OFFICE OF RESEARCH OVERSIGHT

FOCUSED REVIEW REPORT

Research Safety and Security Program
Animal Care and Use Program

South Texas Veterans Health Care System
San Antonio, Texas

November 12, 2019

Veterans Health Administration

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ORO FOCUSED REVIEW REPORT

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San Antonio, TX

On-Site Review Dates: August 13 – 16, 2019
Date of Report: November 12, 2019

EXECUTIVE SUMMARY

The Office of Research Oversight (ORO), Veterans Health Administration (VHA), conducted an on-site Focused Review of the Animal Care and Use Program (ACUP) and Research Safety and Security Program (RSSP) at South Texas Veterans Health Care System (STVHCS) on August 13-16, 2019. 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: emergency eye wash equipment was not readily accessible in areas where hazardous chemicals were used; information necessary to appropriately inform the facility's research safety committee's risk assessment of proposed research involving hazardous chemicals was not consistently provided to the committee; academic affiliate inspection reports of laboratories where VA research was conducted were not reviewed by the facility's research safety committee; a serious work-related injury was not reported to the facility's research safety committee; the facility's Institutional Animal Care and Use Committee (IACUC) approved study protocols that omitted critical information about actual procedures that animals would be subjected to (thus, calling into question whether the IACUC was aware of procedures that would subsequently be performed on animals under the auspices of study protocols approved by the IACUC); unapproved study protocol deviations, including a deviation from a pain management regimen that could have negatively impacted animal welfare; and the configuration of heating, ventilation, and air conditioning equipment serving the animal housing room had not been evaluated to ensure that the equipment did not present a potential threat to animals in the case of a malfunction (so as to prevent an overheating event that could jeopardize laboratory animal welfare). 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 conducted an on-site, focused compliance review of the Research Safety and Security Program (RSSP) and Animal Care and Use Program (ACUP) at South Texas Veterans Health Care System (STVHCS) on August 13-16, 2019. In addition, teleconferences were held remotely with selected personnel on May 22 and 23, 2019. ORO's review at STVHCS was initially intended to focus on STVHCS's nonhuman primate research program and Institutional Animal Care and Use (IACUC) operations; however, based on information gathered during ORO's preparation for the on-site review, the scope of the review was expanded to include protocols involving other species and aspects of the Research Safety and Security Program (RSSP) related to animal research. It is further noted that STVHCS research activities involving nonhuman primates were discontinued during the intervening period between the initiation of ORO's review activities and the conducting of ORO's site visit.

II. METHOD OF REVIEW

ORO's review of STVHCS included individual and group interviews of facility leadership, research administrative staff, research oversight committee members and staff, investigators, and/or other personnel associated with the facility's research compliance program (Appendix A). ORO's review evaluated facility research policies, procedures, protocols,[1] memoranda of understanding (MOUs), and related documentation. ORO also conducted a physical inspection of the Veterinary Medical Unit (VMU).

III. FACILITY RESEARCH PROGRAM OVERVIEW

STVHCS is a complexity level 1A quaternary care facility academically affiliated with University of Texas Health San Antonio (UTHSA). It operates a research program involving human subjects, laboratory animals, and hazardous agents, with a research project budget of $29,202,859 in FY18,[2] of which $10,412,344 was provided by the VHA Office of Research and

[1] The corresponding titles for protocols referenced by numerical identifiers in the Findings and Observations in this report are provided in Appendix B.
[2] Data from the facility's filed Research and Development Information System (RDIS) report.

Development (ORD). Foundation for Advancing Veterans' Health Research (FAVHR) provides a flexible funding mechanism for non-VA sponsored research at STVHCS.

At the time of ORO's review, there were 41 active animal care and use research protocols conducted by 25 principal investigators (PIs). The research portfolio included studies on aging, cardiac surgery, cancer, Post Traumatic Stress Disorder, Alzheimer's, and diabetes.

STVHCS maintains its own IACUC, Subcommittee on Research Safety (SRS), and Institutional Biosafety Committee (IBC).

STVHCS has a current Public Health Service (PHS) Animal Welfare Assurance D16-00423 (A3720-01) expiring March 31, 2023, on file with the National Institutes of Health – Office of Laboratory Animal Welfare (NIH-OLAW); holds full accreditation with the Association for the Assessment and Accreditation of Laboratory Animal Care, International (AAALAC; Unit No. VA-063); is registered with the U.S. Department of Agriculture – Animal and Plant Health Inspection Service (USDA-APHIS; Registration No. 74-V-0009); and the STVHCS IBC is registered with the NIH Office of Science Policy (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, STVHCS 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.

A. RESEARCH SAFETY and SECURITY

1. Emergency eyewash equipment was not provided in animal facility areas where paraformaldehyde[3]/formalin[4] were used.

Finding:
A walk-through of the VMU and interviews with key personnel revealed the presence of paraformaldehyde/formalin, a hazardous chemical; discussions with research staff confirmed that these chemicals were routinely used in rooms U224 and U233. None of the animal procedure rooms, including rooms U224 and U233, were equipped with an emergency eyewash for quick drenching or flushing of the eyes. The VMU had emergency eyewash/shower equipment located in the hallway; however, exiting the animal procedure rooms to access the emergency eyewash in the hallway required

[3] Paraformaldehyde is a solid polymerized form of formaldehyde that is converted to formaldehyde upon dissolution in aqueous medium.
[4] Formalin is a solution of formaldehyde in water, varying from 37% to 50% by volume and usually containing some methanol.

activation of a button located on the wall in order to release the locking mechanism of the door.

Reference(s):
VHA Directive 7704(1) §3. "It is VHA policy to provide employees, trainees, volunteers, and contractors with emergency eyewash and shower stations where there is a reasonable probability of injury to the eyes or skin occurring as a result of exposure to hazardous chemicals or materials."

VHA Directive 7704(1), Appendix A §2.b. "The emergency eyewash or shower units are not to be located in an area where employees must pass through a locked or latched doorway or weave around equipment to obtain access."

29 CFR §1910.151(c). "Where the eyes … of any person may be exposed to injurious corrosive materials, suitable facilities for quick drenching or flushing of the eyes … shall be provided within the work area for immediate emergency use."

Required Action A1:
The facility must ensure that emergency eyewash equipment is provided in all animal facility areas where personnel may be exposed to paraformaldehyde/formalin.

2. **The SRS did not ensure that research personnel working with formalin/paraformaldehyde were provided with all the required information and training as specified by OSHA.**

Finding:
Based on document review, interviews with key personnel, and assessment of training records provided on-site, ORO determined that research personnel who were working with formalin, or paraformaldehyde, which is an Occupational Health and Safety Administration (OSHA) regulated chemical, and at corresponding risk of exposure, had not completed the required safety-related training for working with formaldehyde [formaldehyde is an OSHA-regulated chemical][5].

References(s):
VHA Directive 1200.08 §5.n(11)(a). "The SRS is responsible for…: … Managing safety-related training."

VHA Directive 1200.08 §10.a(1). "All individuals (VA employees appointed as full-time, part-time, intermittent, fee-basis, or [without compensation (WOC)], as well as contractors), and individuals appointed through [Intergovernmental Personnel Act (IPA)] actions, either working in or directly administering VA research laboratories, must be appropriately trained to ensure safety and security within research

[5] *See 29 CFR 1910.1048.*

laboratories. These training requirements must include … initial and annual refresher training on … OSHA-regulated chemicals…."

29 CFR §1910.1450(f)(3). "*Information*. Employees shall be informed of: … (iii) The permissible exposure limits for OSHA regulated substances or recommended exposure limits for other hazardous chemicals where there is no applicable OSHA standard; (iv) Signs and symptoms associated with exposures to hazardous chemicals used in the laboratory…."

29 CFR §1910.1450(f)(4)(i). "Employee training shall include: … (B) The physical and health hazards of chemicals in the work area; and (C) The measures employees can take to protect themselves from these hazards, including specific procedures the employer has implemented to protect employees from exposure to hazardous chemicals, such as appropriate work practices, emergency procedures, and personal protective equipment to be used."

Required Action A2:
The SRS must ensure all laboratory personnel working with formalin/paraformaldehyde are provided with safety training and information that includes the potential physical and health hazards of formaldehyde, signs and symptoms of exposure, applicable OSHA exposure limits (e.g., Short Term Exposure Limit, Time Weighted Average), appropriate work practices, emergency procedures, and personal protective equipment to be used.

3. **The Research Office did not maintain safety training records.**

Finding:
An interview with the Deputy Associate Chief of Staff for Research and Development (DACOS/R&D) and the Administrative Officer for Research and Development (AO/R&D) revealed that the Research Office had not maintained any initial or refresher safety training records for training that had been provided.

Reference(s):
VHA Directive 1200.08 §10.d. "Training records must be maintained by the facility Research Office for both initial and refresher training. At a minimum, these records must include the identity of the individual, the date of completion of the training, and a description of the training."

Required Action A3:
The Research Office must ensure initial and refresher safety training records are maintained.

4. **During initial review of research, the SRS did not consistently assess the risks of chemical hazards to personnel, the facility, and the environment.**

Finding:
Based on document review and interviews with key personnel, including the SRS Chair, ORO determined that during the initial review of research the SRS did not consistently assess all research-related hazards, and therefore did not perform an adequate risk assessment. For example, VA research associated with Protocols #1702-002, #1608-002, and #1610-001 involved the use of hazardous chemicals (e.g., tamoxifen, isoflurane, dimethyl sulfoxide, drugs administered to animals, and proprietary compounds) that were not documented on the Research Protocol Safety Survey (RPSS) or otherwise communicated to the SRS; therefore, the SRS did not have the opportunity to assess the risks associated with the use of these chemicals in the proposed research.

Reference(s):
VHA Directive 1200.08 §6.e(1). "The SRS must assess at least the following in the initial review: (a) The risks associated with the research including, but not limited to, risks to personnel, research subjects, the facility, and the environment."

Required Action A4:
The SRS must ensure that all risks to personnel, the facility, and the environment are assessed during the initial review of research involving hazards.

5. **The SRS did not ensure that annual inspection reports of affiliate laboratories where VA research was conducted were reviewed by the SRS as required by VHA policy.**

Finding:
Based on document review and interviews with key personnel, it was determined that annual inspection reports of affiliate laboratories where VA research was conducted were not reviewed by the SRS. The SRS Chair revealed that the SRS had not received any laboratory inspection reports from the affiliate for affiliate laboratories where VA research was conducted.

Reference(s):
VHA Directive 1200.08 §5.n(6). "The SRS is responsible for managing implementation of the RSSP, which includes: … Reviewing inspection reports of each VA research laboratory annually, to ensure that appropriate safety equipment and procedures and security measures are in place for all of the projects/protocols being conducted in that laboratory. ***NOTE:*** *For VA research conducted in approved off-site facilities that are not owned, leased by VA, or occupied by VA under a legal agreement the SRS may rely on inspections conducted by non-VA entities with primary responsibility for the space (e.g., academic affiliate) provided that the inspections are conducted at least annually and the SRS reviews the results of those inspections.*"

Required Action A5:

The SRS must ensure that it reviews annual inspection reports for each affiliate laboratory where VA research is conducted.

6. **The effectiveness of the Research Chemical Hygiene Plan (CHP) was not reviewed and evaluated annually.**

Finding:
A review of SRS minutes and an interview with the SRS Chair revealed that the SRS (or any other STVHCS authority) did not review and evaluate the effectiveness of the Research CHP annually as required.

Reference(s):
29 CFR §1910.1450(e)(4). "The employer shall review and evaluate the effectiveness of the Chemical Hygiene Plan at least annually…."

STVHCS Research Service Policy Memorandum* "Chemical Hygiene Plan" *16-04 §4B(7).
"CHEMICAL HYGIENE OFFICER/CHAIRMAN, [Research Laboratory Safety Subcommittee (RLSS)] [shall] [e]nsure the Chemical Hygiene Plan is reviewed annually by the Safety Subcommittee for any possible changes or updates. Minutes should reflect review."

Required Action A6:
The effectiveness of the CHP must be reviewed and evaluated annually.

7. **Initial exposure monitoring was not conducted to determine if formaldehyde exposure limits outside of a chemical fume hood were being exceeded.**

Finding:
A review of documents and interviews with research and facility safety personnel revealed that relevant baseline exposure monitoring of research personnel was not conducted to accurately determine if exposure limits were exceeded while working with paraformaldehyde/formalin outside of a chemical fume hood, such as when laboratory staff performed animal perfusions using paraformaldehyde, and tissue harvesting using formalin. Baseline formaldehyde monitoring, conducted in 2013 and 2014, was limited to research procedures that were conducted inside of a chemical fume hood; therefore, those monitoring results were not applicable in "accurately determining" exposure to paraformaldehyde/formalin used outside of a chemical fume hood.

Reference(s):
29 CFR §1910.1048(d)(2). "*Initial monitoring.* The employer shall identify all employees who may be exposed [to formaldehyde] at or above the action level or at or above the [short term exposure limit (STEL)] and accurately determine the exposure of each employee so identified."

OSHA Interpretation Letter, dated March 23, 2017. "Pursuant to 29 CFR 1910.1450(a)(2), in [non-production research] labs, the Laboratory Standard 29 CFR 1910.1450] supersedes all other requirements of the Formaldehyde Standard [29 CFR 1910.1048], except for compliance with: 1. The permissible exposure limit (PEL) (0.75 parts per million (ppm)), action level (0.5 ppm), and short-term exposure limit (STEL) (2 ppm for 15 minutes) for formaldehyde (see 29 CFR 1910.1048(b), 1910.1048(c), and 29 CFR 1910.1048(d)(2)). 2. Use of chemical protective clothing made of materials impervious to formaldehyde and the use of other personal protective equipment, such as goggles and face shields, as appropriate to the operation to prevent all contact of the eyes and skin with liquids containing 1 percent or more formaldehyde (see 29 CFR 1910.1048(h)(1)(i)-(iv))."[6]

VHA Directive 1200.08 §5.n(11). "The SRS is responsible for managing implementation of the RSSP, which includes: … [c]oordinating the safety and security measures that apply to all of the facility's VA research laboratories. This includes: … (b) Ensuring that a process is in place to identify individuals who require … exposure monitoring, on the basis of their involvement in specific VA research projects, or their other risks of exposure to hazards involved in VA research."

Required Action A7:
The SRS, in conjunction with the Facility Industrial Hygienist, must identify research employees working with paraformaldehyde/formalin outside of a chemical fume hood and determine their exposure level through exposure monitoring.

8. The SRS meeting minutes did not document the recusal of individual members and verification that quorum was maintained.

Finding:
Review of SRS meeting minutes from October 7, 2017, March 6, 2018, and January 8, 2019, revealed that the minutes did not document the recusal of individual members with a conflict of interest and verification that quorum was maintained during the review of protocols. For example, the PI for Protocols #0807-004[7] and #1111-001, was a voting member of the SRS; however, the SRS minutes did not reflect if this individual had recused themselves during deliberations and voting.

References(s):
VHA Directive 1200.08 §6.d(3)(c). "The recusal of the individual [SRS member because of a conflict of interest] and verification that quorum is maintained [for the SRS meeting] must be documented in the SRS meeting minutes."

Required Action A8:

[6] *Accessible at* https://www.osha.gov/laws-regs/standardinterpretations/2017-03-23-0
[7] Macrophage-Mediated Gene Therapy of Atherosclerosis

The SRS must ensure its meeting minutes document the recusal of individuals having a conflict of interest and verification that quorum was maintained during such recusal.

9. A serious work-related injury was not reported to the SRS for evaluation.

Finding:
Through interviews with key personnel, ORO was informed that a workplace injury that occurred in March 2019 had not been reported to and evaluated by the SRS as required by VHA policy. The injury, which involved a needlestick that occurred while disposing of a butterfly needle contaminated with human blood, was serious enough to meet OSHA criteria for a recordable injury.[8]

Reference(s):
VHA Directive 1200.08 §5.n. "The SRS is responsible for managing implementation of the RSSP, which includes: … (8) Ensuring that each of the following is evaluated, addressed, and reported according to regulatory requirements, including those of VHA Handbook 1058.01, Research Compliance Reporting Requirements, dated June 17, 2015: … (b) Any serious accident, injury, illness, or exposure (other than those that result in death) that may be the result of work (or other activity) in a research laboratory or dedicated research area (e.g., research specimen storage area)...."

VHA Handbook 1058.01 §8.b. "VA personnel, including WOC and IPA appointees, must ensure written notification of the SRS within 5 business days after becoming aware of any serious accident, injury, illness, or exposure (other than those that result in death) that may be the result of work (or other activity) in a research laboratory or dedicated research area (e.g., research specimen storage area)."

STVHCS Research Service Policy Memorandum Research Standard Operating Procedures (SOP) Handling of Research Non-Compliance and/or Reportable Incidents/Unexpected Events Involving Research Safety and Laboratory Security 16-19 3.a(1). "Within 5 business days of becoming aware of any reportable incident/unexpected event, members of the VA research community are required to ensure that the incident has been reported in writing to the SRS."

Required Action A9:
The Research Service must ensure that serious workplace accidents, injuries, and illnesses are reported and evaluated in accordance with VHA policy.

10. Additional safety concerns were identified in specific research laboratories.

[8] Per 29 CFR §1904.8(a): "***Basic requirement.*** You must record all work-related needlestick injuries and cuts from sharp objects that are contaminated with another person's blood or other potentially infectious material (as defined by 29 CFR 1910.1030). You must enter the case on the OSHA 300 Log as an injury. To protect the employee's privacy, you may not enter the employee's name on the OSHA 300 Log…."

Finding:
The nature and location of regulatory and policy deficiencies identified during ORO's laboratory inspections are provided in **Appendix C, Table 1**.

Reference(s):
Relevant regulatory citations are provided in Appendix C.

Required Action A10:
The SRS must ensure deficiencies identified during laboratory inspections, as listed in Appendix C, are appropriately remediated.

B. ANIMAL CARE and USE

1. Some IACUC members continued to participate in official IACUC business as voting members despite lapses in their appointments.

Finding:
Several IACUC member appointments lapsed; however, the IACUC was not aware these lapses had occurred and continued to utilize each of these members to contribute to quorum and to conduct official business during the lapses. Specific examples included:

- One scientific voting member was appointed from September 2013 through September 2016 via a letter dated September 16, 2013. The next appointment letter included a term from September 2016 to August 2019, but was not issued until June 6, 2017, resulting in a lapse of approximately 8.5 months.
- Another scientific voting member was appointed from November 2015 to October 2018 via a letter dated November 4, 2015. The next appointment letter dated May 1, 2019, included a term of May 2019 through April 2022, resulting in lapse of approximately 6 months.
- A third scientific voting member was appointed from June 2015 through May 2018 via an undated letter. The next appointment letter, dated August 16, 2018, included a term from August 2017 to July 2020, resulting in a lapse of approximately 2.5 months.
- A nonscientific voting member was appointed from June 2015 through May 2018 via an undated letter. The next appointment letter, dated August 16, 2018, indicated a term of August 2017 through July 2020, resulting in a lapse of approximately 2.5 months.

Reference(s):
VHA Handbook 1200.07 §8.a. "The medical facility Director must officially appoint members in writing, to include specifying the length of the appointments…."

Public Health Service Policy on Humane Care and Use of Laboratory Animals (PHS Policy) §IV.A.3.a.[9] "The Chief Executive Officer shall appoint an IACUC, qualified through the experience and expertise of its members to oversee the institution's animal program, facilities, and procedures."

Office for Protection from Research Risks (OPRR)[10] ***Reports, June 2, 1997, Maintenance of Properly Constituted IACUCs.***[11] "[T]he requirement that the IACUC be properly constituted in order to conduct official business is explicit in not only the PHS Policy and USDA Animal Welfare Regulations, but also in the corresponding authorizing statutes. Accordingly, **the validity of IACUC actions is always predicated on the existence of a properly constituted IACUC.** When it becomes apparent that an improperly constituted IACUC has approved a research proposal or taken other official action, that action is, by definition, invalid. It follows that animal-related activities without valid approval must be suspended until appropriate review and approval have occurred. In addition, prompt reporting of such findings and corrective actions to [OLAW] … is expected. Careful attention to PHS Policy language regarding IACUC membership, quorum, and procedures should prevent this problem from arising."

VHA Handbook 1200.07 §8.a(1). "Only a properly constituted IACUC may conduct official business."

Required Action B1a:
The IACUC must evaluate the impact of the continued participation of these IACUC members without valid appointments on official business, namely on the validity of IACUC business, and remediate any noncompliance identified.

Required Action B1b:
The Research Service must develop a system to ensure appointments are monitored, and that reappointments are approved in a timely and appropriate manner to prevent future lapses in membership.

2. **The VA IACUC did not maintain appropriate oversight of off-site VA animal research.**

Finding:
An MOU regarding shared oversight for collaborative animal research had been executed with the affiliate in 2011. Document review and interviews with key personnel revealed that the VA IACUC was not sending a review team to the affiliate and that no information regarding the affiliate's semi-annual evaluations had been received between May 2017 and September 2018. Additionally, when information had

[9] ***VHA Handbook 1200.07 §4.b(4).*** "[A]ll VA facilities conducting animal research must comply with … the PHS Policy."
[10] The Animal Welfare Division of OPRR was renamed Office of Laboratory Animal Welfare (OLAW) in 2000.
[11] *Accessible at* https://olaw.nih.gov/guidance/articles/dc97-3.htm

been received, it was incomplete (i.e., it did not include facility inspection results regarding all VA animal research conducted at the affiliate or information about the affiliate's program review).

Reference(s):
VHA Handbook 1200.07 §8.f(1)(a). "If a formal arrangement has been made between the VA IACUC and a satellite or affiliate's facility, the VA IACUC may review that facility's semi-annual self-assessment review as an IACUC business item in lieu of sending a VA IACUC review team to the facility. If the VA IACUC does not set up such an agreement, the other facility and its animal care and research use program must be evaluated (by the VA IACUC), and a report of that facility's evaluation included as part of the semi-annual self-assessment review."

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

Memorandum of Understanding between University Texas Health Science Center at San Antonio and Audie L. Murphy Veterans Memorial Hospital (STVHCS) (signed February 25, 2011) §11. "Each institution's IACUC shall conduct its own semi-annual program and facilities evaluations. The University Texas Health Science Center at San Antonio[12] IACUC-approved semi-annual reports will be made available to STVHCS upon request…."

Required Action B2:
The IACUC must ensure appropriate oversight of VA research conducted at UTHSA, including the regular receipt and review of the affiliate's semiannual reports.

3. **The IACUC did not ensure that all animal research protocols received appropriate and timely review and approval.**

Finding:
The VA IACUC did not consistently perform timely continuing/annual reviews of protocols and, in one case, did not perform a timely triennial/*de novo* review of a protocol. Specific examples included:

- Protocol #1704-001 received initial approval from the VA IACUC at the May 10, 2017, meeting. In 2018, the VA IACUC did not conduct a continuing review until the July 11, 2018, meeting, resulting in a lapse of approximately 2 months.

[12] This was the previous name of the University of Texas Health San Antonio.

- Protocol #1608-002 received initial approval from the VA IACUC at the September 14, 2016, IACUC meeting. No continuing review was noted in the IACUC meeting minutes during 2017; the first continuing review documented in the IACUC minutes was recorded during the August 8, 2018, IACUC meeting, resulting in a lapse of almost one year.
- Protocol #1610-001 received initial approval from the VA IACUC at the November 9, 2016, and its first continuing/annual review was conducted at the November 8, 2017, IACUC meeting. The next continuing/annual review was not conducted by the VA IACUC until January 9, 2019, resulting in a lapse of approximately 2 months.
- Protocol #1702-002 received initial approval from the VA IACUC at the June 14, 2017, meeting. In 2018, the VA IACUC did not conduct a continuing review until the July 11, 2018, meeting, resulting in a lapse of approximately 1 month.
- Protocol #1510-001 underwent continuing review by the VA IACUC at the September 24, 2018, meeting; initial review had originally been granted on September 23, 2015, so the protocol should have received a *de novo*/triennial review rather than a continuing review. *Note: This protocol was closed subsequent to review by ORO.*
- Four additional protocols with lapses were identified via RCO audits and discussed during the course of this review; specifically:

    - Protocol #0410-001 did not receive continuing/annual review in 2017 or triennial/*de novo* review in 2018.
    - Protocol #1209-001 did not receive continuing/annual review in 2018.
    - Protocol #1603-002 did not receive continuing/annual review in 2017 or 2018 and did not receive triennial/*de novo* review in 2019.
    - Protocol #1602-002 did not receive continuing/annual review from the VA IACUC in 2017; it received continuing/annual review at the February 14, 2018, IACUC meeting but did not receive triennial/*de novo* review until May 8, 2019, where it was found to require modifications to secure approval.

Reference(s):

PHS Policy §IV.C.5. "The IACUC shall conduct continuing review of each previously approved, ongoing activity covered by this Policy at appropriate intervals as determined by the IACUC, including a complete review in accordance with [*PHS Policy*] at least once every three years."

VHA Handbook 1200.07 §§8.g(1)-(3). "**First and Second Annual Review of Protocols.** The IACUC must review the conduct of all animal protocols annually…. **Third Annual Review.** Prior to the third anniversary, the IACUC must conduct a complete re-review of the protocol…. The funding period of a project has no bearing on the need for annual reviews and triennial reviews."

9 CFR §2.31(d)(5). "The IACUC shall conduct continuing reviews of activities covered

by [the Animal Welfare Act Regulations and Standards] at appropriate intervals as determined by the IACUC, but not less than annually."

Required Action B3a:
The IACUC must evaluate current practices and procedures and modify as necessary to ensure that all protocols receive timely continuing/annual and triennial/*de novo* reviews.

Required Action B3b:
The IACUC must evaluate the aforementioned protocol lapses (and any others subsequently identified by the committee during remediation of this finding), determine if any animal research activities took place during the lapses, and remediate all identified noncompliance.

4. **Several instances of study protocol noncompliance occurred.**

Finding:
Document review and interviews with key personnel revealed that actual research practices deviated from those described in approved protocols. Specific examples included:

- Protocol #1702-002 described post-surgical dosing of buprenorphine to mice at a frequency of every 12 hours for 48 hours. A review of surgical records revealed that mice routinely received only a single daily dose of buprenorphine during that time period. Buprenorphine was the only analgesic described in the protocol to be administered to mice in the peri-operative period. Review of surgical records and interviews with the PI revealed that mice were also administered acetaminophen in the drinking water. This analgesic was stored in the VMU and observed during the ORO facility inspection.
- Protocol #1608-002 described a 7-day period of food restriction for rats prior to behavioral testing; Section T, regarding endpoints, indicated that these animals would be weighed daily during the period of food restriction. A review of records for 8 rats during the period of food restriction demonstrated that animals were only weighed twice during the 7-day period rather than daily.
- Interviews with key personnel revealed that Protocol #1610-001 had been amended via the affiliate IACUC to add three different investigational antifungal agents; however, these amendments were not reviewed/approved by the VA IACUC prior to implementation.

Reference(s):
NIH-OLAW Frequently Asked Question (FAQ) B.9, "May an IACUC suspend (stop) animal activities that it did not initially approve?"[13] "The PHS Policy, *Guide*, and the

[13] *Accessible at* https://olaw.nih.gov/guidance/faqs

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 … because it constitutes serious noncompliance."

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

The Guide for the Care and Use of Laboratory Animals, Eighth Edition (The Guide), p. 25.[14] "[The IACUC] is responsible for oversight and evaluation of the entire [Animal Care & Use] Program and its components … [including] review and approval of proposed animal use (protocol review) and of proposed significant changes to animal use…."

NIH-OLAW NOT-OD-14-126, Guidance on Significant Changes to Animal Activities (dated August 26, 2014). "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 … [and] some activities that may not have a direct impact on animal welfare…."

Required Action B4:
The IACUC and Principal Investigators must ensure that research is conducted in accordance with the approved protocol and that any proposed modifications to animal research protocols are approved prior to implementation.

5. **Engineering Services had not evaluated the configuration of Heating, Ventilation, and Air Conditioning (HVAC) equipment to ensure that the reheat boxes, which fail in the last set position, serving the rooms housing research animals did not present a potential threat to animals in the case of a malfunction.**

[14] ***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)…."

Finding:
At the time of ORO's on-site review, the Research Service thought the reheat boxes failed in the "off" position.[15] Interviews with personnel from Engineering Services revealed that those reheat boxes did *not* fail in the "off" position but instead failed at the last set position. Engineering services had not evaluated this configuration to determine if failing in the last set position was "safe" or if this setting represented a potential threat to animal welfare (i.e., by delivering excessive heat) in the event of a malfunction. Although the facility had environmental monitoring systems in place, VHA policy recognizes that catastrophic air handler failures could still occur despite the presence of high-temperature alarms and requires that VA animal research facility personnel work with Engineering Services to evaluate such HVAC systems to ensure they do not pose a potential threat to the animals.

Reference(s):
VHA Handbook 1200.07 §§7.a(2)(b)1.&2. "**Animal Research Facility Heating, Ventilation, and Air Conditioning (HVAC) Equipment and Testing.** If an air handler serving one or more animal rooms contains … equipment that could deliver excessive heat to animal rooms, engineering staff must determine if the equipment represents a potential threat to animals in case of a malfunction, and record findings in writing for IACUC review. If such a threat is identified, preventative action such as installation of a preheat coil-fan interlock must be undertaken with due consideration of preventing damage to cooling coils or other air handler equipment. Catastrophic air handler failures occur despite the presence of high-temperature alarms in animal rooms; thus the ability of facility personnel to detect high temperatures in animal rooms does not eliminate the need to comply with subparagraph 7a (2)(b)."

The Guide, p. 140. "It is essential that life-threatening heat accumulation or loss be prevented during mechanical failure [of the HVAC system]."

Required Action B5:
Engineering Services must evaluate the reheat coils servicing the animal research rooms to determine if failing in the last set position represents a potential threat to animals in the case of a malfunction (i.e., by delivering excessive heat) and provide the outcome of this evaluation to the IACUC in writing for review. If any potential threats are identified, the IACUC must then work with Engineering Services to implement the corrective actions necessary to ensure that a failure of the HVAC system does not result in life-threatening heat accumulation.

[15] ***VHA Handbook 1200.07 §7.a(2)(a).*** "All HVAC reheat boxes serving one or more rooms housing animals must be designed so that they fail in the "off" or "safe" position, to prevent the loss of animals due to excessive temperature. Laboratory animals can not be housed at any VA facility in rooms that are not so equipped."

6. **Veterinary site visits were not consistently documented as occurring at the frequency required by the facility's standard operation procedure (SOP) for veterinary care.**

Finding:
The facility's written plan for the provision of adequate veterinary care stipulated that veterinary site visits conducted by the Veterinary Medical Consultant (VMC), who was employed via contract on a part-time basis, would occur twice per week. A review of documentation of veterinary site visits between January 1, 2018, and June 30, 2019, revealed only four weeks in which two veterinary site visits were documented; twelve weeks during this period had no documented veterinary site visits, and 61 weeks had one documented visit.

Reference(s):
VHA Handbook 1200.07 §§6.b(8)(a)-(c). "When a VA medical facility obtains veterinary medical services through a contract rather than employment of a [Veterinary Medical Officer], arrangements must be made for regularly scheduled visits…. A written plan of providing adequate veterinary care to laboratory animals must be developed … [which] must include the frequency of visits.... Visits by a VMC must be documented in writing."

Research Service Policy Memorandum 16-10 Research Standard Operating Procedures (SOP) Animal Care and Use Program Veterinary Care (dated February 1, 2016) §3.b. "**FREQUENCY OF VETERINARY VISITS:** The VMC will make regular visits to the VMU at least two times per week. Situations creating a need for veterinary oversight may determine the timing of visits."

Required Action B6:
The Research Service must assess whether the VMC is conducting veterinary site visits at the frequency stipulated in the facility's SOP for veterinary care and ensure that all such visits are documented in writing.

7. **IACUC semi-annual evaluations were conducted in a manner that was not fully compliant with regulatory and policy requirements.**

Finding:
Review of IACUC reports of the semi-annual evaluations and interviews with key personnel revealed that semi-annual facility inspections and program reviews were not conducted and reported in a manner that fully complied with all requirements. Specific examples included:

- The June 2018 program review was conducted by one voting IACUC member with the Research and Development (R&D) Liaison, who was a nonvoting member, rather than by three IACUC members (at least two of whom were voting).

- IACUC semi-annual evaluation reports did not consistently include a plan or schedule for correction of each identified deficiency. Specific examples included:

  - The semi-annual program reviews conducted in December 2018, June 2018, and December 2017 each included a minor deficiency related to the facility's post-approval monitoring program; however, none of the tables of deficiencies included this item, and the report did not include a specific plan and schedule for correction.
  - The June 2018 semi-annual evaluation report did not include plans for correction of deficiencies or designation of personnel responsible for overseeing correction of at least three of the facility deficiencies that were identified.
- The reports of the semi-annual evaluations were not consistently signed by the majority of the voting members (i.e., at least 4 voting members). In both June and December 2018, the reports were only signed by one voting member and two alternates.

Reference(s):
PHS Policy §IV.B.3.d. "[The semi-annual IACUC evaluation] reports must contain a reasonable and specific plan and schedule for correcting each deficiency."

VHA Handbook 1200.07 §8.f(1)(d)5. "At least three IACUC members (including the veterinarian) need to conduct the program and facilities [semi-annual self-assessment] review, unless exceptional circumstances prevent such attendance. All members of the IACUC are strongly encouraged to participate in the semi-annual self-assessment review; however, the review team must include at least two voting members of the IACUC."

VHA Handbook 1200.07 §8.f(1)(e). "A majority (of all voting IACUC members) must vote to approve the [semi-annual IACUC evaluation] report; each member must indicate approval by signatures next to the typed name and committee role."

VA SEMIANNUAL EVALUATION of the INSTITUTIONAL ANIMAL CARE AND USE PROGRAM AND FACILITIES, Part 2 -- Table of Deficiencies and Departures (dated February 28, 2013).[16] "Instructions: 3) Enter each new deficiency…. Include sufficient detail for an outside observer to recognize when it has been corrected), a description of any underlying programmatic or systemic conditions that may have led to the deficiency, and a description of the plans both for correcting the deficiency and for addressing underlying factors so as to prevent recurrence. Be sure to include the name of the individual who will be responsible for overseeing progress on the corrective action, on behalf of the IACUC."

[16] *Accessible at* https://www.research.va.gov/programs/animal_research/documents.cfm

South Texas Veterans Health Care System D16-00423 (A3720-01) Animal Welfare Assurance (Effective Date March 28, 2019) §§III.D.1-2. "The IACUC will … [r]eview at least once every six months the Institution's program for humane care and use of animals…. At least three IACUC members (including the veterinarian) will conduct the review…. [R]eviewers must include at least two voting members…. Inspect at least once every six months all of the Institution's Veterinary Medical Unit…. At least three IACUC members (including the veterinarian) will conduct the review…. [R]eviewers must include at least two voting members…. The report is compiled by the IACUC Administrator and then presented to the committee during its next general meeting. A majority of the voting members must vote to approve and sign the report, which is then provided to the Institutional Official for review…."

South Texas Veterans Health Care System D16-00423 (A3720-01) Animal Welfare Assurance (Effective Date March 28, 2019) §IV. "Where program or facility deficiencies are noted, reports [of the semi-annual evaluation] will contain a reasonable and specific plan and schedule for correcting each deficiency."

Required Action B7:
The IACUC must ensure that semi-annual evaluations are conducted and documented as required by relevant regulations and policies.

8. **The use of non-pharmaceutical grade compounds was not adequately described in some of the approved protocols.**

Finding:
For some animal research protocols reviewed, the description of non-pharmaceutical grade compounds to be used in the protocols did not provide adequate information regarding preparation of the compound to assure the welfare of the animals. Specific examples included:

- Protocol #1610-001 was amended three times to add investigational antifungal compounds. Although the protocol acknowledged that these compounds were not pharmaceutical grade, no information was provided regarding how the compounds would be prepared to assure the welfare of the animals considering factors such as grade, purity, sterility, pH, pyrogenicity, osmolality, stability, etc.
- Protocol #1608-002 acknowledged that non-pharmaceutical grade compounds would be used and described how sterility would be assured; however, the investigator did not provide any information regarding other factors that could impact animal welfare such as pH, pyrogenicity, osmolality, and stability.

Reference(s):

NIH-OLAW FAQ F.4., "May investigators use non-pharmaceutical-grade substances in animals?"[17] "The IACUC is responsible for evaluating the potential adverse consequences of non-pharmaceutical-grade substances when used for research. In making its evaluation, the IACUC may consider factors including, for example: grade, purity, sterility, acid-base balance, pyrogenicity, osmolality, stability, site and route of administration, compatibility of components, side effects and adverse reactions, storage, and pharmacokinetics."

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…"

Instructions for Completion of the ACORP Appendix 3, Biosafety (Version 4), §2.[18] "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 <u>not</u> 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…."

See also *AAALAC FAQ C.9, "Non-Pharmaceutical-Grade Compounds."*[19]

Required Action B8:
The IACUC must ensure that the use of non-pharmaceutical grade compounds is adequately described in protocols, including in the protocols identified in this Finding.

9. The IACUC did not consistently ensure approved protocols included complete, clear, and accurate information.

Finding:
Review of IACUC approved protocols revealed that some protocols contained inconsistent (i.e., incomplete, unclear, or inaccurate) information. Specific examples included:

[17] *Accessible at* https://olaw.nih.gov/guidance/faqs
[18] *Accessible at* https://www.research.va.gov/programs/animal_research/documents.cfm
[19] *Accessible at* https://aaalac.org/accreditation/faq_landing.cfm#B9

- Protocols #1903-001, involving mice, and #1608-002, involving rats, described body weight loss of 20% as an endpoint to determine when animals would be removed from the protocol or euthanized; however, the frequency at which animals would be weighed to determine when endpoints were reached was not specified.
- Protocol #1903-001 included descriptions of four different behavioral tests; however, the frequency and number of tests per animal were not described.
- Protocol #1903-001 also did not specify what euthanasia methods would be utilized.
- Protocol #1111-01, involving mice, mentioned administration of a medicated diet for at least one experiment; further detail or description of this diet was not included in the approved Animal Component of Research Protocol (ACORP).
- Protocol #1111-01 also mentioned use of behavioral testing of mice following experimental manipulations; further detail or description of any type of behavioral test was not included in the approved ACORP. Interviews with the PI revealed use of at least three different behavioral tests.

References(s):

PHS Policy §IV.C.1. "In order to approve proposed research projects or proposed significant changes in ongoing research projects, the IACUC shall conduct a review of those components related to the care and use of animals and determine that the proposed research projects are in accordance with this [PHS] Policy. In making this determination, the IACUC shall confirm that the research project will be conducted in accordance with the Animal Welfare Act insofar as it applies to the research project, and 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…; impact of the proposed procedures on the animals' well-being; … description and rationale for anticipated or selected endpoints; … [and] method of euthanasia or disposition of animals…."

VHA Handbook 1200.07 §§8.f(2)(a)5, 9 & 11. "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 …: … Unusual housing and husbandry requirements; … Criteria and process for timely intervention, removal of animals from a study, or euthanasia if painful or stressful outcomes are anticipated; … [and] Method of euthanasia or disposition of animal."

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…."

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

Required Action B9:
The IACUC must ensure that approved protocols contain complete, clear, and accurate information, including the protocols identified in this Finding.

10. IACUC meeting minutes did not consistently document recognition and management of apparent conflicts of interest.

Finding:
Document review revealed that the IACUC meeting minutes did not consistently identify and manage apparent conflicts of interest (e.g., committee members who were personally involved in protocols under review and approval) or document recusals during voting activities to ensure that members with conflicts of interest did not contribute to quorum. Specific examples included:

- The Deputy Associate Chief of Staff for Research and Development (DACOS/R&D) was a nonvoting member of the IACUC and a PI. She was present during the January 9 and March 6, 2019, IACUC meetings when two of her protocols were reviewed. The IACUC minutes did not document recognition and appropriate management of this conflict of interest (i.e., leaving the room for the vote) during the review and approval of either of these protocols.
- At the January 9, 2019, IACUC meeting, 14 protocols were considered *en bloc* for continuing review; the minutes did not document recognition or management of any conflicts of interest or list any recusals. Specific examples of apparent conflicts of interest for IACUC members who were present included: The DACOS/R&D, a nonvoting IACUC member, was PI for two of the protocols; the primary VMC, a voting IACUC member, was PI for one of the protocols; a Scientific Voting Member was PI for one of the protocols; and the Vice-Chair, who was a nonvoting member except in the absence of the Chair, was PI for one protocol.
- At the August 7, 2018, IACUC meeting, five protocols were considered *en bloc* for continuing review; the minutes did not document recognition or management of any conflicts of interest or list any recusals. Specific examples of apparent conflicts of interest for IACUC members who were present included: A scientific member was present for the meeting and was PI for two of the protocols; and the DACOS/R&D, a nonvoting IACUC member, was present at the meeting and was PI for one of the protocols.

Reference(s):

VHA Handbook 1200.07 §§8.e(2)-(3). "[N]o IACUC member may participate in the IACUC review, or in the approval of a research project in which the member is personally involved in the project, except to provide information requested by the IACUC…. The IACUC is responsible for ensuring that the protocol review process is not compromised by conflicts of interest arising from members participating in animal research reviewed by the IACUC. IACUC members should not participate in the IACUC review or approval of a research project in which the member has a financial conflict, except to provide information requested by the IACUC prior to the deliberations."

VHA Handbook 1200.07 §8.h(1)(i). "The [IACUC meeting] minutes must note which members recused themselves for which project(s) to prevent conflicts of interest."

PHS Policy §IV.C.2. "No member may participate in the IACUC review or approval of a research project in which the member has a conflicting interest (e.g., is personally involved in the project) except to provide information requested by the IACUC; nor may a member who has a conflicting interest contribute to the constitution of a quorum."

South Texas Veterans Health Care System D16-00423 (A3720-01) Animal Welfare Assurance (Effective Date March 28, 2019) §III.D.6.a(2). "Any member with a conflict of interest is asked to identify oneself prior to beginning the review of protocols. No member may participate in the IACUC approval process if he/she has a conflicting interest, (e.g., personnel involved in the project) except to provide information requested by the committee. The member who has a conflicting interest may not contribute to the constitution of a quorum and will remove oneself from the meeting during the vote. When a member is recused for a conflict of interest, a count of the voting members is taken by the IACUC Chair to ensure that there is a quorum."

Required Action B10:
IACUC meeting minutes must document recusals during voting activities to ensure appropriate management of conflicts of interest and that members with such conflicts do not contribute to the constitution of a quorum.

11. IACUC meeting minutes did not contain sufficient information to clearly document committee attendance, votes, activities, and/or deliberations.

Finding:
Document review revealed that IACUC meeting minutes did not clearly document accurate records of attendance, votes, activities, and/or deliberations of the committee. Specific examples included:

- At the June 9, 2019, IACUC meeting, when Protocol #1601-001 was considered, the committee voted to "approve Amendment, pending minor modifications to secure approval." The minutes did not provide any information regarding the specific

amendment requested, the committee deliberations regarding the modifications, or the nature of the recommendations made.

- At the May 8, 2019, IACUC meeting, when Protocol #1905-010 was considered, the committee voted to "table ACORP, due to substantive issues." The minutes did not describe nature of the review, the committee deliberations regarding the protocol, or the nature of the recommendations made.
- At the February 14, 2018, IACUC meeting, the committee voted to approve an anesthesia modification for Protocol #1601-001 pending non-substantive recommendations. The minutes did not provide any information regarding the details of the modification requested, the committee deliberations regarding the modifications, or the nature of the non-substantive recommendations made.
- In some instances, the number of IACUC members recorded as voting for each motion was not congruent with the attendance information documented in the minutes. Specific examples included:
  - The roster at the beginning of the minutes for the June 12, 2019, IACUC meeting marked four voting members as present and one alternate present and voting in lieu of an absent primary member; however, the vote to approve continuing reviews of protocols only amounted to four votes rather than five, and did not indicate that any members had abstained, been recused, or left the meeting.
  - The roster at the beginning of the minutes for the May 8, 2019, IACUC meeting marked six voting members as present; however, all votes at the meeting only amounted to five votes rather than six, and did not indicate that any members had abstained, been recused, or left the meeting.
  - The roster at the beginning of the minutes for the March 6, 2019, indicated that four voting members and the alternate nonscientific member, in lieu of an absent primary member, were present; however, all votes at the meeting only amounted to four votes rather than five, and did not indicate that any members had abstained, been recused, or left the meeting.

Reference(s):

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

VHA Handbook 1200.07 §§8.h(1)(g)&(h). "For each new project, the motion passed by the committee … must be recorded with the exact vote, which must include the number voting for the motion, the number voting against, and the number abstaining. Committee deliberations on each project must be reflected in the minutes so that an outside observer can understand the issues discussed, and recognize the specific revisions and clarifications requested for each protocol under consideration."

See *OLAW FAQ B.7, "What Information should be in IACUC minutes?"*[20]

Required Action B11:
The IACUC must ensure that meeting minutes include sufficient details regarding exact votes, committee deliberations, motions passed, specific revisions/clarifications requested, and other activities of the committee.

12. In at least one instance, the VA IACUC did not provide written notification to the PI regarding the outcome of its protocol review.

Finding:
Document review and interviews with key personnel revealed that Protocol #1704-001 received initial approval from the STVHCS IACUC on May 10, 2017, and was initiated; however, the investigator had not been notified in writing of the committee's decision.

Reference(s):
PHS Policy §IV.C.4. "The IACUC shall notify investigators and the institution in writing of its decision to approve or withhold approval of those activities related to the care and use of animals, or of modifications required to secure IACUC approval. If the IACUC decides to withhold approval of an activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing."

Required Action B12:
The IACUC must ensure that investigators are notified in writing of decisions to approve or withhold approval of protocols.

13. Additional animal care and use concerns were identified during facility inspections.

Finding:
The nature and location of regulatory and policy deficiencies identified during facility inspections are provided in **Appendix C, Table 2**.

Reference(s):
Relevant regulatory citations are provided in Appendix C.

Required Action B13:
The IACUC must ensure deficiencies identified during facility inspections, as listed in Appendix C, are appropriately remediated.

[20] *Accessible at* https://olaw.nih.gov/guidance/faqs

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.

A. RESEARCH SAFETY and SECURITY

1. **Observation:**
The R&D Service should consider working with the facility Industrial Hygienist to ensure that an exposure assessment and, as appropriate, personal exposure monitoring are conducted for laboratories using anesthetic gases (isoflurane) outside of a chemical fume hood.

Reference(s):
VHA Directive 1200.08 §5.n(11). "The SRS is responsible for managing implementation of the RSSP, which includes: … [c]oordinating the safety … measures that apply to all of the facility's VA research laboratories. This includes: … (b) [e]nsuring that a process is in place to identify individuals who require … exposure monitoring, on the basis of their involvement in specific VA research projects, or their other risks of exposure to hazards involved in VA research."

VHA Directive 7702 §4.f(6). "The VA medical facility Director or designee is responsible for: … Ensuring a documented Qualitative and/or Quantitative Baseline Comprehensive Industrial Hygiene Exposure Assessment is conducted and documented for all work locations within a facility, including satellite facilities, by fiscal year 2020."

VHA Directive 7702 §4.f(8). "The VA medical facility Director or designee is responsible for: … Developing and implementing an industrial hygiene program with Standard Operating Procedures (SOP) that include, but are not limited to: (a) Basic characterization that collects and organizes information on the workplace, worker, task, agent, and exposure potential or estimate. Basic characterization may include: … 6. Evaluations for OSHA substance-specific regulated chemicals, reproductive hazards (pregnant workers), select agents, carcinogen risk assessments, and Waste Anesthetic Gas [e.g., isoflurane]."

2. **Observation:**
The SRS should consider developing a process to ensure member appointments do not lapse and that appointment letters are signed by the Medical Center Director prior to the start date of such appointment. Although the appointment lapses noted by ORO did not impact committee composition or impact quorum at individual SRS meetings, the committee needs to be aware of these potential issues and ensure that appointments/reappointments are made in a timely manner.

3. **Observation:**
To assist Occupational Health Services (OHS) in preparing for potential biological or chemical exposures, the SRS should consider providing information to OHS regarding hazardous substances planned for use in research (e.g., lentiviral vectors, hazardous drugs).

Reference(s):
VHA Directive 1200.08 §5.n(11)(c). "The SRS is responsible for managing implementation of the RSSP, which includes: … Coordinating the safety … measures that apply to all of the facility's VA research laboratories. This includes: … Working with Occupational Health … to ensure that appropriate surveillance and monitoring is provided."

4. **Observation:**
The SRS should consider including details in its meeting minutes which summarize discussions that occurred during official business and review of protocols and amendments. SRS meeting minutes provided to the R&D committee did not contain any detail of the SRS's discussion for annual reviews and amendments nor for other official business that was conducted.

Reference(s):
VHA Directive 1200.01 §9.b(4). "The R&D Committee does not need to approve continuing reviews and amendments but should be provided sufficient documentation in the subcommittee minutes that are provided to the R&D Committee."

B. ANIMAL CARE and USE

1. **Observation:**
At some point during 2017, the IACUC changed a nonscientific member from a voting to a nonvoting member; however, the facility Director was not involved in the process to change the nature of this individual's appointment. The authority to appoint members to the IACUC was solely given to the CEO (the facility Director in the VA system) by relevant regulatory frameworks including the Animal Welfare Act Regulations and Standards, PHS Policy, and VHA Handbook 1200.07. All regulatory sources are silent regarding acceptable procedural changes in the status of IACUC members subsequent to appointment. The Research Service, in consultation with the facility Director, is strongly encouraged to develop and document a procedure to follow in the event that the committee desires to change the voting status of a member with a current appointment. Such a procedure would ensure that the committee composition continues to meet the Director's intentions and expectations with regards to the appropriateness of its qualifications, experience, and expertise to oversee the facility's animal care and use program.

Reference(s):
Public Health Service Policy on Humane Care and Use of Laboratory Animals (PHS Policy) §IV.A.3.a. "The Chief Executive Officer shall appoint an IACUC, qualified through the experience and expertise of its members to oversee the institution's animal program, facilities, and procedures."

2. **Observation:**
The current MOU with the affiliate, signed in 2011, did not accurately describe current practices for shared oversight of collaborative animal research. The Research Service indicated that it was preparing to begin developing a new MOU. ORD Guidance Document #AR2015-005[21] regarding drafting MOUs may be a helpful resource during this process.

3. **Observation:**
The IACUC should consider developing a mechanism to ensure that all IACUC members, including new members, concur in advance and in writing to use the Designated Member Review subsequent to Full Committee Review (DMR-s-FCR) processes, as described in the facility's PHS assurance. According to PHS Policy, unless all members are present at a meeting, DMR-s-FCR may only be used if the vote of the quorum of members present is unanimous and the IACUC has documented concurrence to utilize this practice in advance and in writing by all committee members.

Reference(s):
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 January 8, 2009). "When substantive information is lacking from a protocol, the committee may have questions requiring a response from the PI. In such situations, the IACUC may take the following actions: 1. If **all** members of the IACUC **are** present at a meeting, the committee may vote to require modifications to secure approval and have the revised research protocol reviewed and approved by designated member review (DMR), or returned for FCR at a convened meeting. 2. If **all** members of the IACUC **are not** present at a meeting, the committee may use DMR subsequent to FCR according to the following stipulations: a. All IACUC members agree **in advance in writing** that the quorum of members present at a convened meeting may decide by unanimous vote to use DMR subsequent to FCR when modification is needed to secure approval. However, any member of the IACUC may, at any time, request to see the revised protocol and/or request FCR of the protocol" (emphases in original).

4. **Observation:**

[21] *Accessible at* https://www.research.va.gov/programs/animal_research/guidance.cfm

The AAALAC Program Description stated that "Personnel who decline to participate in the program are not allowed to work with research animals." The Research Service should consider revising this document to more accurately reflect VHA Handbook requirements, which do allow personnel declining certain optional occupational health and safety services to work with research animals.

Reference(s):
VHA Handbook 1200.07 §10.b. "**Right to Decline Services**. Personnel may decline to receive services not required by the VA facility to protect the health of the animals or other personnel (e.g., TB testing or chest radiography). Personnel who decline optional services are considered to be enrolled in the OHSP as long as the VA facility documents that they were given the opportunity to receive these services."

5. **Observation:**
The IACUC should consider developing a system to track the numbers of rodents born at the facility, including those that do not survive to weaning but were present at the first cage manipulation after birth, to facilitate accurate reporting of animals used on each protocol and accurate annual reporting of animal numbers. ORO noted that the number of rodents born in breeding colonies were counted at weaning, rather than at the first cage manipulation, and that there was no system in place to ensure that all animals present at the first cage manipulation were included in the facility's annual reporting of animal usage and taken into consideration when tracking protocol related animal use.

Reference(s):
Bennett BT and Bailey MR. 2019. Update on the Oversight of Animal Care and Use Programs. Lab Animal 48(3): 73.[22] "OLAW was also asked for its position on counting vertebrate animals at or around birth. The OLAW representative indicated that neonatal rodents should be accounted for when they are first manipulated, such as during the first cage change or at genotyping."

See *NIH-OLAW FAQ F.2, "Is the IACUC responsible for tracking animal usage?"*[23]

6. **Observation:**
The IACUC should consider revising local policies and postings for reporting animal care and use concerns to ensure that they are congruent and contain all information specified in the *Guide*. Neither the local SOP nor postings observed during the walkthrough inspections of the VMU included a senior leadership point of contact such as the Institutional Official (IO; facility Director, in the VA system). In addition, no anonymous route of reporting was available.

[22] *Accessible at* https://www.nature.com/articles/s41684-019-0244-7
[23] *Accessible at* https://olaw.nih.gov/guidance/faqs

Reference(s):
The Guide, p. 24. "Mechanisms for reporting 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 [Attending Veterinarian (AV)], are recommended. The process should include a mechanism for anonymity…."

7. **Observation:**
The Research Service should consider the potential value of expanding the information contained in the local policy regarding reporting to ORO and other regulatory oversight and accreditation entities to ensure expectations for reporting research noncompliance events to research review committees, facility officials, and ORO are clear.

Reference(s):
See VHA Handbook 1058.01 §7 *for specific reporting requirements related to animal research noncompliance reporting requirements.*

8. **Observation:**
The June 9, 2019, IACUC meeting minutes contained information about a subsequent IACUC meeting. The IACUC should consider revising committee practices to ensure that IACUC meeting minutes only contain information regarding activities that took place during the convened meeting; if subsequent business takes place or additional information is discovered after the meeting, such information should be documented separately, rather than within the preceding meeting's minutes.

9. **Observation:**
The IACUC should consider updating local Research Service Policy Memorandum 16-16 *Animal Care and Use Program: Euthanasia* and VMU postings regarding the euthanasia of animals, to incorporate specific, detailed information from the American Veterinary Medical Association (AVMA) *Guidelines for the Euthanasia of Animals* (2013) regarding the special welfare concerns presented by the euthanasia of neonatal rodents. Additionally, the IACUC should ensure that the written policy and postings are congruent.

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: emergency eye wash equipment was not readily accessible in areas where hazardous chemicals were used; information necessary to appropriately inform the facility's research safety committee's risk assessment of proposed research involving hazardous chemicals was not consistently provided to the committee; academic affiliate inspection reports of laboratories where VA research was

conducted were not reviewed by the facility's research safety committee; a serious work-related injury was not reported to the facility's research safety committee; the facility's IACUC approved study protocols that omitted critical information about actual procedures that animals would be subjected to (thus, calling into question whether the IACUC was aware of procedures that would subsequently be performed on animals under the auspices of study protocols approved by the IACUC); unapproved study protocol deviations, including a deviation from a pain management regimen that could have negatively impacted animal welfare; and the configuration of heating, ventilation, and air conditioning equipment serving the animal housing room had not been evaluated to ensure that the equipment did not present a potential threat to animals in the case of a malfunction (so as to prevent an overheating event that could jeopardize laboratory animal welfare). 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 Workgroup, ORO

APPENDIX A
ORO REVIEW TEAM and FACILITY REPRESENTATIVES

ORO On-Site Review Team:

(b)(6)

Facility Representatives:

Christopher Sandles, MBA, FACHE Medical Center Director

(b)(6)

(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.

- 0410-001 Strong Center for Testing Potential Anti-Aging Interventions
- 1111-001 Macrophage-Mediated Gene Delivery of Neurotrophic Factors of Parkinson's Disease
- 1209-001 Glutaredoxin 2, Mitochondrial Protein Glutathionylation and Alzheimer's Disease
- 1510-001 The Role of mTOR Inhibition on Longevity and Healthy Aging in a Non-Human Primate *(now closed)*
- 1601-001 Analysis of Olfactory Dysfunction for Early Diagnosis of Parkinson's Disease
- 1602-002 New Insights in Mechanisms of Renal Injury
- 1603-002 Inhibition of Ferroptosis by Gpx4 as a New Therapy Strategy for ALS
- 1608-002 Treating PTSD and Depression: Mechanism of Pharmacotherapy and Psychotherapy in Rats
- 1610-001 Task Order A98: Antifungal *in vivo* Efficacy Testing - *Coccidioides*
- 1702-002 The Influence of ApoE4 on Signaling & Poor Outcome after Trauma Brain Injury
- 1704-001 Organ Dysfunction in Invasive Pneumococcal Disease
- 1903-001 Beta2-Adrenergic Receptor Activation and Risk of Parkinson's Disease
- 1905-010 Development of Potent Inhibitors of Proto-Oncogene PELP1 for Treating Advanced Breast Cancer

APPENDIX C
AREAS INSPECTED WITH ASSOCIATED FINDINGS/OBSERVATIONS

Table 1. Research Safety and Security		
Location	**Finding (F) / Observation (O)**	**Notes/References**
Veterinary Medical Unit (VMU), Rm. R222	**(F)** Oxygen compressed gas cylinder was not secured.	*29 CFR §1910.101(b); Compressed Gas Association (CGA) Pamphlet P-1-2008 §5.8.4; National Fire Protection Association (NFPA[1] 45 (2015) §10.1.5.1; NFPA 55 (2016) §7.1.8.4*
VMU, *general area*	**(F)** Egress from Veterinary Medical Unit rooms required specialized knowledge (use of a push button/latch to exit each room).	*29 CFR §1910.36(d)(1); NFPA 101- The Life Safety Code® §7.2.1.5.3.*
VMU, Rm. R222	**(F)** Recapped needles present in sharps container.	*Biosafety in Microbiological and Biomedical Laboratories[2] (BMBL) 5th Ed., §V.A.11.b "Disposable needles must not be … recapped … before disposal."*

Table 2. Animal Care and Use		
Location	**Finding (F) / Observation (O)**	**Notes/References**
VMU, Rm. R222	**(O)** Neither initial weight nor hours of use were documented on the F/AIR® charcoal canister used to scavenge waste anesthetic gas; last weight was recorded in January 2019.	*As a best practice, initial weights need to be provided on charcoal canisters to determine when to replace the unit. In this instance, manufacturer recommendations included documentation of hours in use (to discard after 12 hours).*
VMU, Rm. U224	**(F)** Expired anesthetic present: isoflurane (expired August 2017).	*The Guide for the Care and Use of Laboratory Animals,*

[1] ***VHA Fire Protection Design Manual, Office of Safety, Health, and Environmental Compliance (10NA8) §1.3.B***. "VA has adopted the National Fire Codes (NFC) published by the National Fire Protection Association (NFPA)...."
[2] ***VHA Directive 1200.08 §4***. "It is VHA policy that each VA medical facility conducting research must safeguard the safety of personnel, the public and the environment, and the security of research laboratories and other applicable research space in compliance with all applicable VA policies, Federal statutes and regulations from … CDC guidelines…."

Table 2. Animal Care and Use		
Location	**Finding (F) / Observation (O)**	**Notes/References**
		Eighth Edition (The Guide), p. 105; [3] *VHA Handbook 1200.07 §7.f(4); NIH-OLAW FAQ F.5., "May investigators use expired pharmaceuticals, biologics, and supplies in animals?"* [4]
VMU, Rm. U224	**(O)** Injectable fluids bag labeled for single use (Lactated Ringers Solution) marked as opened on 02/19/19 and had been used with multiple animals.	*As a best practice, medical products should be used and disposed of as directed by manufacturers' label instructions unless the facility works with the veterinarian to develop a local SOP describing appropriate practices, including duration of use, for opened veterinary medical products.*

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

[4] *Accessible at* https://olaw.nih.gov/guidance/faqs

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: **March 11, 2020**

A. Research Safety and Security. ORO Case Number: **671-0049-S**

Required Action A1: The facility must ensure that emergency eyewash equipment is provided in all animal facility areas where personnel may be exposed to paraformaldehyde/formalin.	
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 A2: The SRS must ensure all laboratory personnel working with formalin/paraformaldehyde are provided with safety training and information that includes the potential physical and health hazards of formaldehyde, signs and symptoms of exposure, applicable OSHA exposure limits (e.g., Short Term Exposure Limit, Time Weighted Average), appropriate work practices, emergency procedures, and personal protective equipment to be used.	
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 A3: The Research Office must ensure initial and refresher safety training records are 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 A4: The SRS must ensure that all risks to personnel, the facility, and the environment are assessed during the initial review of research involving hazards.	
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 A5: The SRS must ensure that it reviews annual inspection reports for each affiliate laboratory where VA research is conducted.	
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 A6: The effectiveness of the CHP must be reviewed and evaluated annually.	
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 A7: The SRS, in conjunction with the Facility Industrial Hygienist, must identify research employees working with paraformaldehyde/formalin outside of a chemical fume hood and determine their exposure level through exposure monitoring.	
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 A8: The SRS must ensure its meeting minutes document the recusal of individuals having a conflict of interest and verification that quorum was maintained during such recusal.	
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 A9: The Research Service must ensure that serious workplace accidents, injuries, and illnesses are reported and evaluated in accordance with VHA policy.	
Facility Response	*ORO Comments*

Response #1 ([DATE of response submission]) **Facility Action:** [TEXT] **Proposed Completion Date:** [DATE]	[ORO comments will be inserted here]
Required Action A10: The SRS must ensure deficiencies identified during laboratory inspections, as listed in Appendix C, are appropriately remediated.	
Facility Response	***ORO Comments***
Response #1 ([DATE of response submission]) **Facility Action:** [TEXT] **Proposed Completion Date:** [DATE]	[ORO comments will be inserted here]

B. Animal Care and Use. ORO Case Number: **671-0047-A**

Required Action B1a: The IACUC must evaluate the impact of the continued participation of these IACUC members without valid appointments on official business, namely on the validity of IACUC business, and remediate any noncompliance identified.	
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 B1b: The Research Service must develop a system to ensure appointments are monitored, and that reappointments are approved in a timely and appropriate manner to prevent future lapses in membership.	
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 B2: The IACUC must ensure appropriate oversight of VA research conducted at UTHSA, including the regular receipt and review of the affiliate's semiannual reports.	
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 B3a: The IACUC must evaluate current practices and procedures and modify as necessary to ensure that all protocols receive timely continuing/annual and triennial/*de novo* reviews.	
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 B3b: The IACUC must evaluate the aforementioned protocol lapses (and any others subsequently identified by the committee during remediation of this finding), determine if any animal research activities took place during the lapses, and remediate all identified noncompliance.	
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 B4: The IACUC and Principal Investigators must ensure that research is conducted in accordance with the approved protocol and that any proposed 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 B5: Engineering Services must evaluate the reheat coils servicing the animal research rooms to determine if failing in the last set position represents a potential threat to animals in the case of a malfunction (i.e., by delivering excessive heat) and provide the outcome of this evaluation to the IACUC in writing for review. If any potential threats are identified, the IACUC must then work with Engineering Services to implement the corrective actions necessary to ensure that a failure of the HVAC system does not result in life-threatening heat accumulation.	
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 B6: The Research Service must assess whether the VMC is conducting veterinary site visits at the frequency stipulated in the facility's SOP for veterinary care and ensure that all such visits are documented in writing.	
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 B7: The IACUC must ensure that semi-annual evaluations are conducted and documented as required by relevant regulations and policies.	
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 B8: The IACUC must ensure that the use of non-pharmaceutical grade compounds is adequately described in 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 B9: The IACUC must ensure that approved protocols contain complete, clear, and accurate information, including the protocols identified in this Finding.	
Facility Response	***ORO Comments***
Response #1 ([DATE of response submission]) **Facility Action:** [TEXT] **Proposed Completion Date:** [DATE]	[ORO comments will be inserted here]
Required Action B10: IACUC meeting minutes must document recusals during voting activities to ensure appropriate management of conflicts of interest and that members with such conflicts do not contribute to the constitution of a quorum.	
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 B11: The IACUC must ensure that meeting minutes include sufficient details regarding exact votes, committee deliberations, motions passed, specific revisions/clarifications requested, and other activities 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 B12: The IACUC must ensure that investigators are notified in writing of decisions to approve or withhold approval of protocols.	
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 B13: The IACUC must ensure deficiencies identified during facility inspections, as listed in Appendix C, are appropriately remediated.	
Facility Response	***ORO Comments***
Response #1 ([DATE of response submission]) **Facility Action:** [TEXT] **Proposed Completion Date:** [DATE]	[ORO comments will be inserted here]