Focused Report

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OFFICE OF RESEARCH OVERSIGHT

FOCUSED REVIEW REPORT

Animal Care and Use Program

Minneapolis VA Health Care System
Minneapolis, Minnesota

October 2, 2019

Veterans Health Administration

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ORO FOCUSED REVIEW REPORT

Minneapolis VA Health Care System
Minneapolis, Minnesota

On-Site Review Dates: July 17-18, 2019
Date of Report: October 2, 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 at the Minneapolis VA Health Care System (MVAHCS) on July 17 and 18, 2019. This review primarily evaluated research involving nonhuman primates (NHPs) and related Institutional Animal Care and Use Committee (IACUC) operations. ORO identified several 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. Of particular concern, ORO identified serious noncompliance that posed a risk to the well-being of the NHPs used in research at the facility. Specifically, ORO identified that NHPs were subjected to restricted water intake for longer than specified in the approved study protocol and monitoring of these animals for signs of dehydration was not performed as specified in the protocol. During the course of its review, ORO also made an incidental finding pertaining to activities involving commercial product testing involving the use of rabbits housed at the facility. Specifically, ORO identified that the facility's IACUC served as the IACUC of record for a private company and that the facility's IACUC and Research & Development Committee had approved as a VA research activity the quality control testing of the company's commercial products in rabbits. However, VA IACUCs are prohibited from serving as the IACUC of record for a non-VA entity, and the approved quality control testing of commercial products in rabbits had no apparent relevance to VA's mission. 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 Animal Care and Use Program (ACUP) at Minneapolis VA Health Care System (MVAHCS) on July 17 and 18, 2019. In addition, teleconferences were held remotely with selected personnel on July 1-2 and 9-11, 2019. ORO's review at MVAHCS focused primarily on research involving nonhuman primates (NHPs) and related Institutional Animal Care and Use Committee (IACUC) operations; however, in response to information gathered during the course of the review, activities involving the use of rabbits were evaluated as well.

II. METHOD OF REVIEW

ORO's review of MVAHCS 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 NHP laboratory spaces and select portions of the Veterinary Medical Unit (VMU).

III. FACILITY RESEARCH PROGRAM OVERVIEW

MVAHCS is a complexity level 1a acute care research hospital and tertiary referral center academically affiliated with the (b) (6) [redacted] It operates a research program involving human subjects, laboratory animals, and hazardous agents, with a research project (direct cost) budget of approximately $25.1 million in FY18,[2] of which approximately $10.2 million was provided by the VHA Office of Research and Development (ORD). The Center for Veterans Research and Education provides a flexible funding mechanism for non-VA sponsored research at MVAHCS.

At the time of ORO's review, there was one active NHP research protocol conducted by a single principal investigator (PI) studying schizophrenia and one holding protocol covering care and use of NHPs when not assigned to a particular study.

[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.

MVAHCS maintains its own Research and Development Committee (R&DC), IACUC, and Subcommittee on Research Safety (SRS).

MVAHCS has executed an MOU with (b) for collaborative animal research. On behalf of a company, (b) (6), the MVAHCS IACUC provided oversight of the company's quality control testing of its commercial products using rabbits, an activity that was conducted in MVAHCS' animal research facility. Further, MVAHCS maintained a contract with (b) (6) (b) to provide services for rabbit housing, husbandry, and veterinary care. (*See Finding #8 of this report.*)

MVAHCS has a current Public Health Service (PHS) Animal Welfare Assurance D16-00308 (A3493-01) expiring May 31, 2022, 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-083); and is registered with the U.S. Department of Agriculture – Animal and Plant Health Inspection Service (USDA-APHIS; Registration No. 41-V-0001).

ORO noted the following strength in the MVAHCS NHP research oversight program: The veterinary and technical staff members and the NHP laboratory manager were dedicated to ensuring the MVAHCS ACUP provided the NHPs with highly complex environmental enhancement to promote psychological well-being, meeting high standards for the NHPs housed in the VMU. In particular, the commitment to ensuring a diverse enrichment program was evident not only from the complex enrichment enclosure (i.e., the "zoo") and thoughtful rotation of manipulanda and food objects but also from the appearance, behavior, and health of the animals observed onsite.

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

1. **Several instances of study protocol noncompliance occurred, and in some instances, the unapproved deviations from the protocol posed a potential risk to the well-being of NHPs used in research.**

   Finding:
   Based on interviews and document review, ORO identified that actual research practices regarding water intake regulation and anesthetic/intraoperative procedures deviated from those described in approved protocols. It was further ascertained that facility personnel with oversight responsibilities were unaware of these significant protocol deviations.

Protocol No. 150402D (now closed) provided for periodic restriction of *ad libitum* water intake by the NHPs. During such periods, the protocol specified that animals receive a daily water ration of a minimum volume of 20 to 30 milliliters (mL) per kilogram (kg) body weight. In addition, each individual animal subjected to water intake regulation for research activities was to receive *ad libitum* water for 1 day every 7 days.[3] To assess for signs of dehydration, required monitoring procedures described in the protocol included measurement of urine specific gravity (USG) one to two times every 2 weeks and body weights at least once weekly.

Interviews with the veterinarian and Laboratory Manager and review of animal medical and research records revealed:

- NHP #10048 had no opportunities for *ad libitum* access to water between July 1, and September 3, 2017. No documentation was noted indicating that the animal met protocol criteria for an exception to *ad libitum* access. During this time, there were also at least 19 days where the minimum amount of daily fluid required by the protocol was not provided.
- For this same animal, USG was measured on December 21, 2016, and not measured again until March 8, 2017, despite being subject to periodic water restriction during this time period. A similar lapse in protocol procedure (i.e., failure to measure USG) was noted between August 8, 2017, until return to full *ad libitum* water access on September 4, 2017. Thus, monitoring of USG to assess for signs of dehydration, and corresponding animal well-being, was not conducted as required during periods of restricted water intake.
- On August 2, 2017, after a period with no *ad libitum* access to water and multiple days where the minimum water volume was not provided, the measured USG for NHP #10048 was higher (a potential indication of dehydration) than the target range specified in the Animal Component of Research Protocol (ACORP). Although the protocol indicated that during periods of fluid regulation the veterinarian was to be kept informed of any deviation of the measurements from the normal values, no corresponding entry was found in study or veterinary medical records indicating that the veterinarian was consulted. Additionally, records did not indicate that the animal was provided additional water or water access in response to the indication of dehydration, and USG was not documented as being measured again until six days later.

Protocol No. 170601 described procedures to ensure that animals received a daily water ration at a minimum volume of 20 mL per kilogram body weight. Required monitoring procedures described in the protocol included measuring USG periodically and body weights at least once weekly.

[3] The protocol provided for an exception to this requirement in the event of excessive drinking during the *ad libitum* period.

Interviews with the PI and Laboratory Manager and review of animal medical and research records revealed:

- NHP #06006 did not receive the minimum daily fluid intake on multiple occasions as documented on the animal training record.
  - Between January 30 and March 7, 2016, actual fluid volume provided to the animal was 30 mL less than the required minimum on all 23 days with water restriction.
  - Between April 4 and May 11, 2016, actual fluid volume provided to the animal was consistently 40 mL less than the required minimum and, in one instance, it was 66 mL less, during the 32 days when water was restricted.
- The body weight of NHP #06006 was not documented on a weekly basis during training or testing periods as required in the approved protocol, including time spans between April 16 and May 8, 2016; August 26 and October 2, 2016; December 31, 2016, and January 19, 2017, and July 18 and August 4, 2017.

A review of study, veterinary medical, and IACUC records for these time periods and interviews with key personnel revealed that these protocol deviations were not recognized via the facility's continuing review activities or informal post-approval monitoring practices. Protocol deviations such as these have the potential to affect the well-being of these individual NHPs as ongoing unidentified noncompliance could increasingly impact hydration and health status over time.

In addition, in several instances, actual anesthetic and intraoperative practices deviated from that described either in the approved ACORP or in MVAHCS Standard Operating Procedures (SOPs). Specifically:

- Protocol No. 170601 described administration of ketamine, or in some instances a combination of ketamine and xylazine, for select imaging procedures. Per the protocol, approximately halfway through the imaging procedure, depth of anesthesia was to be evaluated and augmented as necessary with approximately half the original dose of ketamine *alone*. Review of research records documenting anesthesia for these procedures revealed that additional doses (varying from ¼ to ½ of the original dose) of *both* ketamine and xylazine were routinely provided two to three times following the initial dose.
- Also described in section C.2.c. of Protocol No. 170601 was the administration of ketamine *alone* for placement of additional hardware (i.e., a "halo") following surgery #1. Medical records for NHP #037 documented use of a combination of ketamine and xylazine for this procedure on March 16, 2019.
- Intraoperative Monitoring Records maintained for Protocol No. 170601 inconsistently documented the time of administration and the dose of preanesthetic and anesthetic drugs given to the animal, which was not

consistent with local policy. VMU Postoperative Care Records listed names of drugs without corresponding doses. Also, in at least one surgical procedure where records were maintained in multiple locations, discrepancies existed between the Intraoperative Monitoring Record and other research records; specifically, the records for implantation of chamber and head holding hardware onto NHP #06006 in January 2018 were inconsistent regarding time of administration of the intraoperative antibiotic cefazolin.

Reference(s):

NIH-OLAW Frequently Asked Question #B.9.[4,5] "The PHS Policy, *Guide* , and the USDA Animal Welfare Regulations presume that all ongoing animal activities have received the required prospective review and approval. An activity that has been undertaken without prior approval should be halted and subsequently reported … because it constitutes serious noncompliance."

9 Code of Federal Regulations (CFR) §2.31(d)(1). "In order to approve proposed activities or proposed significant changes[6] in ongoing activities, the IACUC shall conduct a review of those components of the activities related to the care and use of animals and determine that the proposed activities are in accordance with the [Animal Welfare Act and Regulations] unless acceptable justification for a departure is presented in writing…."

The Guide for the Care and Use of Laboratory Animals, Eighth Edition (The Guide), p. 25.[7] "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…."

Public Health Service Policy on Humane Care and Use of Laboratory Animals (PHS Policy) §IV.B.7. "As an agent of the institution, the 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…."

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

[5] Per ***VHA Handbook 1200.07§4.b(4)***, "[A]ll VA facilities conducting animal research must comply with … the PHS Policy … [which includes by reference compliance with the] Guide for the Care and Use of Laboratory Animals…."

[6] See NIH-OLAW website on "Significant Changes to Animal Activities," accessible at: https://olaw.nih.gov/guidance/significant-changes.htm, "In brief, significant changes include changes that have, or have the potential to have, a negative impact on animal welfare…. In addition, some activities that may not have a direct impact on animal welfare are also considered to be significant…."

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

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."

The Guide, p. 31. "The animals [undergoing food or fluid regulation] should be closely monitored to ensure that food and fluid intake meets their nutritional needs…. Body weights should be recorded at least weekly and more often for animals requiring greater restrictions…. Written records should be maintained for each animal to document daily food and fluid consumption, hydration status, and any behavioral and clinical changes used as criteria for temporary or permanent removal of an animal from a protocol…."

The Guide, p. 122. "Agents that provide anesthesia and analgesia must … [have] their use recorded."

MVAHCS-VMU-OPR-201f Preoperative, Intraoperative Monitoring, and Postoperative Care of Non-Rodents, §6.15. "Administer preanesthetic agents as indicated in the IACUC-approved protocol and document the drug, the dose and time given on the animal's VMU Postoperative Care Record, as well as on the Intraoperative Monitoring Record."

MVAHCS-VMU-OPR-201f Preoperative, Intraoperative Monitoring, and Postoperative Care of Non-Rodents, §6.16. "Administer the anesthetic agent as indicated in the protocol and document the drug, the dose and the time of administration on the animal's VMU Postoperative Care Record, as well as on the Intraoperative Monitoring Record."

MVAHCS-VMU-OPR-201f Preoperative, Intraoperative Monitoring, and Postoperative Care of Non-Rodents, §6.20.1.3. "[Complete the VMU Postoperative Care Record and Medical Records forms….] [s]pecify[ing] the name and dose of all drugs administered before or during surgery."

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

Required Action 1:
The IACUC and Principal Investigator for the remaining, active NHP research protocol 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.

2. **The preparation and maintenance of a nonpharmaceutical grade compound administered to NHPs was neither adequately described in the approved protocol nor performed in a compliant manner.**

Finding:
Protocol No. 170601 described use of nonpharmaceutical grade phencyclidine (PCP) to be administered to NHPs via intramuscular injection for research purposes. Preparation as described in the approved protocol included dilution in sterile saline and filtration prior to injection; however, no information regarding stability (to ensure the compound would work as expected for the protocol) and sterility (to protect the welfare of the animals) of solutions maintained for extensive periods of time was included. Interviews with key personnel indicated that vials currently stored in the laboratory containing the PCP solution were mixed under aseptic conditions in July 2018 and were retained for future use as needed; however, vials were not labeled with an expiration date despite the fact that personnel were uncertain how long the contents could be safely utilized. The protocol also did not address other considerations pertaining to the diluting of the PCP in the saline solution, such as changes in pH, pyrogenicity, and osmolality, which could impact the welfare of the animals when the solution was administered.

Reference(s):
The Guide, p. 31. "The use of pharmaceutical-grade chemicals and other substances ensures that toxic or unwanted side effects are not introduced into studies conducted with experimental animals.... 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...."

NIH-OLAW Frequently Asked Question #F.4.[8] "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."

Instructions for Completion of the ACORP Appendix 3, Biosafety (Version 4).[9]
"OLAW requires that only pharmaceutical grade compounds be administered to animals unless the use of non-pharmaceutical grade compounds is justified by scientific necessity and the lack of availability of an acceptable veterinary or human pharmaceutical grade compound (*OLAW FAQs*, F.4).... Mark with a * each material, diluent, or vehicle to be administered to the animals on this protocol that is not

[8] Accessible at https://olaw.nih.gov/guidance/faqs.
[9] Accessible at https://www.research.va.gov/programs/animal_research/documents.cfm#docs-c.

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.[10] "The method of preparation, labeling (i.e., preparation and use-by dates), administration and storage of formulations should be appropriately considered with the aim of maintaining their stability and quality (i.e., to prevent inadvertent co-administration of infectious agents or contaminants)."

Required Action 2:
The IACUC must ensure that the use of nonpharmaceutical grade compounds is adequately described in protocols, including in the protocol identified in this Finding.

3. **In one instance, a significant change to an NHP ACORP was approved by a noncompliant method.**

Finding:
As documented in the September 2017 IACUC meeting minutes, the IACUC approved by an administrative process the addition of an injection of a nontoxic dye during a terminal procedure prior to euthanasia of the NHPs on Protocol No. 150402D. This addition of a new substance to the procedure for use in animals constituted a significant change to the protocol, and the IACUC had not established a policy that would have allowed this change to have been approved administratively.[11] Consequently, this significant change should have been approved via full committee review (FCR) or designated member review (DMR).

Reference(s):
9 CFR §2.31(d)(1). "In order to approve proposed activities or proposed significant changes in ongoing activities, the IACUC shall conduct a review of those components of the activities related to the care and use of animals and determine that the proposed activities are in accordance with the [Animal Welfare Act and Regulations] unless acceptable justification for a departure is presented in writing...."

PHS Policy §IV.C.1. "In order to approve ... proposed significant changes in ongoing research projects, the IACUC shall conduct a review of those components related to the care and use of animals and determine that the proposed research projects are in accordance with this [PHS] Policy."

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[10] Accessible at https://aaalac.org/accreditation/faq_landing.cfm#B9.
[11] See NIH-OLAW website on "Significant Changes to Animal Activities," accessible at: https://olaw.nih.gov/guidance/significant-changes.htm.

Required Action 3:
The IACUC must ensure that significant changes are approved by either DMR or FCR unless the IACUC develops and approves an SOP detailing the use of Veterinary Verification and Consultation (VVC) for certain types of significant changes as described in OLAW guidance.

4. **The IACUC did not consistently ensure that different protocol sections contained clear, congruent information.**

Finding:
Review of IACUC approved protocols revealed that some protocols contained unclear, incongruent information. Specific examples from Protocol No. 150402D, involving NHPs, included:

- Section C.2.c. and Appendix 3 indicated that ketamine would be given at a dose of 5-10 mg/kg for dural scraping and minor procedures (which would include dural scraping), respectively. Section J indicated that ketamine would be given at a dose of 2-10 mg/kg for the same procedure. [12]
- Appendix 6, regarding special husbandry and procedures, indicated that ketamine would be given at a dose of 1.5 mg/kg for electromyographic (EMG) recordings. However, Appendix 3 indicated that ketamine would be used at a dose of 5-10 mg/kg for minor procedures, which would include EMG recordings.
- Appendix 3 indicated that buprenorphine would be given at a dose of 0.005-0.02 mg/kg IM or IV twice per day up to 3 days post-operatively. Appendix 5 Section 7.c. indicated that buprenorphine would be given at a dose of 0.01-0.05 mg/kg at the same frequency.

Reference(s):
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 …; [and] appropriate sedation, analgesia, and anesthesia…."

VHA Handbook 1200.07, App. D, §1.z(1)(e). "The information provided in [an] ACORP must be complete and accurate."

Required Action 4:
The IACUC must ensure procedures described in approved protocols are clear and consistent between different sections.

5. **The IACUC failed to conduct timely annual reviews of at least three protocols, resulting in lapsed approvals.**

[12] Ketamine is typically dosed at 10 mg/kg for macaques, and a dose of 2 mg/kg (or lower) creates potential risk of the animal waking up during experimental procedures.

Finding:
Review of IACUC approved protocols and interviews with key personnel revealed at least three lapses in annual approval of protocols involving USDA regulated species. Specifically:

- Protocol No. 140702 (renumbered as Protocol No. 170601), involving NHPs, was initially approved on August 8, 2014. The first annual/continuing review was completed on June 24, 2015; however, the second annual/continuing review was not completed until July 21, 2016, resulting in a lapse of approximately one month.
- Protocol No. 150402D (now closed), involving NHPs, was initially approved on May 12, 2015. The first annual/continuing review was completed on March 28, 2016; however, the second annual/continuing review was not completed until April 27, 2016, resulting in a lapse of approximately one month.
- Further, Protocol No. 150601, involving rabbits used for testing procedures, received annual/continuing review on May 18, 2017, via FCR. The protocol then did not receive subsequent review and approval until June 13, 2018, resulting in lapse of approximately one month.

Reference(s):
9 CFR §2.31(d)(5). "The IACUC shall conduct continuing reviews of activities … at appropriate intervals as determined by the IACUC, *but not less than annually"* (emphasis added).[13]

VHA Handbook 1200.07 §8.g(1). "**First and Second Annual Review of Protocols.** The IACUC must review the conduct of all animal protocols annually."

Required Action 5:
The IACUC must ensure required annual protocol reviews are conducted in a timely manner.

6. **Overheat tests in the VMU were not conducted in a manner compliant with VHA policy.**

Finding:
Interviews with key personnel revealed that environmental overheat tests in the VMU were conducted on a regular basis; however, the VMU staff overheating the

[13] Per the VHA Office of Research & Development guidance document Regulatory Requirements Regarding IACUC Annual Continuing Protocol Reviews (accessible at https://www.research.va.gov/programs/animal_research/): "Recent guidance from USDA APHIS has clarified that continuing reviews are considered compliant if they are completed within the anniversary month of the most recent previous approval or completion of a continuing review… [F]ailure to complete the annual continuing review in time is considered non-compliance with 9 CFR §2.31(d)(5) of the USDA Animal Welfare Act Regulations (AWAR)."

sensor contacted facilities management staff upon receipt of automated notification of temperature deviations rather than waiting for facilities management personnel to respond. Thus, this action compromised the intended ability of the test to adequately assess for facilities management personnel to detect and respond to the alert (a capability that would be of particular importance in the event that an actual overheat incident were to occur during a time when VMU staff were not in the VMU).

Reference(s):
VHA Handbook 1200.07 §7.a(2)(c). *"To test the ability of facilities management personnel to properly detect and respond to elevations in animal room temperatures*, at least once every fiscal year research personnel must purposely overheat a temperature sensor (e.g., with a hair dryer, with input from facilities management personnel) in at least one animal room in each animal research facility without notifying engineering or facilities management personnel in advance. The response must be carefully noted, and reported to the IACUC by VMU staff at the next convened IACUC meeting. 1. The IACUC must decide if the response to the excessive temperature was timely and adequate. If the response is not deemed timely or adequate, corrective action must be taken immediately by the medical facility to ensure a proper emergency response. 2. Unannounced repeat tests must be conducted monthly until the IACUC approves the adequacy of the response. The IACUC minutes must reflect all reviews of testing" (emphasis added).

Required Action 6:
VMU overheat tests must be conducted as described in VHA policy.

7. **Some sanitation practices for USDA regulated species were not compliant.**

Finding:
Sanitized rabbit enclosures contained organic material from previous use. Enclosures used to house rabbits were not effectively cleaned before being sanitized in preparation for the introduction of new rabbits. Inspection of the rabbit housing room revealed that leftover hay pieces were evident in multiple sanitized cages on two different housing racks. Interviews with key personnel revealed that these racks were considered ready for use upon receipt of new animals. Failure to remove all organic material can compromise the ability to achieve effective sanitization.

Reference(s):
9 CFR §§3.56(a)(1)&(b)(2). *"Cleaning of primary enclosures.* Primary enclosures shall be kept reasonably free of … debris by periodic cleaning…. Prior to the introduction of rabbits into empty primary enclosures previously occupied, such enclosures shall be sanitized…."

Required Action 7:

Rabbit housing enclosures must be thoroughly cleaned prior to sanitization procedures.

8. **The MVAHCS IACUC served as the IACUC of record for a private company, and, together with the MVAHCS R&DC, approved as VA research the quality control testing of the company's commercial products on rabbits housed in the MVAHCS VMU. Correspondingly, MVAHCS resources intended to support VA research were directed toward commercial product testing on behalf of a company, an activity that was not consistent with VA's mission.**

Finding:
Document review and interviews with key personnel incidentally revealed that the MVAHCS Research Service had established a contract with a private company, (b) (6) (b) (6), to provide services in support of quality control testing of the company's commercial products in rabbits. Services listed on the contract included, but were not limited to, MVAHCS provision of housing, husbandry, veterinary care, and postoperative monitoring of the rabbits. It was further ascertained that the MVAHCS IACUC and R&DC reviewed and approved as a VA research activity[14] the testing in rabbits of newly produced lots of the company's commercial surgical products using the U.S. Food and Drug Administration's (FDA) Current Good Manufacturing Practices (CGMP).[15] As such, the MVAHCS IACUC served as the IACUC of record for a non-VA institution, in violation of VHA policy. Moreover, it was not evident from interviews with VA facility personnel and a review of the approved ACORP, which described the product testing in the rabbits, that the research activity was consistent with or supported VA's mission, including VHA's research mission.[16,17]

It was further noted that none of the personnel listed in the approved ACORP by these committees were VA Investigators, as none had VA appointments as full, part-time employees, or without compensation (WOC) employees, and none of the

[14] Per ***VHA Handbook 1200.07 §3.d***, "Animal research ... refers to any use of laboratory animals in research, testing, or training."
[15] CGMP refers to the Current Good Manufacturing Practice regulations enforced by the FDA and to assure proper design, monitoring, and control of manufacturing processes and facilities. Adherence to the CGMP regulations assures the identity, strength, quality, and purity of drug products by requiring that manufacturers of medications adequately control manufacturing operations. *For more information see* https://www.fda.gov/drugs/pharmaceutical-quality-resources/facts-about-current-good-manufacturing-practices-cgmps
[16] Per ***VHA Directive 1200 §2.b.*** "The mission of the R&D program is to discover knowledge and create innovations that advance health care for Veterans and the Nation."
[17] Per the VHA Office of Research & Development website (https://www.research.va.gov/about/default.cfm): "The mission of VA Research is fourfold: to improve Veterans' health and well-being via basic, translational, clinical, health services, and rehabilitative research; to apply scientific knowledge to develop effective individualized care solutions for Veterans; to attract, train, and retain the highest-caliber investigators, and nurture their development as leaders in their fields; and to assure a culture of professionalism, collaboration, accountability, and the highest regard for research volunteers' safety and privacy."

individuals were appointed or detailed to VA under the Intergovernmental Personnel Act (IPA).

Reference(s):
VHA Handbook 1200.07 §8. "The VA IACUC may not serve as the IACUC of record for any non-VA institution."

VHA Directive 1200.01 §5.h(4). "The R&D Committee is responsible for ... [e]nsuring that all research in which the facility is engaged is consistent with the VA mission and complies with all applicable statutory and regulatory requirements."

VHA Directive 1200.01 §9.b(3). "The R&D Committee may disapprove a study even if approved by all subcommittees. The disapproval may be based on such issues as inadequate qualifications of the investigator(s) [and] insufficient relevance to the VA's mission...."

VHA Directive 1200.02 §11.e(4). "Other responsibilities of the VA medical facility Director include ... [e]nsuring that Investigators meet the requirements of paragraph 14 in [Directive 1200.02, which requires per paragraph 14.a(5) that 'all research proposals, from any source, support VHA's mission']."

VHA Directive 1200 §4.c(11). "The VA medical facility Director is responsible for ... [e]nsuring that VA investigators and research team members have been officially appointed as paid employees, without compensation employees (WOC) employees, or either appointed or detailed through the authority of the Intergovernmental Personnel Act (IPA)."

Required Action 8:
The MVAHCS IACUC must cease serving as the IACUC of record for this non-VA entity. Additionally, the R&DC and VA facility Director must reassess whether the quality control testing of commercial products in rabbits supports VA's mission.

9. **Physical Security of (b) (6) which contained the VMU, did not meet appropriate security standards as determined by the Police Service, and an action plan to remediate the security issues had not been developed.**

Finding:
A review of the 2019 annual physical security survey completed by the Police Service revealed several long-standing findings, including deficiencies related to VMU windows, doors, and room access; lack of a motion detection system; lack of perimeter barriers; and exterior access points not being in compliance with VA Handbook 0730/4, *Security and Law Enforcement*. SRS meeting minutes for the March 2019 meeting documented discussion of this survey and acknowledged the repeat nature of the findings. The SRS minutes indicated that facility remodeling was

expected in fiscal year 2021 or 2022; however, no action plan was developed to remediate the security risks or to mitigate the risks in the intervening period.

Reference(s):

VHA Directive 1200.08 §5.n(7). "The SRS is responsible for managing implementation of the [Research Safety and Security Program], which includes: … Reviewing the results of all research laboratory and safety-related inspections (e.g., Environment of Care, Annual Workplace Evaluations, Security Vulnerability Assessments, inspections by regulatory bodies, etc.) and ensuring the implementation and completion of corrective actions, as appropriate."

VHA Directive 1200.08 §8. "Access to VA research laboratories must be controlled at all times. Physical security of all VA research areas must meet appropriate standards determined by the facility police service (see VA Directive 0730, and VA Handbook 0730/4), applicable regulatory agencies (e.g., [Centers for Disease Control and Prevention (CDC)], APHIS, [Nuclear Regulatory Commission (NRC)]), and cognizant VA oversight offices (e.g., radiation or nuclear medicine offices)."

VHA Handbook 1200.07 §7.i. "Measures must be implemented to exclude the entry of unauthorized personnel into the animal research facility."

VHA Handbook 0730/4, Appendix B, §8.c. "Results of each [physical security] survey will be routed through the VA facility director to the service chief with responsibility for the protected space. An action plan for mitigation of security risks will be sent by the responsible service chief to the VA chief of police."

Required Action 9:

The Research Service must ensure that the physical security of all VA research areas meets appropriate standards as determined by the facility's Police Service and when deficiencies are identified, that an action plan for mitigation of security risks is developed.

10. **In one instance, IACUC meeting minutes did not identify members who were recused from voting on actions for which they had a conflict of interest, making it unclear if conflicts of interest were recognized and appropriately managed.**

Finding:

In one instance, noted in the April 2019 IACUC meeting minutes, the name of the IACUC member recused from the vote on Protocol No. 170301 was not listed. In addition, current formatting of the minutes combined numbers of members who were recused or abstained into a single category making it unclear whether these members still counted towards meeting quorum.

Reference(s):

9 CFR §2.31(d)(2). *"IACUC review of activities involving animals….* No member may participate in the IACUC review or approval of an activity in which that member has a conflicting interest (e.g., is personally involved in the activity), except to provide information requested by the IACUC, nor may a member who has a conflicting interest contribute to the constitution of a quorum…."

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."

VHA Handbook 1200.07 §8.e(2). "**Avoiding Conflicts of Interest in IACUC Reviews**…. Both the USDA AWA (see 9 CFR §2.31(d)(2)) and PHS Policy (IV.C.2) stipulate that no 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."

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."

Required Action 10:
The IACUC must ensure that potential conflicts of interest are recognized and appropriately managed, including noting in the meeting minutes which members recuse themselves from votes on activities for which they have a conflict of interest.

11. 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**.

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

Required Action 11:
The IACUC or other appropriate subcommittee must ensure deficiencies identified during facility inspections, as listed in Appendix C, are appropriately remediated.

V. ADDITIONAL OBSERVATIONS

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

1. **Observation:**
   The Research Service should consider developing an SOP for cleaning and disinfecting human radiology equipment in patient care areas following NHP scans in order to prevent cross contamination between humans and NHPs. Interviews with key personnel revealed that current practices include both use of a barrier between the NHP and the scanning bed and use of disinfecting wipes available in each imaging suite following scans. This SOP should align with or be more stringent than any SOPs in place for disinfection between consecutive human patients.

   Reference(s):
   The Guide, pp. 146-147. "In vivo imaging offers noninvasive methods for evaluating structure and function at the level of the whole animal, tissue, or cell, and allows for the sequential study of temporal events.... Consideration should be given to the location of the imaging resource. Whether located in the animal facility or in a separate location, cross contamination between groups of animals, different animal species, or between animals and humans (if the device is used for both animal and human subjects) is possible because these devices may be difficult to sanitize...."

   INSTRUCTIONS FOR COMPLETION OF THE ACORP APPENDIX 7 -- USE OF PATIENT CARE EQUIPMENT AND/OR AREAS FOR ANIMAL STUDIES (ACORP APP. 7 INSTRUCTIONS) VERSION 4.[18] "Describe the specific protocol to be followed to prevent contamination of the human patient care room surfaces by animal feces, urine, saliva, blood, or other body fluids, and for any cleaning/sanitizing necessary before subsequent use of the room for human patients. *The procedures used should be at least as thorough as the procedures established by the clinical facility for cleaning and sanitizing the room between human patients*" (emphasis added).

2. **Observation:**
   The IACUC should consider the potential value of implementing a more formalized post-approval monitoring (PAM) program. While a variety of mechanisms may be used, the current, informal approach to PAM at MVAHCS may be inadequate as study noncompliance findings described in this report may have been identified by facility personnel had a more robust program (potentially including unannounced laboratory visits or periodic reviews of medical, surgical, and experimental records) been in place.

   Reference(s):

[18] Accessible at https://www.research.va.gov/programs/animal_research/documents.cfm#docs-c.

The Guide, pp. 33-34. "PAM helps ensure the well-being of the animals and may also provide opportunities to refine research procedures. Methods include continuing protocol review; laboratory inspections (conducted either during regular facilities inspections or separately); veterinary or IACUC observation of selected procedures; observation of animals by animal care, veterinary, and IACUC staff and members; and external regulatory inspections and assessments."

3. **Observation:**
The IACUC should consider implementing a more formalized process to track individual animals that have undergone a survival major operative procedure. In document review, ORO noted at least one transfer of an NHP between two protocols, both of which described major operative procedures. Interviews with key personnel revealed that, while no repeat major operative procedures had occurred, this determination took place informally by checking medical and research records as well as by personal knowledge of the individual animal. A more formalized process would ensure continued compliance and be less reliant on the memories of personnel.

Reference(s):
9 CFR §2.31(d)(1)(x). "No animal will be used in more than one major operative procedure from which it is allowed to recover, unless: (A) Justified for scientific reasons by the principal investigator, in writing; (B) Required as routine veterinary procedure or to protect the health or well-being of the animal as determined by the attending veterinarian; or (C) In other special circumstances as determined by the [USDA APHIS] Administrator on an individual basis."

The Guide, p. 30. "Conservation of scarce animal resources may justify the conduct of multiple major surgeries on a single animal, but the application of such a practice on a single animal used in separate protocols is discouraged and should be reviewed critically by the IACUC. When applicable, the [Institutional Official (IO)] must submit a request to the USDA/APHIS and receive approval in order to allow a regulated animal to undergo multiple major survival surgical procedures in separate unrelated research protocols...."

4. **Observation:**
Investigators, together with the VMOs and IACUC, should reconsider current practices regarding clinical assessment of sedated NHPs during imaging procedures, which involved scanning time lengths of approximately 30 to 60 minutes. Monitoring of NHPs sedated by means of injectable anesthetics for imaging procedures on Protocol No. 170601 included periodic checks of respiratory rate and reflex response between scans as confirmed via interviews with key personnel; however, no additional real-time monitoring of vital parameters was performed while NHPs were undergoing scans (to alert personnel to the NHPs regaining of consciousness or signs of distress). The development of a more rigorous monitoring program for sedated animals during

imaging procedures would increase animal welfare and ensure careful handling of animals.

Reference(s):
9 CFR §2.38(f)(1). "Handling of all animals shall be done as expeditiously and carefully as possible in a manner that does not cause trauma, overheating, excessive cooling, behavioral stress, physical harm, or unnecessary discomfort."

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. Of particular concern, ORO identified serious noncompliance that posed a risk to the well-being of the NHPs used in research at the facility. Specifically, ORO identified that NHPs were subjected to restricted water intake for longer than specified in the approved study protocol, and monitoring of these animals for signs of dehydration was not performed as specified in the protocol. During the course of its review, ORO also made an incidental finding pertaining to activities involving commercial product testing involving the use of rabbits housed at the facility. Specifically, ORO identified that the facility's IACUC served as the IACUC of record for a private company, and that the facility's IACUC and Research & Development Committee had approved as a VA research activity the quality control testing of the company's commercial products in rabbits. However, VA IACUCs are prohibited from serving as the IACUC of record for a non-VA entity, and the approved quality control testing of commercial products in rabbits had no apparent relevance to VA's mission. All identified noncompliance must be addressed in a Remedial Action Plan that will be monitored by ORO until satisfied.

OFFICE OF RESEARCH OVERSIGHT

(b) (6)

(b) (6)

Date: 2019.10.02 13:09:37 -04'00'

(b) (6)

APPENDIX A
ORO REVIEW TEAM and FACILITY REPRESENTATIVES

ORO On-Site Review Team:

(b) (6)	Animal Care and Use (ACU) review team lead
(b) (6)	(b) (6)

Facility Representatives:

Patrick Kelly	Medical Center Director
Hanna Bloomfield, MD	Associate Chief of Staff (ACOS) for Research
(b) (6)	(b) (6)
(b) (6)	(b) (6)
Matthew Rassette, DVM, DACLAM	Veterinary Medical Officer (VMO), Attending Veterinarian
(b) (6)	(b)
(b) (6)	(b) (6)
Janeen Trembley, PhD	Institutional Animal Care and Use Committee (IACUC), Chairperson
(b) (6)	(b) (6)
(b) (6)	(b) (6)
(b) (6)	(b) (6)
(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.

• 150402D	Decoding of Force from Neural Signals in Motor Cortex
• 150601	A Comparative Vitreous Replacement Study in the Rabbit Model
• 170301	Investigation into Targeting CK2 in Melanoma
• 170601 (previously 140702)	Cellular and Synaptic Basis of Cognitive Function in Prefrontal Cortical Networks; Characterizing Thalamocortical Prefrontal Network Dynamics Underlying Cognitive Control in a Model of Schizophrenia

APPENDIX C
AREAS INSPECTED WITH ASSOCIATED FINDINGS/OBSERVATIONS

Location	Finding (F) / Observation (O)	Notes/References
(b) (6)	**(F)** Expired antibiotic present: injectable cefazolin (subsequent to reconstitution).	*9 Code of Federal Regulations (CFR) §2.33(b)(2).*
(b) (6)	**(F)** Expired veterinary medical supplies: intravenous catheters (expired 05/31/2019).	*9 CFR §2.33(b)(2).*
(b) (6)	**(F)** A razor available for surgical preparation was soiled with hair and other materials.	*9 CFR §2.33(b)(2).*
(b) (6)	**(F)** An electrical panel was partially blocked by a storage cabinet.	*29 CFR §1910.303(g)(1).*
(b) (6)	**(F)** Expired analgesic present: injectable meloxicam (expired 01/2019).	*9 CFR §2.33(b)(2); The Guide for the Care and Use of Laboratory Animals, 8th Edition, p. 122; VHA Handbook 1200.07 §7.f(4).*
(b) (6)	**(F)** Personal protective equipment was in disrepair: leather gloves provided for use to prevent bite/scratch injuries when handling nonhuman primates (NHP) were damaged with hole present on thumb of left glove	*29 CFR §1910.132(a).*
(b) (6)	**(F)** Egress from the NHP housing room required specialized knowledge (use of a latch to exit the room).	*29 CFR 1910.36(d)(1); National Fire Protection Association (NFPA)[1] 101®- The Life Safety Code® 7.2.1.5.3.*
(b) (6)	**(F)** A plumbed eyewash was last flushed in June of 2016.	*American National Standards Institute, Inc. (ANSI) Z358.1-2014 §5.5.2; VHA Directive 7704(1) Appendix D§4.*

[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)...."

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: **January 30, 2020**

Animal Care and Use. ORO Case Number: **618-0103-A**

Required Action 1: The IACUC and Principal Investigator for the remaining, active NHP research protocol 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 2: The IACUC must ensure that the use of nonpharmaceutical grade compounds is adequately described in protocols, including in the protocol 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 3: The IACUC must ensure that significant changes are approved by either DMR or FCR unless the IACUC develops and approves an SOP detailing the use of Veterinary Verification and Consultation (VVC) for certain types of significant changes as described in OLW guidance.	
Facility Response	***ORO Comments***

Response #1 ([DATE of response submission]) **Facility Action:** [TEXT] **Proposed Completion Date:** [DATE]	[ORO comments will be inserted here]
Required Action 4: The IACUC must ensure procedures described in approved protocols are clear and consistent between different sections.	
Facility Response	***ORO Comments***
Response #1 ([DATE of response submission]) **Facility Action:** [TEXT] **Proposed Completion Date:** [DATE]	[ORO comments will be inserted here]
Required Action 5: The IACUC must ensure required annual protocol reviews are conducted in a timely manner.	
Facility Response	***ORO Comments***
Response #1 ([DATE of response submission]) **Facility Action:** [TEXT] **Proposed Completion Date:** [DATE]	[ORO comments will be inserted here]
Required Action 6: VMU overheat tests must be conducted as described in 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 7: Rabbit housing enclosures must be thoroughly cleaned prior to sanitization procedures.	
Facility Response	***ORO Comments***
Response #1 ([DATE of response submission]) **Facility Action:** [TEXT] **Proposed Completion Date:** [DATE]	[ORO comments will be inserted here]
Required Action 8: The MVAHCS IACUC must cease serving as the IACUC of record for this non-VA entity. Additionally, the R&DC and VA facility Director must reassess whether the quality control testing of commercial products in rabbits supports VA's mission.	
Facility Response	***ORO Comments***
Response #1 ([DATE of response submission]) **Facility Action:** [TEXT] **Proposed Completion Date:** [DATE]	[ORO comments will be inserted here]
Required Action 9: The Research Service must ensure that the physical security of all VA research areas meets appropriate standards as determined by the facility's Police Service and when deficiencies are identified, that an action plan for mitigation of security risks is developed.	
Facility Response	***ORO Comments***

Response #1 ([DATE of response submission]) **Facility Action:** [TEXT] **Proposed Completion Date:** [DATE]	[ORO comments will be inserted here]
Required Action 10: The IACUC must ensure that potential conflicts of interest are recognized and appropriately managed, including noting in the meeting minutes which members recuse themselves from votes on activities for which they have a conflict of interest.	
Facility Response	***ORO Comments***
Response #1 ([DATE of response submission]) **Facility Action:** [TEXT] **Proposed Completion Date:** [DATE]	[ORO comments will be inserted here]
Required Action 11: The IACUC or other appropriate subcommittee 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]