OFFICE OF RESEARCH OVERSIGHT

FOR-CAUSE REVIEW:

CANINE RESEARCH STUDIES AND ASSOCIATED FACILITY OVERSIGHT

Hunter Holmes McGuire VA Medical Center
Richmond, Virginia

May 30, 2017

Veterans Health Administration

CONTENTS

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EXECUTIVE SUMMARY

On March 30, 2017, the VA Office of Inspector General (OIG) referred a complaint regarding canine studies conducted at the Hunter Holmes McGuire VA Medical Center (HHMVAMC) in Richmond, VA, to the Office of Research Oversight (ORO) for investigation. The OIG referral outlined eight allegations, seven of which pertained to alleged animal welfare concerns, recordkeeping and reporting violations, and a failure to make appropriate public disclosure of the studies. An eighth allegation that pertained to the clinical privileges of an HHMVAMC study team member was determined, in consultation with OIG, to fall outside the scope of ORO's purview.

To address the allegations, ORO: conducted interviews with HHMVAMC personnel responsible for providing local oversight of animal research and study team personnel conducting research involving dogs; reviewed various facility documents pertaining to the oversight and conduct of the studies referenced in the complaint; and conducted an on-site inspection at the facility on April 18-21, 2017.

With regard to the specific allegations referred by OIG:

- ORO was able to substantiate some but not all aspects of the allegations constituting animal welfare concerns. ORO substantiated the inappropriate administration of a sedative, a failure to provide appropriate postoperative care, and the occurrence of unanticipated surgical complications. However, ORO could not conclusively determine that the surgical complications referenced in the allegations were evidence of "negligence" or "incompetence" on the part of the Principal Investigator (PI) as alleged. ORO also ascertained that after each of these incidents, which had been previously self-identified and appropriately reported by HHMVAMC personnel, the local Institutional Animal Care and Use Committee (IACUC) appropriately implemented progressive corrective actions to address the concerns, including ultimately suspending the privileges of the Principal Investigator to conduct animal research.
- ORO did <u>not</u> substantiate the allegation that HHMVAMC failed to report to the U.S. Department of Agriculture (USDA) that <u>any</u> dogs were used in research at the facility in fiscal year (FY) 2016. USDA provided ORO with a copy of HHMVAMC's annual report for FY2016 and this report did in fact indicate that HHMVAMC reported dogs were used in research at the facility during FY2016. However, ORO did identify that there were inaccuracies in reporting the precise numbers of dogs used in research.

- ORO did not substantiate that there was a regulatory failure to adhere to "requirements" to publicly disclose the dog experiments in a federal reporting database used to capture information regarding federally supported grants. Further, ORO did not substantiate that there were any violations of the Animal Welfare Act with regard to the reporting of the adverse events referenced in the complaint.
- ORO did not substantiate the allegation pertaining to HHMVAMC lacking tracking records of oversight and experimental failures. Specifically the facility was able to provide records of adverse events and other incidents that were reported to the IACUC.

In addition to the findings made with regard to the allegations referred by OIG, ORO made a number of additional findings related to the canine research studies and associated oversight by HHMVAMC, including:

- Lack of documentation to establish whether animals were appropriately evaluated and received supportive care;
- Non-adherence to provisions of the written Program of Veterinary Care;
- Deviations from approved study procedures and implementation of changes to studies without prior IACUC approval;
- Protocols that lacked necessary information to inform the IACUC's review and approval process; and
- Deficient reporting and recordkeeping practices with regard to animal usage and disposition.

Within 30 days of receipt of this report, HHMVAMC will be required to develop a remedial action plan specifying the actions to address the findings in the report and timely completion dates. HHMVAMC has notified ORO that a number of corrective actions have already been initiated that will address the findings contained in this report.

FOR-CAUSE REVIEW:

CANINE RESEARCH AND ASSOCIATED FACILITY OVERSIGHT

Hunter Holmes McGuire VA Medical Center
Richmond, Virginia

On-Site Review Dates: April 18 - 21, 2017
Date of Report: May 30, 2017

I. INTRODUCTION AND METHOD OF REVIEW

The Office of Research Oversight (ORO) serves as the primary Veterans Health Administration (VHA) office for advising the Under Secretary for Health (USH), and conducting compliance oversight, relative to the protection of human research subjects, laboratory animal welfare, research safety, research laboratory security, research information protection, and research misconduct. ORO also oversees Governmentwide debarments for research impropriety and conducts education programs for facility Research Compliance Officers (RCOs).

The ORO Research Safety and Animal Welfare (RSAW) group conducted an On-Site For-Cause Review (FCR) of facility oversight of canine research at the Hunter Holmes McGuire VA Medical Center (HHMVAMC) on April 18-21, 2017.

This review was initiated in response to a VA Office of Inspector General (OIG)[1] referral that included allegations of animal abuse and recordkeeping violations associated with canine research performed at HHMVAMC.

The scope of ORO's review included: (1) conducting a post-incident investigation to determine the merit of allegations presented in the OIG complaint; (2) determining if the Principal Investigator(s) (PIs) conducting canine research at the HHMVAMC followed adequate protocol procedures while performing surgeries and administering postoperative care; and (3) evaluating local oversight mechanisms, including the HHMVAMC Institutional Animal Care and Use Committee (IACUC), and animal care procedures for active canine studies, to determine the level and adequacy of oversight provided for canine research. Specific responses regarding the

[1] VAOIG Hotline Referral Case No. 2017-02763-HL-0912; (2017-16882); VAMC Richmond, VA. RP. 12, dated March 30, 2017

merit of each allegation listed in the OIG request are provided in Section III of this report. Additional findings from ORO's review are provided in Section IV of this report.

The ORO review team conducted group and individual interviews with facility leadership, research service leadership, the Veterinary Medical Consultant (VMC), PIs, animal research personnel, and members of the IACUC, including the Chair (*see* Appendix A). The ORO review team conducted a review of selected Animal Care and Use Program (ACUP) documents focusing on the canine research program, including: policies, plans, IACUC minutes, standard operating procedures (SOPs), scope of practice records, training materials and documentation, canine Animal Component of Research Protocols (ACORPs), canine acquisition/disposition records, and surgical and medical records (*see* Appendix B). The ORO team also conducted a physical inspection of the Veterinary Medical Unit (VMU) (*see* Appendix C).

II. PROGRAM AND RESEARCH OVERVIEW

Oversight of the HHMVAMC research program was provided through the HHMVAMC Research and Development Committee (R&DC) and corresponding subcommittees with delegated authority for specific program areas. Primary oversight of the ACUP was provided by the HHMVAMC IACUC. The ACUP maintained a current Public Health Service (PHS) Animal Welfare Assurance (No. A 4369-01) with the National Institutes of Health - Office of Laboratory Animal Welfare (NIH-OLAW) and full accreditation with the Association for the Assessment and Accreditation of Laboratory Animal Care, International (AAALAC; Unit No. VA-061), and was registered with the U.S. Department of Agriculture - Animal and Plant Health Inspection Service (USDA-APHIS; Registration No. 52-V-0003). The HHMVAMC was affiliated with the Virginia Commonwealth University (VCU), Richmond, VA; however, at the time of ORO's review, no VA canine research was conducted at this or other off-site location(s).

The HHMVAMC research program was supported by a VMC, contracted through the nonprofit corporation, the McGuire Research Institute. The VMC provided coverage of the entire animal research program, not solely the canine research, and during onsite interviews stated that he was present at the facility between 20 to 60 minutes per week to provide program oversight and animal care. The facility had a full-time VMU supervisor and two full-time animal husbandry staff, supporting the entire ACUP. Two full-time research technicians supported the four Principal Investigators (PIs) who conducted canine research, providing support during surgeries and other experimental interventions as well as intra/postoperative monitoring of the dogs; additionally, one of these technicians had part-time animal care duties. Some of these

staff also had rodent care responsibilities and participated in other research-related activities and committees.

The HHMVAMC had six approved research protocols involving the use of a canine animal model. See Appendix B, Item 36. A seventh protocol was pending IACUC approval at the time of ORO's site visit. The canine research portfolio focused primarily on cardiac physiology and function, and reflected a range of scientific aims and potential applications. Four PIs were involved in the research. Three of the six studies were investigating the underlying physiology and consequences of premature ventricular contractions by: (a) comparing the effects of premature contractions of the upper and lower heart chambers, the atria and ventricles, respectively; (b) assessing the impact of premature contractions (arrhythmias) on the development of cardiomyopathy (disease of the heart muscle often leading to heart failure); (c) investigating the relationship between the nerves that innervate the heart and kidney and the development of arrhythmia and cardiomyopathy; (d) determining if injection of nanoparticles containing different compounds can prevent arrhythmias; and (e) assessing how the time interval between the premature ventricular contractions and normal contractions affects the development of ventricular dysfunction. A fourth study sought to determine if the incidence and inducibility of atrial fibrillation (upper chamber arrhythmia) could be inhibited by exposing cardiac nerves to pharmacologic agents such as botulinum toxin or calcium chloride. A fifth study aimed to assess and define the effects of two techniques used to destroy cells in specific regions of the heart, to treat rhythmic abnormalities in humans. The sixth study examined the physiology of left ventricular remodeling after a heart attack, and to assess the relationship between arrhythmia and left ventricular remodeling, with and without a premature ventricular contraction challenge.

The procedures approved for the studies included: surgery (thoracotomy, survival surgery, multiple survival surgeries, and terminal surgery with tissue harvest); implantation of pacemakers; insertion of catheters into heart chambers for blood sampling; induction of cardiac contractions and arrhythmias; cardiac biopsies; implantation of subcutaneous radiotelemetry devices with channel connections to permit recording of cardiac and renal nerve activities; injections of active substances (e.g., nanoparticles releasing botulinum toxin); cardiac tissue ablation (destruction) using catheters to apply radiofrequency energy (heating) or cycles of freezing and thawing (cryoablation); the injection of liquid latex into the coronary artery to cause a myocardial infarction (heart attack); echocardiograms; intravenous administration of short acting vasoactive drugs; and treadmill exercise.

The stated goal of the research was to gain a better understanding of the underlying mechanisms behind the development of cardiac abnormalities and cardiac physiology, with the

ultimate goal of developing treatments for these conditions in humans. The PIs justified the use of canine subjects (in lieu of alternate animal models) based upon: (a) the similarities between canine and human cardiac physiology, including the cardiac electrical conduction systems; (b) the size of canine hearts (permitting pacemaker implantation, the induction of sustained arrhythmia, and the insertion of ablation catheters); and (c) the adaptability of canines to instrument implantation compared to other large animals.

Funding for the dog projects conducted at HHMVAMC was provided by various sources including the US Public Health Service (NIH), the American Heart Association, the McGuire Research Institute (the VA's nonprofit research foundation), and other non-profit entities.

Between December 2015 and November 2016, several incidents involving canine research were reported to the ORO RSAW team and to the National Institutes of Health Office of Laboratory Animal Welfare (NIH-OLAW). These reports, involving one Principal Investigator (PI), detailed a series of adverse events, including animal deaths that occurred as a result of the research conducted under an IACUC-approved protocol at HHMVAMC. In response to these adverse events, the HHMVAMC IACUC implemented a series of progressive restrictions and conditions on the PI and the research. After discussions with the Medical Center Director and the Associate Chief of Staff for Research (ACOS/R), the IACUC suspended the PI's animal research privileges and mandated that another investigator assume primary responsibility for all animal work, although the original PI was permitted to be involved in aspects of the research that did not include handling animals. These incidents were specifically referenced in the allegations referred by OIG to ORO.

III. ASSESSMENT OF ALLEGATIONS REFERRED TO ORO BY THE VA OFFICE OF INSPECTOR GENERAL

On March 30, 2017, the VA OIG referred several allegations to ORO that pertained to dog research conducted at HHMVAMC (VAOIG Hotline Referral Case No. 2017-02763-HL-0912; (2017-16882)). These allegations stemmed from a complaint dated March 21, 2017, that was received by VA OIG. The allegations, which are reproduced verbatim from the VA OIG referral, and ORO's assessment of the allegations, are presented below.

1. Allegations

a. *Animal welfare abuse concerning dog experimental laboratories between December 2015 and November 2016. Specifically:*

(1) December 2015, the Principal Investigator negligently gave a dog a sedative overdose during an experimental surgery and failed to provide adequate post-procedural veterinary care that nearly killed the dog.

(2) April 2016, following a surgery by the Principal Investigator to sever a dog's cardiac nerves, the dog drastically deteriorated in health and ultimately died of a heart attack during an experiment. Additionally, another dog that underwent the same surgery by the Investigator experienced rapid health decline and was killed. The report determined sloppy and incompetent surgeries killed the animals.

(3) November 2016, the Principal Investigator killed another dog by cutting into the dog's chest to expose the heart and incompetently sliced into the dog's lung.

b. Record Keeping violations:

(1) VAMC submitted a report to U.S. Department of Agriculture, indicated that no dogs were held or used in experiments in FY 2016; however, the self-reported dog abuse violations listed are incontrovertible evidence that dogs were subjected to painful and distressful experiments in FY16.

(2) VAMC failed to publicly disclose dog experimental projects in the Federal Reporter System.

(3) These incidents have not been reported to the Secretary of the VA as required by law.

(4) VAMC lacks tracking records of oversight and mismanagement of experimental failures.

c. The Principal Investigator whose repeated botched surgeries on dogs led to revocation of their experimentation privileges is still listed as an active physician treating veterans at McGuire VAMC.

2. Assessment of Allegations

a. Allegation 1a(1). *"December 2015, the Principal Investigator negligently gave a dog a sedative overdose during an experimental surgery and failed to provide adequate post-procedural veterinary care that nearly killed the dog."*

(1) Method(s) used by ORO to review the allegation.

(a) Review of documents related to this incident, including: surgical and medical records for this dog, IACUC meeting minutes, facility reports to ORO, OLAW, and AAALAC, and ORO case files.

(b) Interviews with IACUC members, the PI, study staff, the VMC, and VMU staff.

(2) Determination by ORO regarding the substance of the allegation.

(a) This allegation is **substantiated**.

(b) Review of documents and interviews with facility personnel indicated that a dog on protocol 02002 received an overdose of pentobarbital during a surgical procedure conducted on December 1, 2015, and that the PI failed to provide adequate postoperative care. The overdose was a result of the infiltration of an intravenous catheter, failure of staff to detect the infiltration, and failure to consider that the extravasated drug would be absorbed slowly over time and could result in an overdose. At the conclusion of the procedure, the PI monitored the animal for several hours but left the facility before the animal had fully recovered without arranging for another individual to monitor the dog. The situation was compounded when a technician arrived the next morning and administered a narcotic for pain relief, as specified in the approved protocol, without realizing that the dog had already received an overdose of pentobarbital or fully assessing the dog's condition. The IACUC reviewed these events at a convened meeting and determined the Principal Investigator "failed to provide adequate veterinary care by failing to monitor the IV line during surgery, giving an overdose of pentobarbital during surgery, failing to provide adequate postoperative support in the way of IV fluids and proper warming, failed to monitor the dog until it was completely recovered and left the dog in a state that could have led to death." ORO concurs with the IACUC's determination and finds that collectively these failures constituted negligence[2] on the part of the PI.

(3) Summary of corrective actions taken and/or required to address and resolve the issues and to prevent a recurrence.

(a) Initial responses. The morning after the animal's surgical procedure, the VMU Supervisor was notified of the dog's condition upon arrival, and immediately contacted both the PI and VMC. Under the direction of the

[2] Failure to exercise the care that a reasonably prudent person would exercise in like circumstances.

VMC, emergency supportive treatments were initiated. The dog's condition slowly improved and by the following day, the animal had recovered.

(b) Additional responses. The IACUC reviewed the event on December 2, 2015, and initiated the following corrective actions: (1) additional survival surgeries were placed on veterinary hold; (2) the PI was required to revise the protocol to address intraoperative anesthesia, include procedures for monitoring animals during surgery, and update postoperative monitoring procedures; (3) the PI was required to submit a letter to the IACUC detailing the incident and provide a plan to prevent a recurrence, including descriptions of titration methods for anesthetics and emergency procedures to be used in case of adverse events; (4) the PI was required to maintain detailed intra/postoperative records for each animal; (5) the PI and technician were required to complete additional training, including training on controlled substances and anesthesia agents, their side effects and contraindications, and procedures to deal with postoperative distress; (6) all investigators were required to certify (with signature) that they understood the requirement for postoperative monitoring until the animals are sternal and responsive and to have access and contact information for 24-hour emergency procedures; (7) revision of the Animal Handler competency form to add sections on controlled substance safety and postoperative care; (8) all research staff using barbiturates or opiates were required to receive specialized training; (9) the next survival surgery was required to be observed by the VMC; and (10) the incident was determined to be reportable to ORO, OLAW, and AAALAC.

(4) Timeframe for corrective actions (i.e., completed and/or required).

(a) On February 3, 2016, the IACUC determined that all required actions had been completed and rescinded restrictions it had placed on the research.

(b) ORO was initially notified of the event on December 3, 2015, and after receiving an update notifying that all corrective actions had been completed, closed the case on February 23, 2016. *Note: ORO tracked this incident as Case No. 652-0017-A.*

(5) Summary of documentation supporting the determination

(a) Facility report to ORO (Supporting Document I)

(b) Relevant portions of IACUC Minutes

(c) IACUC/Research Service Protocol File

(6) The value of recovery or savings: N/A

(7) Name and position of the reviewer: ORO RSAW (Appendix A §II)

b. Allegation 1a(2). *"April 2016, following a surgery by the Principal Investigator to sever a dog's cardiac nerves, the dog drastically deteriorated in health and ultimately died of a heart attack during an experiment. Additionally, another dog that underwent the same surgery by the Investigator experienced rapid health decline and was killed. The report determined sloppy and incompetent surgeries killed the animals."*

(1) Method(s) used by ORO to review the allegation.

(a) Review of documents related to this incident, including: surgical and medical records for these dogs, IACUC meeting minutes, and facility reports to ORO, OLAW, and AAALAC, and ORO case files.

(b) Interviews with the IACUC, PI and study staff, the VMC, and VMU staff.

(2) Determination by ORO regarding the substance of the allegation.

(a) This allegation is **partially substantiated**.

(b) Review of documents and interviews with facility personnel confirm that in March 2016, two dogs on protocol 02002 underwent surgery to isolate and ablate certain cardiac nerves and subsequently developed severe gastrointestinal complications and were provided supportive care. The surgical procedure required isolating cardiac nerves from the main trunk of the vagal nerve; this main trunk also contains fibers innervating other organs in addition to the heart. The IACUC determined that although the other fibers were not intentionally disturbed, manipulation of both the left and right vagal nerves in a single procedure likely disrupted nervous control of digestive function, resulting in significant nausea, lethargy, anorexia, and weight loss. Neither of the dogs had a heart attack or myocardial infarction. One of these dogs developed ventricular fibrillation and died while undergoing a subsequent IACUC-approved procedure; the second dog was euthanized during an IACUC-approved terminal procedure. Neither the IACUC report provided by the facility nor interviews with facility personnel suggested that "sloppy and

incompetent surgeries" resulted in the deaths, as stated in the allegation. In sum, ORO concludes that unanticipated surgical complications did occur and that one dog subsequently died while undergoing an approved research procedure, and the second dog was euthanized; however, ORO could not conclusively determine that the surgical complications were evidence of "incompetence" on the part of the PI as alleged.

(3) Summary of corrective actions taken and/or required to address and resolve the issues and to prevent a recurrence.

(a) Initial responses. Both animals were provided with veterinary supportive care.

(b) Additional responses. With the veterinarian and IACUC's approval, one additional dog underwent surgery to perform a unilateral (one-sided) manipulation of the vagal nerve and ablation of the cardiac nerves utilizing extremely careful tissue handling techniques. This animal recovered without any adverse events. The IACUC reviewed the events and devised a corrective action plan including: (1) close veterinary supervision; (2) modification of the protocol to include unilateral surgery on four additional dogs with ongoing IACUC monitoring; (3) oversight of surgeries by an experienced co-investigator; and (4) review/observation by the VMU supervisor. Once completed, the PI submitted a report to the IACUC. Because these four additional animals experienced only mild, manageable clinical signs following the unilateral denervation, the IACUC permitted the PI to submit an amendment, for sequential denervation surgeries (one side at a time, with a recovery period in between), which was subsequently approved. Remaining surgeries were completed without adverse events.

(4) Timeframe for corrective actions (i.e., completed and/or required).

(a) On September 28, 2016, the IACUC determined that all approved additional surgeries (beyond the initial two problematic surgeries) had been completed with only minor complications.

(b) ORO was initially notified of the events involving the first two problematic surgeries, on April 7, 2016, and followed the implementation of corrective actions. ORO was updated by the facility on September 30, 2016, and closed the case on October 4, 2016. *Note: ORO tracked this incident as Cases No. 652-0021-A.*

(5) Summary of documentation supporting the determination.

(a) Facility report to ORO (Supporting Document II)

(b) Relevant portions of IACUC Minutes

(c) IACUC/Research Service Protocol Files

(6) The value of recovery or savings: N/A

(7) Name and position of the reviewer: ORO RSAW (Appendix A §II)

c. Allegation 1a(3). *"November 2016, the Principal Investigator killed another dog by cutting into the dog's chest to expose the heart and incompetently sliced into the dog's lung."*

(1) Method(s) used by ORO to review the allegation.

(a) Review of documents related to this incident, including: surgical and medical records for this dog, IACUC meeting minutes, facility reports to ORO, OLAW, and AAALAC, and ORO case files.

(b) Interviews with the IACUC, PI and study staff, the VMC, and VMU staff.

(2) Determination by ORO regarding the substance of the allegation.

(a) This allegation is **partially substantiated**.

(b) The PI was performing a survival surgery on a dog on protocol 02235 three weeks after a previous surgery on the same dog. He encountered a number of tissue adhesions (a known potential complication of repeated thoracotomies), with some of the adhesions being more prominent than typically seen. As the PI released a particularly dense adhesion, it appears (in hindsight) that damage to the lung tissue occurred, but was not detected at that time. At the conclusion of the surgical procedure and upon removal of the tracheal tube, blood was noted on the tube. The animal quickly became hypoxic and died before emergency treatment or euthanasia could be provided. On necropsy, it was noted that the animal had a laceration and damage to the lung, which likely contributed to the animal's death. ORO notes that during a review of the incident by the IACUC, one member submitted a minority opinion indicating that "[t]he lack of foresight and preparation by the investigator prior to [the] surgery [led the IACUC member] to believe the investigator has a general sense of unintended reckless behavior." However, an extensive review of documents and interviews with a range

of facility personnel did not produce sufficient evidence that the surgical complication was a result of the PI's incompetence or that the PI acted recklessly with regard to the removal of the tissue adhesions.

(3) Summary of corrective actions taken and/or required to address and resolve the issues and to prevent a recurrence.

(a) Immediate actions. The cause of death was investigated.

(b) Additional actions. The VMC stopped all planned surgeries on animals with no prior procedures, but allowed activities to continue on animals already involved in the study with additional veterinary observation (those procedures were conducted without complications). The PI was required to meet with the IACUC Chair. The IACUC discussed this event and determined that it was a reportable event to ORO, OLAW, and AAALAC. The IACUC required the PI to submit an amended ACORP to add a description of the risk of pleural adhesions and to re-characterize this study as a pilot protocol that could lead to unexpected outcomes. Additionally, the IACUC required the following corrective actions: (1) updating of the postoperative monitoring section of the protocol to provide additional safeguards and monitoring; (2) limiting surgical procedures to once a week; (3) requiring the PI to contact other cardiac researchers conducting similar procedures to gain information on potential procedural complications; and (4) requiring a second surgeon to be present for all surgical procedures. The IACUC acknowledged the previous counseling and veterinary monitoring.

At a subsequent convened IACUC meeting, the Institutional Official (IO) (the Facility Director in the VA system) and the Associate Chief of Staff for Research (ACOS/R&D) were in attendance to discuss an unrelated matter. With input from the IO, the IACUC determined that the current study PI should be replaced with a more experienced surgeon (an individual who had previously participated as a sub-investigator on protocol 02235). The IACUC also determined that the more experienced surgeon would replace the current PI on another protocol (02002, the study related to the first two allegations above), and that the current PI could remain on both protocols in a non-PI capacity, but would not be permitted to participate in any animal work (i.e., limited to observation only).

A special IACUC meeting was convened on December 12, 2016, to approve modifications to the protocol. At the next convened IACUC meeting in January, the IACUC approved an action plan for all protocols involving the former PI (i.e., the PI who was replaced as a result of these incidents). The action plan noted that: the investigator was removed as PI from protocols 02002 and 02235, and is not permitted to participate in any animal procedures related to these protocols. The new lead PI, who replaced the investigator, will perform all animal surgeries and procedures. The former PI is permitted to continue with scientific development and data analysis. The former PI may remain as a sub-investigator on two additional protocols (01549 and 01946), but may only observe animal procedures on those protocols. As of the date of this report, the IACUC continues to monitor the situation and has not restored any animal procedure privileges to the former PI. Additionally, the IACUC requested that a cardiothoracic surgeon observe and consult with the new lead surgeon regarding lung tissue hemostasis techniques.

(4) Timeframe for corrective actions (i.e., completed and/or required).

(a) As of the writing of this report, all corrective actions have been implemented and/or completed. The IACUC has not restored any of the former PI's animal procedure privileges.

(b) ORO was initially notified of this event on November 14, 2016, and was continuing to monitor progress at the time the OIG referral was received. Future follow-up of this matter will be combined into this for-cause review case. *Note: ORO continues to track this incident as Case No. 652-0030-A.*

(5) Summary of documentation supporting the determination

(a) Facility report to ORO (Supporting Document III)

(b) Portions of IACUC Minutes

(c) IACUC/Research Service protocol file

(6) The value of recovery or savings: N/A

(7) Name and position of the reviewer: ORO RSAW (Appendix A §II)

d. Allegation 1b(1). *"VAMC submitted a report to U.S. Department of Agriculture, indicated that no dogs were held or used in experiments in FY 2016; however, the*

self-reported dog abuse violations listed are incontrovertible evidence that dogs were subjected to painful and distressful experiments in FY16."

(1) Method(s) used by ORO to review the allegation.

(a) Review of the report provided by the complainant.

(b) Review of a copy of the HHMVAMC annual report for FY 2016 obtained directly from USDA, Animal Plant Health Inspection Service, Animal Care (USDA-APHIS-AC).

(c) Interviews with key personnel including the VMU Supervisor.

(2) Determination by ORO regarding the substance of the allegation.

(a) The allegation is **not substantiated**.

(b) A document accompanying the complaint that was provided to OIG was purported to represent HHMVAMC's FY16 filing to USDA on the number of regulated species used in research at the facility. This purported filing indicated that "0" dogs were reported as being used at the facility. This document, however, does not reflect what USDA has on file as being submitted by HHMVAMC for FY16. Specifically, the HHMVAMC's "Annual Report of Research Facility" on file with the USDA (a copy of which was provided to ORO by USDA-APHIS-Animal Care), signed by the MCD October 12, 2016[3], indicates that a total of 29 dogs were reported as being used for research or held under the control of the HHMVAMC in FY2016. Thus, the information submitted in support of the complainant's allegation (that no dogs were reported for FY16) does not match that which is contained in USDA's official records.

While the allegation that the facility did not report *any* dog use in FY2016 is <u>not</u> substantiated, ORO did determine that the reported number of dogs used at HHMVAMC in fiscal years 2014-2016 was not accurate (*See* Section IV of this report, Finding 4.b). This discrepancy appears to be the result of a misunderstanding of the appropriate reporting practices rather than an intentional misrepresentation of animal numbers (e.g., if a dog was present in multiple years it appears the dog was only reported once rather than in each year it was present).

[3] Forms available via the APHIS website for the <u>FY2016</u> reporting cycle contained a pre-populated date field indicating "Fiscal Year 2015," but APHIS confirmed to ORO that these not-yet-updated forms were used to report FY2016 data.

(3) Summary of corrective actions taken and/or required to address and resolve the issues and to prevent a recurrence.

(a) When ORO questioned facility staff regarding the animal numbers reported, the facility acknowledged they had recently recognized the errors.

(b) ORO will request submission of amended annual reports to USDA to correct the under-reporting of animal use.

(4) Timeframe for corrective actions (i.e., completed and/or required).

(a) ORO will track remediation of this noncompliance via a Remedial Action Plan, to be initiated after issuance of this report.

(5) Summary of documentation supporting the determination

(a) A copy of the HHMVAMC USDA Annual Report of Research Facility for FY16, obtained by ORO from USDA-APHIS and email correspondence with USDA-APHIS. (Supporting Document IV)

(b) "Canine admissions" forms, the "Dog Log", and animal records obtained from HHVAMC.

(6) The value of recovery or savings: N/A

(7) Name and position of the reviewer: ORO RSAW (Appendix A §II)

e. Allegation 1b(2). *"VAMC failed to publicly disclose dog experimental projects in the Federal Reporter System."*

(1) Method(s) used by ORO to review the allegation.

(a) Access to and queries of the Federal RePORTER website at https://federalreporter.nih.gov (accessed on May 3, 2017). Federal RePORTER database search [search criteria included Funding Agency; Principal Investigator (PI) Name; Organization; State/City; Fiscal Year (FY)], and access to the STAR METRICS® website at https://www.starmetrics.nih.gov/Star/About (accessed on May 3, 2017).

(b) Email query to Federal RePORTER contact listed on the website.

(c) Review of HHMVAMC protocol lists, ACORPs, and other related documentation in protocol files.

(d) Interviews with key personnel including the Research Service, IACUC, and PIs.

(2) Determination by ORO regarding the substance of the allegation.

(a) The allegation is **not substantiated** with regard to any regulatory noncompliance.

(b) Federal RePORTER is a federally funded searchable database, managed by STAR METRICS®, that utilizes existing administrative data from federal funding agencies to enable public access and assessment of the impact of federally funded research and development investments. ORO identified the funding sources for all IACUC-approved canine research at HHMVAMC. The VA was not listed as a funding source on any of these projects. Of the six dog studies, one funded entirely by PHS was retrieved from Federal RePORTER. The remaining five canine studies at HHMVAMC were supported by funds from non-Federal sources, and per the FAQ section of the STAR METRICS® website, projects sponsored by non-federal sources should not be included in the Federal RePORTER database. Moreover, an NIH contact listed on the Federal RePORTER website indicated to ORO that providing information to the database is voluntary. Thus, to the extent that HHMVAMC did not disclose some or all of its dog studies in the Federal RePORTER system, such disclosure is not required nor in many cases relevant (for studies funded by non-Federal sources).

(3) Summary of corrective actions taken and/or required to address and resolve the issues and to prevent a recurrence.

(a) No corrective actions are required.

(4) Timeframe for corrective actions (i.e., completed and/or required).

(a) N/A

(5) Summary of documentation supporting the determination

(a) Access to and review of the Federal RePORTER and STAR METRICS® websites.

(b) Information provided by email from NIH. (Supporting Document V)

(c) Funding sources as identified in the approved ACORPS for each of the six current canine research studies approved by the HHMVAMC IACUC.

(6) The value of recovery or savings: N/A

(7) Name and position of the reviewer: ORO RSAW (Appendix A §II)

f. Allegation 1b(3). *"These incidents have not been reported to the Secretary of the VA as required by law."*

(1) Method(s) used by ORO to review the allegation.

(a) Review of reporting requirements under the Animal Welfare Act, as written in 9 CFR, Chapter I, Subchapter A, Part 2, Subpart C §§ 2.31 and 2.37.

(b) Review of ORO case records and HHMVAMC semi-annual reviews of program for humane care and use of animals and semi-annual reviews of animal facilities and study areas.

(2) Determination by ORO regarding the substance of the allegation.

(a) The allegation is **not substantiated.**

(b) Based on reporting requirements under the law as found in the Animal Welfare Act (AWA), as written in 9 CFR, Chapter I, Subchapter A, Part 2, Subpart C §§ 2.31[4] and 2.37[5], no events occurred that were reportable to the Secretary of VA (SECVA). The above cited sections of the AWA demonstrate that only uncorrected significant deficiencies and IACUC suspensions of animal activities must be reported to APHIS (or, in the case of federal research facilities, to the Head of the Agency sponsoring the research based on §2.37); neither of these events occurred at HHMVAMC.[6] ORO notes that although none of the incidents set forth in the allegations were reportable to the SECVA under the AWA, ORO oversight cases including the above incidents are summarized in a monthly report that is provided to VHA leadership. Furthermore,

[4] 9 CFR § 2.31(c)(3) states, in part, that "[a]ny failure to adhere to the plan and schedule that results in a significant deficiency remaining uncorrected shall be reported in writing within 15 business days by the IACUC, through the Institutional Official, to APHIS and any Federal agency funding that activity." Section 2.31 (d)(7) states: "If the IACUC suspends an activity involving animals, the Institutional Official, in consultation with the IACUC, shall review the reasons for suspension, take appropriate corrective action, and report that action with a full explanation to APHIS and any Federal agency funding that activity."

[5] Section 2.37(a) states "The Committee shall report deficiencies to the head of the Federal agency conducting the research rather than to APHIS; and (b) The head of the Federal agency conducting the research shall be responsible for all corrective action to be taken at the facility and for the granting of all exceptions to inspection protocol."

[6] The veterinary holds placed in response to the events described under Allegations 1a(1) and 1a(3) were not suspensions imposed by the IACUC, and therefore, were not subject to the reporting requirements of §§2.31 and 2.37.

summaries of these cases are captured in a quarterly and/or annual report sent by the SECVA to the U.S. Congress.

(3) Summary of corrective actions taken and/or required to address and resolve the issues and to prevent a recurrence.

(a) No corrective actions are required.

(4) Timeframe for corrective actions (i.e., completed and/or required).

(a) N/A

(5) Summary of documentation supporting the determination

(a) ORO Case records 652-0017-A, 652-0020-A, and 652-0021-A; HHMVAMC semi-annual program reviews and facility inspections; and the Animal Welfare Act (9 CFR, Chapter I, Subchapter A, Part 2, Subpart C).

(6) The value of recovery or savings: N/A

(7) Name and position of the reviewer: ORO RSAW (Appendix A §II)

g. Allegation 1b(4). *"VAMC lacks tracking records of oversight and mismanagement of experimental failures."*

(1) Method(s) used by ORO to review the allegation.

(a) Review of facility reports to ORO and OLAW/AAALAC, IACUC minutes, research service protocol files, and surgical and medical records.

(b) Interviews with selected staff regarding specific incidents identified in the medical and surgical records.

(2) Determination by ORO regarding the substance of the allegation.

(a) The allegation is **not substantiated.**

(b) The facility maintained and was able to produce for the review team records of adverse events that were reported to ORO and other agencies/organizations. ORO found no evidence that any adverse or other reportable events were received, but not tracked, by the IACUC. ORO did identify a number of other adverse events and protocol violations that had occurred but found no evidence that the IACUC was informed of these incidents so that they could be tracked. (*See* Section IV, Finding 2 and associated footnotes).

(3) Summary of corrective actions taken and/or required to address and resolve the issues and to prevent a recurrence.

(a) No corrective actions are required.

(4) Timeframe for corrective actions (i.e., completed and/or required).

(a) N/A

(5) Summary of documentation supporting the determination

(a) ORO Case records

(b) IACUC minutes, reports to OLAW/AAALAC, ACORPs, and canine records.

(c) Interviews with VMU staff and IACUC members.

(6) The value of recovery or savings: N/A

(7) Name and position of the reviewer: ORO RSAW (Appendix A §II)

h. Allegation 1c. *"The Principal Investigator whose repeated botched surgeries on dogs led to revocation of their experimentation privileges is still listed as an active physician treating veterans at McGuire VAMC."*

ORO did not evaluate this allegation as it was determined, in consultation with OIG, to fall outside the scope of ORO's purview and area of expertise. ORO notes, however, that the complaint submitted to OIG and referred to ORO did not provide any documentation to support a nexus between the adverse events that occurred in the animal research and the competency and clinical skills of the PI with regard to the treatment of human patients.

IV. ADDITIONAL FINDINGS AND REQUIRED ACTIONS

In addition to ORO's findings with regard to the allegations referred by OIG, additional findings of noncompliance indicated below were made in conjunction with ORO's review of the HHMVAMC research studies involving canines. Within 30 days after receipt of this report, HHMVAMC must complete the Remedial Action Plan in the Attachment and return it to the ORO RSAW Team. The plan must include specific remedial actions and timely completion dates for each finding as indicated below.

Reference: ***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.

1. **Provisions for Adequate Veterinary Care.**

   a. **Some animal medical records provided insufficient documentation to demonstrate if dogs with health problems were consistently evaluated by a veterinarian, consistently received appropriate care, or were appropriately observed for signs of health problems.**

      (1) ORO noted that several dogs had surgery-related health issues but animal medical records did not document or inconsistently documented that the dogs were evaluated by a veterinarian to ensure that accurate diagnoses and appropriate treatment plans were developed and followed. In some instances, animal medical records did not contain sufficient details to determine if the animals received appropriate treatment, and treatment outcomes were not consistently documented. Specific examples included:

         i. Dog 5945 (protocol 02235) developed subcutaneous emphysema (air under the skin) following a protocol-related surgery on January 5, 2017. Entries in the medial record, which described an evaluation and a plan to monitor the condition, were made by the Principal Investigator (PI), but did not document whether the VMC was consulted to evaluate the animal or provide guidance regarding diagnosis or treatment.

         ii. Dog 5945 (protocol 02235) also developed poor posture, depressed attitude and an abnormal capillary refill time (>2 seconds) postoperatively on January 26, 2017. The medical record did not document additional postoperative supportive treatments or care, and did not indicate if the VMC was consulted to evaluate the animal or provide guidance regarding diagnosis or treatment.

         iii. Dog 5956 (protocol 02235) developed lethargy, signs of dehydration, and abnormal nasal discharge postoperatively on November 1, 2016. The medical record indicated that supportive care such as intravenous (IV) fluids and antibiotics was provided; however, it did not document whether the VMC was consulted to evaluate the animal or provide guidance regarding diagnosis or treatment.

         iv. Numerous entries in dog veterinary medical records referenced re-suturing incisions, draining seromas or other procedures related to surgical implant complications. Medical records did not consistently document if the VMC

was consulted to evaluate the animals and, in some cases, the records lacked sufficient detail to determine who performed the procedure, what anesthetics/analgesics were provided, or how the wound closure was accomplished.

(2) Animal medical records did not document or inconsistently documented that dogs received appropriate supportive care, including preoperative medications, intraoperative monitoring/support, and observations for signs of health problems.

i. Protocol 02002 stated that the analgesic buprenorphine would be given to dogs as a preoperative medication for surgical procedures. However, this drug was not consistently recorded as preoperative medication in the intraoperative and veterinary medical records, so it was not possible to determine if these were provided to all dogs before each surgery.[7]

ii. Protocol 02232 stated that, "Animals will be covered with blankets and a water warming pad to keep them warm." As part of this protocol, dog 117341 had surgery on March 28, 2017, that lasted for 2.25 hours and on April 11, 2017, for almost two hours; no temperatures were recorded during either surgery. A dog's temperature is normally between 100 and 102.5 degrees F, but approximately 1.5 hours after the April 11 surgery, postoperative records show that the dog's temperature was only 93.6 degrees F. The record showed that the dog's temperature went up to 97 degrees F but never described if the VMC was consulted, what supportive care was provided to treat the hypothermia, and did not document the final outcome or when the animal returned to a normal temperature.

iii. Protocol 02235 described discontinuing gas anesthesia and then using one of two approved injectable anesthetic drug options for an electrophysiology study (EPS); however, medical and surgical records did not consistently contain sufficient detail to determine which anesthetics were used or when they were discontinued/resumed intraoperatively to ensure an adequate plane of anesthesia was maintained. For example, dog 6103 had surgery on March 30, 2017. Surgical records stated, "EPS was performed as per protocol," but did not state which of the two IACUC-approved anesthetic options was utilized and did not indicate when gas anesthesia was discontinued. During part of the surgical procedure, the dog's heart rate went as high as 150 and 162, with previously recorded rates having been between 97 and 120. The record did not describe if the high heart rate was recognized and appropriately managed. High heart

[7] Examples of this are found in surgical records for dogs CELMED, CFEMAL, and CFEMBT.

rate can indicate that an animal is experiencing pain and that the depth of anesthesia is not sufficient or could occur for other reasons related to the study protocol.

iv. Medical records did not demonstrate that animals received sufficient monitoring to ensure that facility personnel would recognize when increased levels of support and monitoring were required or when endpoint criteria were met, as described in the approved ACORPs. For example, Protocol 02002 stated that signs of heart failure could include "weight loss of more than 10%," but records did not indicate whether dogs were weighed on a regular basis. Additionally, the protocol stated that "Blood pressure will be monitored weekly and recorded in the chart," but did not define parameters for normal and abnormal blood pressure, and weekly blood pressures were not contained in the dog records provided.

Reference. *VHA Handbook 1200.07 Appendix D §6.q(1)-(4) specifies the following requirements for surgical records: "(1)Daily postoperative medical records of the animal must be maintained, including an evaluation of overall health, a description of any complications noted, treatment provided, and the removal of sutures, staples, wound clips, or other such devices; (2) Records must document administration of all medications and treatments given to animals, including those given to reduce pain or stress; (3) Daily records must cover the post-operative period as defined by local policy and (4) Each entry in the records must include a signature or the initials of the person making the observation or treatment.*

VHA Handbook 1200.07 Appendix E §2.f(7) states that "[i]ntra- and post-operative surgical records must be maintained on larger non-rodent species in accordance with accepted veterinary practice."

USDA APHIS Policy #3 "Veterinary Care" Date March 14, 2014 states that, "The attending veterinarian is to ensure there is adequate preprocedural and post-procedural care in accordance with established veterinary and medical practices," and that "[a]ppropriate post-operative records should be maintained in accordance with professionally accepted veterinary procedures." It goes on to say that, "Every facility should have a system of health records sufficiently comprehensive to demonstrate the delivery of adequate health care." [Emphasis added.]

Title 9 CFR §2.33(b)(2)-(3), Attending Veterinarian and Adequate Veterinary Care states that "Each research facility shall establish and maintain programs of adequate veterinary care that include: . . . The use of appropriate methods to prevent, control, diagnose, and treat diseases and injuries, and the availability of emergency, weekend, and holiday care; [and] . . . Daily observation of all animals to assess their health and well-being; Provided, however, That daily observation of animals may be accomplished by someone other than the attending veterinarian; and Provided, further, That a mechanism of direct and frequent communication is required so that timely and

accurate information on problems of animal health, behavior, and well-being is conveyed to the attending veterinarian."

Section 2.33(b)(5) also states that the facility must provide "Adequate pre-procedural and post-procedural care in accordance with current established veterinary medical and nursing procedures."

The Guide for the Care and Use of Laboratory Animals (hereafter, "The Guide") (p. 114) states that when animals have recurrent or significant problems "all treatments and outcomes should be documented," and that it is the role of the veterinarian or the veterinarian's designee to "expeditiously assess the animal's condition, treat the animal, investigate an unexpected death, or advise on euthanasia" when emergency veterinary care is needed.

The Guide (p. 115) also states that "Medical records are a key element of the veterinary care program and are considered critical for documenting animal well-being as well as tracking animal care and use at a facility." [Emphasis added.]

Required Action 1.a. The facility must develop and implement a system to ensure that animal veterinary medical records (including records related to the intraoperative and postoperative period) contain sufficient details to document the care provided by the facility, to demonstrate that adequate veterinary care was provided to the animals, and to ensure facility personnel can recognize and respond to changes in the animals' health status.

b. The facility's written Program of Veterinary Care was not consistently being followed.

Finding. Because the facility's VMC was employed on a part-time basis, a written Program of Veterinary Care had been developed as required, but it was not consistently being followed as written. For example, the Program of Veterinary Care stated that all dogs would be treated with a topical anti-parasite treatment and an oral dewormer upon arrival to the animal care facility, and would be tested for heartworm prior to arrival. During interviews, the VMC confirmed that it was his understanding that the Program of Veterinary Care was being followed as written. However, interviews with a technician indicated that anti-parasite treatments were not given and oral dewormers were only administered if loose stools were observed. Furthermore, a review of medical records indicated that dogs were not consistently tested for heartworm prior to acquisition.

The Program of Veterinary Care dated November 2012 was signed by the VMC and the VMU Supervisor, but not by the ACOS for R&D, as required by VHA Handbook 1200.07.

Reference. *Title 9 CFR §2.33(a)(1)-(2), Attending Veterinarian and Adequate Veterinary Care, states that: "Each research facility shall have an attending*

veterinarian who shall provide adequate veterinary care to its animals. . . .In the case of a part-time attending veterinarian or consultant arrangements, the formal arrangements shall include a written program of veterinary care and regularly scheduled visits to the research facility. . . . Each research facility shall assure that the attending veterinarian has appropriate authority to ensure the provision of adequate veterinary care and to oversee the adequacy of other aspects of animal care and use...."

USDA Animal Care Policy #3 (March 14, 2014) also states that "The preventive medical program described in the PVC [Program of Veterinary Care] is expected to be in accordance with professionally accepted veterinary practice (e.g., appropriate vaccinations, diagnostic testing). It should include zoonotic disease prevention measures." It also says that, "Records of visits by the attending veterinarian should be kept to include dates of the visits and comments or recommendations of the attending veterinarian or other veterinarians," and that, "The PVC should be reviewed and updated whenever necessary (e.g., as a new species of animal or a new attending veterinarian is obtained, or the preventive medical program changes)."

VHA Handbook 1200.07 §6.b(8)(b) states that "A written plan of providing adequate veterinary care to laboratory animals must be developed and approved by the VMC and ACOS for R&D. This plan must include the frequency of visits, provisions for after hours, weekend, and holiday veterinary coverage, and the VMC's role in VMU operations, as well as IACUC participation. A copy of this plan must be maintained locally, and be provided to the CVMO upon request."

Required Action 1.b. The facility must ensure that the Program of Veterinary Care is implemented as written and updated when changes are necessary. The ACOS for Research and Development and the VMC must develop and approve a comprehensive written Program of Veterinary Care.

2. IACUC Oversight of Animal Activities.

a. In several instances, the IACUC did not ensure that procedures performed were consistent with the procedures described in approved protocols.

Finding. A review of approved ACORPs involving dogs revealed that, in some cases, actual practices deviated from approved procedures. Specific examples include:

(1) Protocol 02235 indicated that a nonsteroidal anti-inflammatory drug (NSAID), Rimadyl©, would be given to dogs for seven days after each survival surgery. However, this dosing was not consistently followed. For example, dog #6103 had survival thoracotomies and although some analgesics were provided for the first 7 days, Rimadyl© (or alternate NSAID) was not provided as described in the protocol. When asked, facility personnel stated that the medication was discontinued prior to seven days based on observations (lack of signs of discomfort/pain) rather than following the description in the approved

protocol.[8]

(2) Protocol 02002 stated that a warming pad would be used during surgery as well as additional "warming blankets placed over non-exposed[9] areas during surgery." Although facility personnel verified the use of a warming pad under the dogs to maintain intraoperative temperatures, they stated that warming blankets were not being placed over "non-exposed" areas (such as lower abdomen and legs) during surgery.

(3) Protocol 02243 stated that pulmonary fistulas were "a possible injury that could occur during surgery, due to the close proximity to the lungs. If this occurs, the animal will be monitored hourly for 24 hours. Blood pressure and pulse oximetry will be recorded hourly. If the animal shows any signs of respiratory distress and vitals decline, the animal will be euthanized via a fatal pentobarbital injection." Dog 108287 on this protocol developed a bronchopleural fistula with subcutaneous emphysema, according to a veterinary medical record entry dated September 28, 2016. The record showed entries approximately hourly for the first 12 hours but not for 24 hours as described in protocol.

(4) Protocol 02243 stated that during surgeries, "Heart rate, blood pressure, and temperature are monitored and recorded every 15 minutes for the duration of this procedure." Dog 984370 had a surgery on this protocol on April 4, 2017, that lasted approximately 5 hours. Only one temperature was recorded during the entire procedure.

(5) When describing endpoints, Protocol 02243 stated that "weekly weights will be recorded. If there is more than a 4% change in weight noted in the animals, weights will be recorded daily." Additionally, the protocol stated that weight loss of more than 10% would be considered as one of several potential signs of heart failure that would require immediate notification of the veterinarian and that this notification would be noted in the chart. Dog 108287 did not have weekly weights in her chart. She had the following weights recorded: September 28, 2016 (date of first surgical study intervention): 18 kg (39.6 pounds); September 29, 2016: 39 pounds; October 4, 2016: 38 pounds; and February 15, 2017 (date of terminal surgery): 16.1 kg (35.49 pounds). From the first study surgery to final surgery the dog lost 10.56% of her weight. Weekly weights were not recorded, so personnel were unable to recognize when the 4% weight loss criterion was met to provide increased monitoring or when the

[8] In addition, this protocol deviation was not reported to the IACUC pursuant to the reporting requirements of the local IACUC SOP.

[9] "Non-exposed" refers to parts of the animals that were covered by a lightweight surgical drape.

dog lost 10% of its weight which required notification of the veterinarian.

b. In several instances, the IACUC did not ensure that modifications to active protocols were approved prior to initiation by the PIs.

Finding. Document review and interviews with key personnel revealed that some new procedures were implemented prior to IACUC review and approval. Specifically, the IACUC did not ensure that significant changes to active protocols received final approval prior to implementation. Specific examples included:

(1) Protocol 02243 described the use of a drug (amiodarone) administered as an intravenous bolus perioperatively. However, interviews with key personnel revealed that several animals had been dosed orally with this medication for multiple days prior to surgery. This discrepancy was self-identified and the PI was working with the IACUC to submit an amendment to include oral dosing of the medication in the approved protocol.[10]

(2) Protocol 02002 described the use of an injectable anesthetic (pentobarbital) only for initiation of anesthesia (i.e., induction), followed by an inhaled agent (isoflurane) used for maintenance of anesthesia. However, on December 1, 2015, one animal (CELMED) underwent a surgical procedure, during which inhalant anesthesia was discontinued and replaced with the injectable drug to maintain surgical level of anesthesia (i.e., the PI used the pentobarbital for both induction and maintenance), which was not approved. This unapproved change, which was made for study-related purposes rather than for purposes of addressing emergent animal health or welfare issues, led to complications in postoperative recovery.

(3) Protocol 01549 described pharmacological challenges that included multiple drugs (i.e., clonidine, adenosine, hydralazine, nitroglycerin, phenylephrine, and atropine). However, the review of several medical records revealed use of an additional drug (isoproterenol) that was not listed in the protocol. ORO was unable to locate an amendment adding this compound to the approved protocol. Examples of use of the drug isoproterenol in protocol 01549 can be found in records for dogs 962791, 963054, 963577, and 964298.[11]

Reference. *Per the Guide (p. 25), 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; regular inspection of facilities and animal use areas; regular review of the Program; ongoing assessment of animal care and use; and establishment of a mechanism*

[10] In addition, this failure to secure approval for a significant protocol change prior to implementation of the change was not reported to the IACUC pursuant to the reporting requirements of the local IACUC SOP.
[11] *See* footnote above.

for receipt and review of concerns involving the care and use of animals at the institution."

PHS Policy, Section IV.B.7 states that 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. . . ." Further, Section IV.C.1 of the Policy states: "In order to approve proposed research projects or proposed significant changes in ongoing research projects, the IACUC shall conduct a review of those components related to the care and use of animals and determine that the proposed research projects are in accordance with [PHS] Policy. In making this determination, the IACUC shall confirm that the research project will be conducted in accordance with the Animal Welfare Act 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."

Title 9 CFR §2.31(d)(1) states that "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 justifications for a departure is presented in writing. . . ."

VHA Handbook 1200.07 §8.f(2) states that "All research projects involving animals must be approved by the IACUC and then by the R&D Committee prior to commencement." Further, Appendix E, §2a(2)(j) states that the IACUC 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."

As a result, there is an expectation that the IACUC will ensure that the procedures conducted in the laboratory or animal housing areas are congruent with those described in the approved protocol.

Required Action 2. The IACUC must ensure that protocols are conducted as approved and that proposed modifications to animal research protocols are approved prior to implementation.

3. IACUC Protocol Review Criteria

a. The IACUC did not consistently ensure that approved protocols included complete descriptions of research activities.

Finding. A review of approved ACORPs involving dogs revealed several instances of incomplete or confusing descriptions of procedures and narratives that did not contain enough details to ensure adequate review and approval. Specific examples included:

(1) Protocol 02232 described myocardial biopsy procedures by stating that percutaneous myocardial biopsies would be performed under fluoroscopy to obtain 8 – 10 samples (1gm) from LV septum and free wall through a femoral approach. It is unclear from this description whether 1 gram of tissue will be

obtained from each biopsy, whether this amount is the total expected to be collected, or whether it is the maximum permitted to be collected. Interviews with laboratory staff clarified that the amount of tissue actually collected in each biopsy was significantly lower than what is ambiguously described in the approved protocol.

(2) Protocol 02002 described "weight loss of more than 10%" as an endpoint criterion. However, the protocol did not describe the frequency with which weighing should occur in order to assess the criterion. In addition, the approved protocol stated that blood pressure will be monitored weekly and recorded in a chart, but did not give the normal parameters expected.

(3) Protocol 02002, section W.4 of the ACORP, did not adequately address refinement methods or provide an explanation on the feasibility of refinements. Instead, the protocol merely described the PI's experience with the animal model and the new components of the study being incorporated.

(4) Protocols 02232 and 01549, in ACORP Appendix 5 section 6.a, listed a paralytic drug (succinylcholine); however, justifications and descriptions of how animals would be monitored to ensure maintenance of an adequate plane of anesthesia during surgery were not included.

(5) Protocol 01946, ACORP Appendix 3, provided a list of pharmaceuticals with source and dose information. A paralytic drug (succinylcholine) was listed in both sections 1 and 2 (tables), with a dose noted as 0.0 mg/kg. The dose of succinylcholine was also located in section 6.a. of Appendix 5 and was listed with a dose of 0.07 mg/kg. These discrepancies within the protocol raise concerns about whether the IACUC actually evaluated whether medication dosing was appropriate.

In addition, ACORP Appendix 3, section 6.b, described that "body temperatures will be maintained at 38-39F." Normal body temperature for a dog is approximately 100 to 102.5 degrees F. This typographical error was apparently not recognized by the IACUC and not corrected in the approved protocol.

(6) Protocols 02002, 02235, and 02243 inconsistently described the required doses of a drug (Brevital), with references to 200-300mg/kg in some sections and 6-10 mg/kg in others. The high doses referenced in the protocol are incorrect and appear to be editing errors in the text of the protocols that were not identified and corrected during the protocol review process. These discrepancies within the protocol raise concerns about whether the IACUC actually evaluated whether medication dosing was appropriate.

Reference. *The Guide (p. 25) states that 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; regular inspection of facilities and animal use areas; regular review of the Program; ongoing assessment of animal care and use; and establishment of a mechanism for receipt and review of concerns involving the care and use of animals at the institution." Pages 25-33 of the Guide (p.24-26), describe the IACUC's responsibilities and considerations that the IACUC should consider in the review of research including "impact of the proposed procedures on the animals' well-being . . . appropriate sedation, analgesia, and anesthesia . . . conduct of surgical procedures . . . postprocedural care and observation . . . description and rationale for anticipated or selected endpoints . . . ."

PHS Policy, Section IV.B.7 states that 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. . . ." Further, Section IV.C.1 of the Policy states: "In order to approve proposed research projects or proposed significant changes in ongoing research projects, the IACUC shall conduct a review of those components related to the care and use of animals and determine that the proposed research projects are in accordance with [PHS] Policy. In making this determination, the IACUC shall confirm that the research project will be conducted in accordance with the Animal Welfare Act 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."

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

Title 9 CFR §2.31(d)(1) states that "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 justifications for a departure is presented in writing....."

Required Action 3.a. The IACUC must ensure that procedures described in approved protocols are clearly written and complete.

b. The IACUC did not consistently ensure that complete justifications were provided for unrelieved pain or distress.

Finding. A review of approved ACORPs involving dogs revealed two protocols (02002 and 01549) that did not include all required information for scientific justifications for unrelieved pain and distress (i.e., USDA pain Category E). Specifically, section K of the ACORP titled, "Justification of Category E procedures," (1) did not state what pain and/or distress was expected; (2) did not state why the pain and/or distress could not be relieved (i.e., how the analgesics/sedatives could interfere with outcome); (3) did not state which analgesic/sedatives were considered and found to be inappropriate

for the study; and (4) did not provide an assurance that the unrelieved pain and/or distress continue for only the time necessary or a description of the expected duration.

Reference. *VHA Handbook 1200.07 Appendix D§1.i(2), indicates that the ACORP must "[d]escribe each USDA Category E procedure, justify completely why pain or distress relief cannot be provided."*

PHS Policy, Section IV.C.1.b states that "[p]rocedures that may cause more than momentary or slight pain or distress to animals will be performed with appropriate sedation, analgesia, or anesthesia, unless the procedure is justified for scientific reasons in writing by the investigator."

The Guide (p.5) states that "[s]tudies that may result in severe or chronic pain or significant alterations in the animals' ability to maintain normal physiology, or adequately respond to stressors, should include descriptions of appropriate humane endpoints or provide science-based justification for not using a particular, commonly accepted humane endpoint."

Title 9 CFR §2.31(d)(1)(iv)(A) states that "[p]rocedures that may cause more than momentary or slight pain or distress to the animals will: (A) Be performed with appropriate sedatives, analgesics or anesthetics, unless withholding such agents is justified for scientific reasons, in writing, by the principal investigator and will continue for only the necessary period of time."

USDA APHIS Animal Care Policy #12 (March 25, 2011), titled "Consideration of Alternatives to Painful/Distressful Procedures," states that "[a]nimals exhibiting signs of pain, discomfort, or distress such as weight loss, decreased appetite, abnormal activity level, adverse reactions to touching inoculated areas, open sores/necrotic skin lesions, abscesses, lameness, conjunctivitis, corneal edema, and photophobia are expected to receive appropriate relief unless written scientific justification is provided in the animal activity proposal and approved by the IACUC."

Required Action 3.b. The IACUC must ensure that all proposed research interventions involving unrelieved pain or distress are appropriately justified, adequately described and contain all required information.

c. The IACUC did not consistently ensure that the use of non-pharmaceutical grade substances were adequately described and scientifically justified in approved protocols.

Finding. The use of non-pharmaceutical grade compounds in animals must be scientifically justified and include an evaluation of relevant animal welfare and scientific considerations. A review of approved ACORPs involving dogs revealed that non-pharmaceutical grade compounds were used in several ACORPs; however, some descriptions lacked key information. Specific examples included:

(1) In Protocol 02002, the PI stated that all formulations used were pharmaceutical grade, and therefore did not include a scientific justification or evaluation of animal welfare and scientific considerations for their use; however, the ACORP Appendix 3 section 1, identified Sigma© as the commercial source for a compound, chloralose, which appeared to be a non-pharmaceutical grade compound.

(2) Protocols 01549 and 02232 also listed the same compound (chloralose) as purchased through Sigma,© but acknowledged that the chemical was considered a non-pharmaceutical grade substance. In the justification section, the protocols described preparation of the compound (i.e., dissolved in sterile sodium chloride solution and filtered), but no other details were provided regarding scientific justifiability.[12]

Reference. *The Guide (p. 31) states that the "[t]he use of pharmaceutical-grade chemicals and other substances ensures that toxic or unwanted side effects are not introduced into studies conducted with experimental animals. They should therefore be used, when available, for all animal-related procedures . . . . 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 addition, USDA APHIS Animal Care Policy #3 (March 14, 2014), titled "Veterinary Care," states that "[p]harmaceutical-grade substances are expected to be used whenever available, even in acute procedures" and that "[n]on-pharmaceutical-grade substances should only be used in regulated animals after specific review and approval by the IACUC. The IACUC should develop a consistent evaluation process which includes but is not limited to the scientific justification and the availability of an acceptable veterinary or human pharmaceutical-grade product."

In OLAW PHS Policy FAQ F.4. "May investigators use non-pharmaceutical-grade substances in animals?" OLAW states that, "Investigators and IACUCs should consider relevant animal welfare and scientific issues including safety, efficacy, availability of pharmaceutical-grade substances, and the inadvertent introduction of new variables."

Required Action 3.c. The IACUC must ensure that the use of non-pharmaceutical grade compounds is adequately described and scientifically justified in approved protocols.

4. Recordkeeping Practices and Requirements

a. Disposition records for dogs were inaccurate or contained conflicting information.

[12] In addition, Protocols 01946 and 02243 also listed chloralose as a substance to be administered to animals. However, the protocol did not establish the source of the compound and consequently, ORO could not determine if the formulation was pharmaceutical grade.

Finding. ORO reviewed facility records of dog acquisitions and dispositions, including "Canine Admission" forms and the facility "Dog Log." In some cases disposition records contained inaccurate or conflicting information. For example, the "Canine admissions" form listed dog 869201 as euthanized on October 13, 2015, but the "Dog Log" listed the date as November 13, 2014.

Additionally, the "Canine admissions" form had a column labeled "Date Euth." According to records reviewed, dogs 5708 and CFDMAV were not euthanized but instead died from other causes. Nonetheless, the dates of death were recorded in the "Date Euth" column. Furthermore, interviews with facility staff indicated that their system for recording the final disposition of dogs did not distinguish between whether dogs were euthanized or died of other causes.

Reference. *Title 9 CFR §2.35 - Recordkeeping requirements. "Every research facility shall make, keep, and maintain records or forms which fully and correctly disclose the following information concerning each live dog or cat purchased or otherwise acquired, owned, held, or otherwise in their possession or under their control, transported, euthanized, sold, or otherwise disposed of by the research facility . . . : [and] [the] date of transportation, sale, euthanasia, or other disposition of the animal...."*

Required Action 4.a. The facility must make and keep records for dogs that fully and correctly disclose all required information.

b. USDA Annual Reports for animal usage in fiscal years 2016, 2015, and 2014 were not accurate.

Finding. A review of facility records related to the care and use of dogs shows that animal usage was underreported to USDA. During the course of this review, ORO learned that in December 2016, in consultation with the Office of Research and Development (ORD), a member of the facility research staff self-identified that their methods for tracking and reporting animal usage was incorrect.

It appears that the facility misunderstood appropriate reporting practices and did not intentionally misrepresent animal numbers (e.g., if a dog was present in multiple years it appears it was only reported once rather than in each year it was present). ORO only reviewed records related to fiscal years 2014, 2015 and 2016.

Specifically, acquisition/disposition, veterinary medical, and study records reviewed by ORO from fiscal year 2016 showed that 34 dogs were present at the facility (31 of which were used for research). The facility's USDA annual report for this time period only listed 29 dogs (23 of which were used for research). Additionally, no dogs were listed by the facility in Column C[13], but records for the reporting period appear to

[13] Column C includes animals used in research; no pain involved; no pain drugs administered.

show that three dogs were in fact used in research involving no pain or distress during this time period.

Records reviewed by ORO from fiscal year 2015 showed that 39 dogs were present at the facility, all of which were used for research. The facility's USDA annual report for this time period only listed 22 dogs used for research. Additionally, no dogs were reported in Column C, but records appear to show at least one animal that should have been reported under that Column.

Records reviewed by ORO from fiscal year 2014 showed that 39 dogs were present at the facility (34 of which were used for research). The facility's USDA annual report for this time period only listed 31 dogs (25 of which were used for research). Although that report lists 6 dogs as being held but not used for research, ORO's review of records shows that only 5 were held but not used for research; during the reporting period, one of the dogs acquired at the very end of the fiscal year, and likely included in Column B[14], had a survival surgery on the last day of the reporting period and should have been reported in Column D[15] instead.

Reference. *Title 9 CFR §2.36(b)(5)-(8): - Annual report. "The annual report shall: . . . (5) State the common names and the numbers of animals upon which teaching, research, experiments, or tests were conducted involving no pain, distress, or use of pain-relieving drugs. Routine procedures (e.g., injections, tattooing, blood sampling) should be reported with this group; (6) State the common names and the numbers of animals upon which experiments, teaching, research, surgery, or tests were conducted involving accompanying pain or distress to the animals and for which appropriate anesthetic, analgesic, or tranquilizing drugs were used; (7) State the common names and the numbers of animals upon which teaching, experiments, research, surgery, or tests were conducted involving accompanying pain or distress to the animals and for which the use of appropriate anesthetic, analgesic, or tranquilizing drugs would have adversely affected the procedures, results, or interpretation of the teaching, research, experiments, surgery, or tests. An explanation of the procedures producing pain or distress in these animals and the reasons such drugs were not used shall be attached to the annual report; (8) State the common names and the numbers of animals being bred, conditioned, or held for use in teaching, testing, experiments, research, or surgery but not yet used for such purposes."*

VHA Handbook 1200.07 §6.b(5)(i) also describes the duties of the VMC to include "Drafting or reviewing regulatory documents required for compliance with applicable regulations, guidelines, and policies. This includes AAALAC Program Descriptions, PHS Assurance documents, USDA Annual Reports (to be signed by the IO), and annual VA

[14] Column B includes animals held by a facility but not used in any research that year.
[15] Column D includes animals used in research; pain involved; pain drugs administered.

VMU reports."

Required Action 4.b. The facility must develop a system to effectively track animal usage to ensure that USDA Annual Reports fully and accurately list the numbers of covered animals used or held for research, teaching or testing and that these animals are reported in the appropriate columns reflecting the nature of their use during the applicable reporting period. The facility must review their animal records and issue amended annual reports that fully and accurately list animal usage for fiscal years 2016, 2015, and 2014. In accordance with VHA Handbook 1200.07 *§6.b(5)(i)*, the VMC must either draft or review USDA annual reports for compliance with applicable regulations, guidelines, and policies.

c. **VA VMU Reports did not accurately report animal usage for fiscal years 2016, 2015, and 2014.**

Finding. A review of facility records related to the care and use of dogs shows that animal usage was not reported accurately on VA VMU reports.

Specifically, acquisition/disposition, veterinary medical, and study records reviewed by ORO from fiscal year 2016 showed that 34 dogs were present at the facility (31 of which were used for research). The facility's VA VMU report for this time period only listed 29 dogs (23 of which were used for research).

Records reviewed by ORO from fiscal year 2015 showed that 39 dogs were present at the facility, all of which were used for research. The facility's VA VMU report for this time period only listed 28 dogs used for research.

Records reviewed by ORO from fiscal year 2014 showed that 39 dogs were present at the facility (34 of which were used for research). The facility's VA VMU report for this time period only listed 31 dogs (25 of which were used for research).

Reference. *VHA Handbook 1200.07 §8.l(4), Annual VA VMU Report, states that "An annual VA VMU Report for the previous fiscal year must be completed using the Web site designed for that purpose by January 15. In contrast to the USDA Annual Report of Research Facility, all animal species used must be included in the Annual VMU Report. Instructions for properly completing this report can be obtained from the CVMO."*

Additionally, VHA Handbook 1200.07 §6.b(5)(i) describes the duties of the VMC to include "Drafting or reviewing regulatory documents required for compliance with applicable regulations, guidelines, and policies. This includes AAALAC Program Descriptions, PHS Assurance documents, USDA Annual Reports (to be signed by the IO), and annual VA VMU reports."

Required Action 4.c. The facility must develop a system to effectively track animal usage to ensure that VA VMU Reports fully and accurately list animal usage during the applicable reporting period. In accordance with VHA Handbook 1200.07

***§6.b(5)(i)*, the VMC must either draft or review VA VMU Reports for compliance with applicable regulations, guidelines, and policies.**

5. **Additional regulatory findings were identified during animal facility inspections.**[16]

   The nature and location of regulatory and policy deficiencies identified during the animal facility inspections are provided in Appendix C.

   Required Action 5. Deficiencies identified during animal facility inspections, as listed in Appendix C, must be appropriately remediated.

V. SUGGESTIONS

ORO would like to offer the following suggestions for the HHMVAMC. Suggestions are offered to further enhance the HHMVAMC's ACUP and implementation is voluntary. HHMVAMC should consider the potential value of each suggestion prior to adoption.

1. The facility should evaluate whether current levels of veterinary staffing and support are adequate, given the number and species of animals used for research each year, the complexity of the research models being used, and in light of the series of adverse events that have occurred with the dog studies. During fiscal year 2016, the facility had 34 dogs and reported 2,439 mice and 172 rats. As noted in this report, several protocols involving the use of dogs were approved that included multiple major survival surgical procedures (thoracotomies), chronic instrumentation, and procedures with unrelieved pain and distress. At the time of ORO's site visit, the VMC stated he visited the facility approximately once a week at the end of the day for 20 to 60 minutes after completing duties at the affiliate university and was also available via telephone, email, and text at times when he was not on-site. Additionally, he stated he was occasionally able to make brief visits to HHMVAMC during the day. In addition to providing consultant services to HHMVAMC, the VMC worked full time at the affiliate university and provided part-time consultant services for four other facilities. At the time of the site visit, HHMVAMC did not employ any other veterinarians or veterinary technicians dedicated to the provision of veterinary care to the animals.

   While the VMC should be available for visits at intervals appropriate to programmatic needs[17], supplemental visits, both scheduled or unscheduled, must be arranged as required to ensure provision of adequate veterinary medical care.[18] Alternatively,

[16] Appendix C contains deficiencies that represent both regulatory noncompliance (Findings), as well as suggestions for best practices (Suggestions). Findings require remediation, whereas suggestions are offered to further enhance the program and their implementation is voluntary.
[17] The Guide for the Care and Use of Laboratory Animals 8th ed. (The Guide) (p.14)
[18] VHA Handbook 1200.07 §6.b(8)(a)

institutions may consider the use of veterinary staff and/or animal health technicians to observe increased risk procedures for adverse events.[19]

2. The facility's whistleblower policy did not include all elements as specified in the *Guide*.[20] The local policy for reporting animal care concerns and/or allegations of improper animal care and use (i.e., whistleblower policy) was displayed in the VMU. The policy included provisions to protect and maintain the confidentiality of individuals reporting animal care concerns or allegations of improper animal care and use and stated that reports could be submitted anonymously. However, the procedure did not include specific instructions on how to anonymously report concerns. In addition, although there were options to report concerns to individuals associated with the IACUC and/or ACUP, the Institutional Official (i.e., the Medical Center Director) or other senior management was not specifically listed as an additional point of contact. The IACUC should review the policy and revise, if and as deemed appropriate, to address the aforementioned issues.

3. IACUC Membership:

   a. The facility should consider regular rotation and appointment of new individuals to the IACUC and to serve as the IACUC Chair. For example, the current IACUC Chair (as well as several other members) has served on the committee for approximately 15 years. While there is no limit to the number of times a chairperson (or other members) may be reappointed, it is a best practice to rotate the Chairperson position to develop a cadre of research staff with experience in filling that role.[21]

   b. The IACUC should consider using IACUC participation as a training opportunity for researchers and staff at the facility. Participation could be achieved by increasing the number of committee members and adding alternate members.

   c. The IACUC should consider using *ad hoc* consultants to assist with the review of protocols that include novel procedures in their developmental stages, development of new animal models, and other complex studies for which refinement techniques may be available.

4. IACUC member appointment letters provided to ORO for review did not designate membership positions. The future appointment letters should be revised to specify membership status (i.e., full or alternate), membership category (i.e., non-scientist, non-affiliated, etc.), voting privileges (i.e., voting or nonvoting), and designation as a liaison to

[19] The Guide (p.34)

[20] Specifically, page 24 of the Guide states that *"[m]echanisms 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, compliance with applicable whistleblower policies, nondiscrimination against the concerned/reporting party, and protection from reprisals."*

[21] VHA Handbook 1200.07 §8.a(7)(a)

another committee (R&DC, SRS, etc.).

5. Protocols should consistently list all potentially painful or distressful procedures in section W of the ACORP titled, "Consideration of Alternatives and Prevention of Unnecessary Duplication." The inclusion of all relevant procedures and key words for procedures and key words is essential for a comprehensive alternatives search, as it could reveal refined techniques to improve proposed research activities.[22] For example, on Protocol 01946 that includes a nonsurvivable thoracotomy surgery, the PI listed "intravenous line placement at the beginning of the protocol" as the only potentially painful or distressing procedure in section W.1 (a procedure that is not considered painful or distressful). This section of the ACORP did not mention any other manipulations that would be considered painful or distressful or include them in the database searches.

6. The IACUC should review current procedures for maintaining version control of protocols, to ensure that the version being utilized is in fact the final approved version. For example, interviews with key personnel revealed that Protocol 02002 had been modified through an amendment in 2016 to remove language describing the use of paralytics during surgeries. However, the protocol released via the Freedom of Information Act (FOIA) process in January 2017 and the version initially provided to ORO for review still listed paralytics as an approved drug.

7. ORO understands that the program has been working on improving techniques to minimize the risk of perioperative hypothermia. We encourage the program to seek alternatives and/or supplements to the equipment currently used, such as commercially available forced-air warming devices for temperature support.

8. Dogs at the facility are instrumented and, at times, have multiple incision sites. During ORO's site visit, dogs could only rest on the elevated coated metal floor surface. Providing alternative, soft resting surfaces and/or bedding for the animals may improve their comfort and welfare.

9. As a means to enhance communications between the VMC and the IACUC, the IACUC should consider adding reports from the VMC as a standing agenda item to the meeting minutes. Information for these reports should include summaries of ongoing treatment interventions, veterinary consults performed, and relevant information regarding complications involving approved protocol procedures.

10. The facility should evaluate the efficiency of their current system of record keeping for dogs. Two handwritten record keeping systems are currently being utilized: the "Dog Log" and "Canine admissions" form. Handwritten records can inherently be challenging to utilize and often contain inadvertent errors due to handwriting difficulties or data entry errors. For example, the identification number listed on facility records for two dogs did

[22] VHA Handbook 1200.07 Appendix D §1.v; USDA APHIS Animal Care Policy #11 and #12 (March 25, 2011)

not match the number on the vendor records. Vendor records for a dog showed tattoo 954691, but this dog was listed as 954697 on the "Canine admissions" form. Vendor records for another dog showed tattoo number CELMCM but the "Dog Log" listed her as "celmch" and the "Canine admissions" form listed her as "CELMCH".

Use of APHIS Form 7002 "Record of Acquisition of Dogs and Cats on Hand" is optional for research facilities but may be a useful resource for the facility. It is available on the USDA APHIS website[23] as a fillable PDF.

VI. CONCLUSIONS

With regard to the specific allegations referred by OIG, ORO was able to substantiate or partially substantiate aspects of those allegations constituting animal welfare concerns. These aspects included inappropriate administration of a sedative, a failure to provide postoperative care, and the occurrence of unanticipated surgical complications. However, ORO also ascertained that after each of these incidents, which had been previously self-identified and appropriately reported by HHMVAMC personnel, the local IACUC implemented progressive corrective actions to address the concerns, including ultimately suspending the privileges of the Principal Investigator to conduct animal research. ORO did not substantiate the remainder of the allegations referred by OIG. In addition to the findings made with regard to the allegations referred by OIG, ORO made a number of additional findings, including findings pertaining to: lack of documentation to establish if animals were appropriately evaluated and received supportive veterinary care; non-adherence to provisions of the facility's written Program of Veterinary Care; deviations from approved study procedures and implementation of changes to studies without prior IACUC approval; and deficient reporting and recordkeeping practices related to animal usage and disposition.

Within 30 days of receipt of this report, HHMVAMC will be required to develop a remedial action plan specifying actions that will be taken to address the findings in this report. HHMVAMC has notified ORO that a number of corrective actions have already been initiated that will address the findings contained in this report.

[23] www.aphis.usda.gov/animalwelfare

OFFICE OF RESEARCH OVERSIGHT

James M. Trout

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May 30, 2017
Date