remaining animals.	
Facility Response	***ORO Comments***
Response #1 ([DATE of response submission]) **Facility Action:** [TEXT] **Proposed Completion Date:** [DATE]	[ORO comments will be inserted here]
Required Action 13: The ACOS/R&D must ensure that all research personnel involved in animal research activities maintain VA appointments.	
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 14: The IACUC must ensure that any proposed use of NPGCs is identified, adequately described and scientifically justified in approved protocols, including in 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 15: VAGLAHS must ensure that all personnel involved in the animal research program, including those mentioned in this Finding, complete all required training.	
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 16: VAGLAHS must ensure that all at-risk personnel involved in the ACUP are included in the PMP and OHSP.	
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 17: The Research Service, in coordination with the IACUC, must ensure all individuals involved in animal research receive annual occupational health evaluations.	
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 18: The IACUC must ensure that meeting minutes contain sufficient detail of the activities and deliberations of the committee.	
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 19: The IACUC must ensure that all significant changes, including changes in PI and animal number increases, are approved by an appropriate method.	
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 20: The IACUC must ensure that the semi-annual evaluation report is routinely sent to the R&D Committee for review.	
Facility Response	***ORO Comments***

Response #1 ([DATE of response submission]) **Facility Action:** [TEXT] **Proposed Completion Date:** [DATE]	[ORO comments will be inserted here]