OFFICE OF RESEARCH OVERSIGHT

FOCUSED REVIEW REPORT

Animal Care and Use Program

Robley Rex VA Medical Center
Louisville, Kentucky

May 18, 2020

Veterans Health Administration

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ORO FOCUSED REVIEW REPORT

Robley Rex VA Medical Center
Louisville, Kentucky

On-Site Review Dates: February 25-27, 2020
Date of Report: May 18, 2020

EXECUTIVE SUMMARY

The Office of Research Oversight (ORO), Veterans Health Administration (VHA), conducted an on-site Focused Review of the Animal Care and Use Program (ACUP) at Robley Rex VA Medical Center (RRVAMC) on February 25 to 27, 2020. Specifically, the review evaluated VA research involving felines and related Institutional Animal Care and Use Committee (IACUC) operations. ORO identified issues that will need to be remediated to come into compliance with applicable laws, regulations, and/or policies pertaining to the review, conduct and/or oversight of research. Identified noncompliance included, but was not limited to: protocol noncompliance was identified in one protocol, IACUC-approved departures from regulatory requirements for cat primary enclosures were not included in semi-annual reports to the VA facility Director, the IACUC did not ensure that an animal research protocol received timely triennial review and approval, and the IACUC did not follow requirements for reviewing and reporting animal research noncompliance. All identified noncompliance must be addressed in a Remedial Action Plan that will be monitored by ORO until satisfied.

I. INTRODUCTION and REVIEW FOCUS

The Office of Research Oversight (ORO), Veterans Health Administration (VHA), reports to the Under Secretary for Health and oversees Department of Veterans Affairs (VA) research program compliance with respect to human subject protections, laboratory animal welfare, research safety and laboratory security, research information security, and research misconduct. ORO is also responsible for conducting education programs for facility Research Compliance Officers (RCOs).

ORO conducts Focused Reviews to assist facilities in complying with VA and other Federal requirements for research, especially in areas that may be of special concern at individual facilities or across the VHA research system as a whole. ORO's decision to conduct a Focused Review, and the scope of said review, are guided by: the size and/or complexity of a facility's research portfolio; specific issues of concern identified by ORO in an earlier Combined Program Review (CPR) or through other mechanisms (e.g., Facility Director's Certification, reports of

noncompliance, etc.); known VHA-wide research compliance issues that might also be of relevance at a given facility; and/or other factors.

ORO conducted an on-site, focused compliance review of the Animal Care and Use Program (ACUP) at Robley Rex VA Medical Center (RRVAMC) on February 25-27, 2020. ORO's review at RRVAMC focused primarily on evaluation of VA research involving felines and related Institutional Animal Care and Use Committee (IACUC) operations.

II. METHOD OF REVIEW

ORO's review of RRVAMC included individual and group interviews of facility leadership, research administrative staff, research oversight committee members and staff, researchers, and/or other personnel associated with the facility's research program (Appendix A). ORO's review evaluated facility research policies, procedures, protocols,[1] memoranda of understanding (MOUs), and related documentation. ORO also conducted a physical inspection of feline housing, surgical and procedural areas.[2]

III. FACILITY RESEARCH PROGRAM OVERVIEW

RRVAMC is a complexity level 1b acute care and tertiary referral facility academically affiliated with the University of Louisville (UL). It operates a research program involving human subjects, laboratory animals, and hazardous agents, with a research project (direct cost) budget of $1,852,530.00 in FY19,[3] of which $1,102,379.00 was provided by the VHA Office of Research and Development (ORD). Clinical Research Foundation, Inc. provides a flexible funding mechanism for non-VA sponsored research at RRVAMC.

At the time of ORO's review, there were two active feline research protocols conducted by a single principal investigator (PI) studying spinal cord injury and novel rehabilitation strategies for muscle function to support recovery of walking.

RRVAMC maintains its own Research and Development Committee (R&DC), IACUC,[4] and Subcommittee on Research Safety (SRS). RRVAMC has executed an MOU with UL for collaborative animal research.

RRVAMC has a current Public Health Service (PHS) Animal Welfare Assurance D-16-00777 (A45310-01) expiring February 28, 2023, on file with the National Institutes of Health – Office of Laboratory Animal Welfare (NIH-OLAW); holds full accreditation with the Association for the Assessment and Accreditation of Laboratory Animal Care, International (AAALAC; Unit No. 094); and is registered with the U.S. Department of Agriculture – Animal and Plant Health Inspection

[1] The corresponding titles for protocols referenced by numerical identifiers in the Findings and Observations in this report are provided in Appendix B.
[2] Feline housing, surgical and procedural areas were located off-site, at the affiliate university.
[3] Data from the facility's filed Research and Development Information System (RDIS) report
[4] Locally referred to as the Research Animal Studies Subcommittee (RASS)

Service (USDA-APHIS; Registration No. 61-V-0002). All RRVAMC feline research takes place at UL, under a separate PHS Animal Welfare Assurance; UL holds full accreditation with AAALAC and is registered with USDA-APHIS.

IV. FINDINGS, REFERENCES, and REQUIRED ACTIONS

The following items describe findings of noncompliance identified in ORO's review. Within 30 days after receipt of this report, RRVAMC must complete the applicable sections of the attached Remedial Action Plan and submit it to ORO as instructed. The plan must include specific remedial actions and timely completion dates for each Finding, as indicated at VHA Handbook 1058.01 §5.c.

1. **Two instances of protocol noncompliance were identified.**

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

   - Protocol #435-0002 described administration of penicillin G benzathine at 100,000 IU/kg pre- or peri-operatively for ovariohysterectomy (OHE) surgeries; however, review of select animal surgical records revealed that only 40,000 IU/kg penicillin G benzathine was administered peri-operatively for OHE surgeries for animals #19009, #19008, #16039, #18033 and #16120.
   - Protocol #435-0002 described administration of acetylpromazine pre-operatively for OHE surgery in §J, Appendix 3, and Appendix 5 of the Animal Component of Research Protocol (ACORP); however, review of selected animal surgical records revealed that acetylpromazine was not administered prior to OHE surgeries for animals #19009, #19008, #16039, #18033 and #16120. Although the PI had amended the affiliate protocol to remove this requirement and permit substitution with another drug, this change had not been incorporated into the VA IACUC approved ACORP.

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

[5] Accessible at: https://olaw.nih.gov/guidance/faqs (last ORO access on April 6, 2020)

Public Health Service Policy on Humane Care and Use of Laboratory Animals (PHS Policy) §IV.B.7.[6] ***"Functions of the Institutional Animal Care and Use Committee.*** [T]he IACUC shall … review and approve, require modifications in (to secure approval), or withhold approval of proposed significant changes regarding the use of animals in ongoing activities."

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

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

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

VHA Directive 1200.02(1) §§14.a(2) and (9). "Specific responsibilities [of VA Investigators] include … [c]omplying with all applicable personnel, applicable law, and VA requirements [and] … [a]ssuming full responsibility for all aspects in conducting the research."

9 Code of Federal Regulations (CFR) §2.31(d)(1)(ix). "In order to approve … proposed significant changes in ongoing activities, the IACUC shall conduct a review of those components of the activities related to the care and use of animals and determine that the proposed activities are in accordance with this subchapter unless acceptable justification for a departure is presented in writing…. Further, the IACUC shall determine that the proposed activities or significant changes in ongoing activities meet the following requirements: … [a]ctivities that involve surgery include appropriate provision for pre-operative and post-operative care of the animals in accordance with established veterinary medical and nursing practices."

Guide for the Care and Use of Laboratory Animals, Eighth Edition (The Guide), p. 25.[7] "[The IACUC] is responsible for oversight and evaluation of the entire [Animal Care & Use] Program and its components … [including] review and approval of proposed animal use (protocol review) and of proposed significant changes to animal use…."

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

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

NIH-OLAW NOT-OD-14-126, Guidance on Significant Changes to Animal Activities (dated August 26, 2014).[8] "The IACUC has some discretion to use IACUC-reviewed and -approved policies to define what it considers a significant change, or to establish a mechanism for determining significance on a case-by-case basis in accordance with the PHS Policy…. [S]ignificant changes include changes that have, or have the potential to have, a negative impact on animal welfare…. [and] some activities that may not have a direct impact on animal welfare…."

Required Action 1:
The IACUC and Principal Investigator must ensure that research is conducted in accordance with the approved protocol and that any proposed significant changes to animal research protocols are approved prior to implementation.

2. **The IACUC did not ensure that all departures from USDA Animal Welfare Act and Regulations (AWARs) were described in the semi-annual report to the Institutional Official (IO).**

Finding:
Review of select protocols revealed that two IACUC-approved VA protocols involving cats described departures from housing requirements for primary enclosures. Specifically, protocols #397-0001 and #435-0002 both described removal of elevated resting platforms from cat primary enclosures following surgery, which is a departure from the AWARs. Both protocols included adequate scientific, veterinary medical, and animal welfare considerations to justify the departures; however, the departures were not described in any semi-annual reports submitted to the facility Director, the IO for RRVAMC.

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

9 CFR §2.31(c)(3). "The [semi-annual] reports [of the IACUC's review of the research facility's program for humane care and use of animals] must contain a description of the nature and extent of the research facility's adherence to this subchapter, must identify specifically any departures from the provisions of title 9, chapter I, subchapter A – Animal Welfare, and must state the reasons for each departure."

[8] Accessible at: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-126.html (last ORO access on April 6, 2020)

RRVAMC PHS Assurance §III.d.3. "Each departure [from the AWARs] will be stated and reported in the semi-annual report to the IO for each six-month reporting period during which the IACUC approved departure is in place."

Required Action 2:
The IACUC must ensure that semi-annual reports to the facility Director identify any departures from the AWARs and state the reasons for each departure.

3. **Affiliate IACUC semi-annual reports were not consistently reviewed as an IACUC business item.**

Finding:
A formal arrangement (i.e., an MOU) was in place with the affiliate, UL, to address aspects of shared oversight of VA animal research activities conducted in affiliate space, including receipt and review by the VA IACUC of the affiliate's semi-annual assessments in lieu of conducting an independent assessment of UL's animal care and use program. However, review of IACUC minutes and interviews with IACUC members confirmed that the RRVAMC IACUC had not reviewed affiliate semi-annual evaluations as a business item since June 12, 2018.

Reference(s):
VHA Handbook 1200.07 §8.f(1)(a). "The semi-annual self-assessment review [of the program of animal care and research use] must include all facilities and investigator areas where laboratory animals purchased with local VA funds are used in procedures, or housed longer than 12 hours. If a formal arrangement has been made between the VA IACUC and a satellite or affiliate's facility, the VA IACUC may review that facility's semi-annual self-assessment review as an IACUC business item in lieu of sending a VA IACUC review team to the facility."

MOU Between the RRVAMC and the UL With Regard to Collaboration on the Use of Animals in Research §F.5. "Each IACUC is responsible for evaluating semiannually the animal use programs and facilities that are covered by its own PHS Assurance, and shall, upon request, make available for review a copy of those portions of the final IACUC approved report of its evaluation that apply to the collaboration…. The other IACUC shall review the report, but may also perform its own independent evaluation of those components of the animal use program and facilities of the first party that are relevant to the collaboration. Each IACUC is independently responsible for reporting the results of each semi-annual evaluation to its own Institutional Official (IO)."

See OLAW FAQ #B.7, "What information should be in IACUC minutes?"[9] "PHS Policy requires that minutes of IACUC meetings, records of attendance, activities of the Committee, and Committee deliberations, be maintained by the institution.

[9] Accessible at: https://olaw.nih.gov/guidance/faqs#B (last ORO access on April 6, 2020)

Accordingly, there should be documentation of major issues discussed by the IACUC and the outcome of the discussions in sufficient detail for an outsider to ascertain the nature of the discussion and the conclusions reached."

Required Action 3:
Per its MOU with UL, the RRVAMC IACUC must consistently review affiliate semi-annual reports as a business item and document the review in its minutes.

4. **The IACUC did not ensure that an animal research protocol received timely triennial review and approval.**

Finding:
Document review revealed that the VA IACUC did not perform timely triennial/*de novo* review of at least one protocol. Protocol #435-0002, involving cats, received initial approval on December 8, 2016, and thus this approval expired on December 7, 2019; however, a triennial review and approval was not performed by that date, and animal research activities continued after the expiration.

Reference(s):
PHS Policy §IV.C.5. *"*The IACUC shall conduct continuing review of each previously approved, ongoing activity covered by this [PHS] Policy at appropriate intervals as determined by the IACUC, including a complete review in accordance with IV.C.1.-4. at least once every three years."

VHA Handbook 1200.07 §§8.g(1)-(3). **"**Prior to the third anniversary, the IACUC must conduct a complete re-review of the protocol…. The funding period of a project has no bearing on the need for … triennial reviews."

Required Action 4:
The IACUC must evaluate current practices and procedures and modify as necessary to ensure that all protocols receive timely triennial/*de novo* reviews, including the protocol identified in this Finding.

5. **Animal research activities that were conducted beyond the expiration date(s) established by the IACUC were not reviewed or reported as required.**

Finding:
Interviews with key personnel and review of select protocols revealed two instances in which animal research activities were conducted beyond the expiration dates established by the IACUC. Specific examples for protocol #435-0002 included:

- An annual/continuing review and approval expired December 7, 2017, but did not occur until January 9, 2018, resulting in a lapse of approximately 1 month; and

- A second annual/continuing review and approval expired January 8, 2019, but did not occur until April 23, 2019, resulting in a lapse of approximately 3 ½ months.

Although the conduct of animal research beyond the established expiration dates was identified by the Veterinary Medical Officer, the noncompliance was not reviewed by the IACUC or reported to ORO or NIH-OLAW, as required.

Reference(s):
VHA Handbook 1200.07 §§8.g(1)-(3). "**First and Second Annual Review of Protocols.** The IACUC must review the conduct of all animal protocols annually…."

9 CFR §2.31(d)(5). "The IACUC shall conduct continuing reviews of activities covered by this subchapter at appropriate intervals as determined by the IACUC, but not less than annually."

VHA Handbook 1058.01 §§7.e.-f. "**Reportable Incidents Under Applicable Federal Standards.** VA personnel, including [without compensation (WOC)] and [Intergovernmental Personnel Agreement (IPA)] appointees, must ensure written notification of the IACUC within 5 business days after becoming aware of any incident that is reportable under relevant VHA Handbooks or applicable Federal requirements related to laboratory animal welfare or research safety…. The IACUC must review any incident described at paragraphs 7.a. through 7.e. at its next convened meeting."

VHA Handbook 1200.07 §8.i. "(1) The main categories of deficiencies that must be reported to outside authorities and the elements needed in the report are … (a) [a]ny serious or continuing non-compliance with PHS Policy…. (5) Deficiencies meeting any of the criteria in [VHA Handbook 1200.07] subparagraph 8i(1) must be reported in writing within 15 business days through the [Associate Chief of Staff (ACOS)] for R&D and the medical facility Director to the following agencies and offices: (a) ORD (by contacting the CVMO's office). (b) OLAW, as required by PHS Policy…. (d) AAALAC, as required by AAALAC rules of accreditation. (e) The affiliate's IACUC, if a joint IACUC is not present and the project involves animals purchased with funds awarded to the affiliate, or if an agreement between the VA and affiliate requires such notification. (f) The VA ORO, as required by ORO policy…."

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

NIH-OLAW NOT-OD-05-034, Guidance on Prompt Reporting to OLAW under the PHS Policy on Humane Care and Use of Laboratory Animals.[10] "Examples of reportable situations [include]: … conduct of animal-related activities beyond the expiration date established by the IACUC…."

RRVAMC Policy and Procedure #38, "Requirements for Compliance Reporting in Animal Research, Research Safety, and Research Laboratory Security (dated April 23, 2019) §4.a(5). "Reportable Incidents Under Applicable Federal Standards: Any incident that is reportable under relevant VHA Handbooks or applicable Federal requirements related to laboratory animal welfare or research safety."

Required Action 5:
The IACUC must ensure that it adheres to all policy and regulatory requirements for reviewing and reporting animal research noncompliance.

V. ADDITIONAL OBSERVATIONS

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

1. **Observation:**
   ORO recommends the IACUC ensure that written appointments and/or reappointments of members, including alternate voting members, are issued prior to the commencement of official service on the committee to ensure that committee composition and quorums are appropriately maintained. In one instance, a scientific voting member of the IACUC was reappointed approximately three weeks after the expiration of his or her previous term; however, during that interval, no meetings were held, and this member did not participate in any official business.

2. **Observation:**
   The IACUC should consider enhancing protocol review processes to ensure that descriptions of experimental animal procedures are internally consistent prior to final approval and that only procedures approved in the VA approved protocol are performed on VA animals. ORO noted minor discrepancies in antibiotic drug doses on two approved protocols. Specifically, protocols #397-0001 and #435-0002 both specified 100,000 IU/kg for pre- and peri-operative doses of Penicillin G benzathine in section J of the approved protocol, but 1,000,000 IU/kg in appendixes 3 and 5 of the approved protocol. Additionally, review of selected animal medical and surgical records revealed that, in one instance, an animal medical record documented that radiographs were performed under protocol #435-0002; however, this procedure was

[10] Accessible at: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-05-034.html (last ORO access on April 6, 2020)

not described or approved in the VA IACUC-approved ACORP. The PI indicated that this may have been a documentation error in the VA-approved protocol, as a similar, affiliate-approved protocol described radiographs as an approved activity. Regular cross checks of VA approved protocols and VA animal medical records may decrease the likelihood that unapproved procedures are performed or documented.

3. **Observation:**
ORO recommends that the IACUC review local policies, standard operating procedures (SOPs) and the PHS Assurance to ensure that descriptions of oversight procedures related to the ACUP are complete, accurate and congruent. Specifically, ORO noted the following issues related to post approval monitoring (PAM) procedures, protocol review processes and meeting minutes documentation:

- The RRVAMC PHS Assurance described periodic (i.e., three to four times a year) PAM inspections of affiliate spaces used for VA animal research to ensure compliance with both affiliate and VA protocols; however, this description was not accurate insofar as such periodic PAM inspections were not being performed.
- The RRVAMC PHS Assurance described annual/continuing reviews of VA animal research protocols via full committee review (e.g., approval by a quorum of committee members at a convened meeting); however, the IACUC local policy permitted such reviews to be conducted by the IACUC or an IACUC-designee.
- Neither the RRVAMC PHS Assurance nor local policies described timeframes for IACUC members to call for full committee review when designated member review (DMR) activities are initiated.
- IACUC meeting minutes did not consistently document IACUC review outcomes and final dispositions of protocol reviews. For example, protocol #397-0001 was reviewed and approved via DMR on September 20, 2018; however, the meeting minutes of September 25, 2018, did not document the review outcome and final disposition of the protocol.

Reference(s):
NIH-OLAW Guidance, "Correct Conduct of Full-Committee and Designated Member [Protocol Reviews]," Lab Animal 31(9):28-31, 2002.[11] "Any [IACUC] member can make the decision to send the protocol to full-committee review at any time during the time period designated for providing this opportunity. It is useful for IACUCs to allow a predetermined time period during which members may indicate which method of review is preferred."

[11] Accessible at: https://olaw.nih.gov/guidance/articles/laba02v31n9.htm (last ORO access on April 6, 2020)

NIH-OLAW FAQ D.3, "What are the possible methods of IACUC approval?"[12] "The specific method of review for a given protocol must be documented, along with the outcome of the review."

NIH-OLAW FAQ B.7, "What information should be in IACUC minutes?"[13] "PHS Policy requires that minutes of IACUC meetings, records of attendance, activities of the Committee, and Committee deliberations, be maintained by the institution. Accordingly, there should be documentation of major issues discussed by the IACUC and the outcome of the discussions in sufficient detail for an outsider to ascertain the nature of the discussion and the conclusions reached."

4. **Observation:**
RRVAMC should evaluate the need for developing a written agreement or MOU for animal procedures performed at all off-site locations. ORO noted that some VA-funded animal procedures were performed as part of a fee-for-service contract at a third institution (i.e., an institution other than RRVAMC and its academic affiliate). Although these activities were conducted as acute terminal experiments under a separate approved protocol at that institution, there was no written agreement in place that described aspects of shared IACUC oversight of these activities. Additionally, it was not clear if animals used or held for VA-funded research purposes were accurately and completely reported in relevant institutional USDA APHIS Annual Reports. Although the animals used for VA research were housed, used and reported by the affiliate institution, it was not clear if transfers of some of these animals to a third institution for terminal procedures were accurately accounted for in these reports. The development of a comprehensive agreement is encouraged, due to the inherent risks (e.g., related to transport of post-operative animals over long distances), and to clarify specific oversight roles and responsibilities, such as reporting requirements when animals are used and transferred between the two institutions.

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

[12] Accessible at: https://olaw.nih.gov/guidance/faqs#D (last ORO access on April 6, 2020)
[13] Accessible at: https://olaw.nih.gov/guidance/topic-index/iacuc-composition.htm#minutes (last ORO access on April 6, 2020)

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

USDA Animal Welfare Inspection Guide (revised March 2020) §7.3.1. "When registered research facilities (RF) contract research out to be conducted at another facility, it is the responsibility of the registrants to determine which party is responsible for … reporting of the animals on the Annual Report. If the research facilities have not delegated responsibilities or projects involving multiple registrants where there are no clearly designated areas of responsibility for each research facility, then: [b]oth registered parties are responsible, and [b]oth IACUCs should perform all required functions, and [o]nly one of the RFs should report the animals on the Annual Report. The inspector should cite both RFs for any noncompliances identified."

VI. CONCLUSIONS

ORO identified issues that will need to be remediated to come into compliance with applicable laws, regulations, and/or policies pertaining to the review, conduct and/or oversight of research. Identified noncompliance included, but was not limited to: protocol noncompliance was identified in one protocol, IACUC-approved departures from regulatory requirements for cat primary enclosures were not included in semi-annual reports to the VA facility Director, the IACUC did not ensure that an animal research protocol received timely triennial review and approval, and the IACUC did not follow requirements for reviewing and reporting animal research noncompliance. All identified noncompliance must be addressed in a Remedial Action Plan that will be monitored by ORO until satisfied.

OFFICE OF RESEARCH OVERSIGHT

(b)(6)

Director, Research Safety & Animal Welfare, ORO

APPENDIX A
ORO REVIEW TEAM and FACILITY REPRESENTATIVES

ORO On-Site Review Team:

(b)(6)

Facility Representatives:

Stephen Black, PT, FACHE Medical Center Director

(b)(6)

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

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

• 397-0001	Training Effects on Recovery of Balance and Limb Accuracy in Cats
• 435-0002	Force Feedback Redistribution and Eccentric Focused Rehab Post-SCI

APPENDIX C
AREAS INSPECTED WITH ASSOCIATED OBSERVATIONS

Location	Observation	Notes/References
Affiliate Animal Research Building, Room 509	One open, partially used bottle of atropine not dated; manufacturer label instructions indicate discard/disposal within 24 hours of use.	As a best practice, use and dispose of drugs per label instructions.
Affiliate Animal Research Building, Room 509	Plexiglas animal anesthetic induction chamber had a significant crack in one of the sides.	As a best practice, consider replacement to avoid further physical deterioration which could lead to leakage of waste volatile anesthetic gases, rough/sharp edges and/or decreased ability to effectively sanitize.

REMEDIAL ACTION PLAN

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

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

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

Deadline for completion of Required Actions: **September 15, 2020**

Animal Care and Use. ORO Case Number: **603-0053-A**

Required Action 1: The IACUC and Principal Investigator must ensure that research is conducted in accordance with the approved protocol and that any proposed significant changes to animal research protocols are approved prior to implementation.	
Facility Response	***ORO Comments***
Response #1 ([DATE of response submission]) **Facility Action:** [TEXT] **Proposed Completion Date:** [DATE]	[ORO comments will be inserted here]
Required Action 2: The IACUC must ensure that semi-annual reports to the facility Director identify any departures from the AWARs and state the reasons for each departure.	
Facility Response	***ORO Comments***
Response #1 ([DATE of response submission]) **Facility Action:** [TEXT] **Proposed Completion Date:** [DATE]	[ORO comments will be inserted here]
Required Action 3: Per its MOU with UL, the RRVAMC IACUC must consistently review affiliate semi-annual reports as a business item and document the review in its minutes.	
Facility Response	***ORO Comments***

Response #1 ([DATE of response submission]) **Facility Action:** [TEXT] **Proposed Completion Date:** [DATE]	[ORO comments will be inserted here]
Required Action 4: The IACUC must evaluate current practices and procedures and modify as necessary to ensure that all protocols receive timely triennial/*de novo* reviews, including the protocol identified in this Finding.	
Facility Response	***ORO Comments***
Response #1 ([DATE of response submission]) **Facility Action:** [TEXT] **Proposed Completion Date:** [DATE]	[ORO comments will be inserted here]
Required Action 5: The IACUC must ensure that it adheres to all policy and regulatory requirements for reviewing and reporting animal research noncompliance.	
Facility Response	***ORO Comments***
Response #1 ([DATE of response submission]) **Facility Action:** [TEXT] **Proposed Completion Date:** [DATE]	[ORO comments will be inserted here]

Department of Veterans Affairs

Memorandum

Date: December 7, 2015

From: Director, (652/00) Richmond VA Medical Center, Richmond, VA 23249

Subj: Report of Incident Involving Animals (120215)

To: Office of Research Oversight, Central Office, Animal Welfare and Research Safety Program, (10R)

1. Enclosed you will find a report of a research incident involving animals that was reviewed by the IACUC and determined to be a serious noncompliance.

2. For further information, please contac (b)(6) IACUC Coordinator (b)(6) (b)(6)

(b)(6)

JOHN A. BRANDECKER

Enclosure

cc: Central Veterinary Medical Officer
Office of Laboratory Animal Welfare
AAALAC, International

Hunter Holmes McGuire VA Medical Center (652)
Report of Incident Involving Animals
OLAW Assurance #A4369-01
AAALAC #VA-061
USDA # 52-V-0003/681

Report Date: December 3,2015 ☒ Initial Report (120215) ☐ Follow-up Report
Report prepared by: (b)(6)

PROTOCOL INFORMATION

PI: Alex Tan, M.D.
Project Title: 1016-02002 Autonomic Nerve Activity and Cardiac Arrhythmias
IACUC #: 02002
Sponsor: N/A
Funding Source: VCU
Species: Canine

DISCOVERY INFORMATION

Discovery Source:
☐ Annual RCO Consent Form Audit
☐ Triennial RCO Regulatory Audit
☒ Other: VMU Supervisor

DESCRIPTION OF INCIDENT

CONCERN:
On 12/1/15, (b)(6) conducted a survival surgery on dog D2 as approved by the IACUC. During the surgery, isoflurane was turned off to monitor nerve activity that would be impaired by isoflurane. In past surgeries, although not detailed in the ACORP nor reviewed and approved by the IACUC, a 2ml bolus of pentobarbital maintained surgical plane of anesthesia for this section of surgery. During the procedure on 12/1, the technician pushed 4 mls of pentobarbital (instead of the normal 2mls due to the first part of the surgery taking longer than normal) but was unaware that the line had infiltrated. When she discovered it was infiltrated another line was placed in the other leg. Another 3 ml of pentobarbital was pushed at that time. The surgery was completed around 5PM.
(b)(6) remained in the facility to monitor the dog post operatively until 12AM. The dog had not recovered from surgery by this time and was unresponsive when he left. From the end of surgery until 7:30AM, the dog was not given any fluids which would have been medically indicated and the dog was not placed on a warming pad per the ACORP post-operative procedures. At 7:15AM on 12/2/15, the PI's technician found the dog completely unresponsive in the cage, temperature of 103.7 with shallow, intermittent respirations and low blood pressure. Without realizing the consequences, she administered Buprenorphine for pain relief (standard of care post operatively). When the VMU Supervisor arrived at 7:30AM and was notified of the dog's condition, the veterinarian and investigator were notified immediately.
As directed by the veterinarian, a 5% Dextrose solution was started and Naloxone was given to reverse the Buprenorphine. Blood was drawn for a CBC and Chemistry and showed normal organ values. She was given 650ml of 5% Dextrose and 2000ml of normal saline throughout the day, placed on a warming pad and monitored constantly. She began to show non-purposeful responses with normal blood pressure and respirations around 11AM and subsequently Carprofen was given for pain relief. By 3PM, she was sternal and trying to stand. At 7:30AM on 12/3/2015, she had fully recovered.

ACTIONS TAKEN (OR TO BE TAKEN) TO ADDRESS EVENT

The VMU Director notified the PI, VMO and IACUC chair of these concerns. Immediate animal welfare concerns were addressed and the animal made a full recovery. (Completed)

A meeting of the convened IACUC was held on December 2, 2015 to discuss the concerns, determine if what actions need to be taken, and to determine if this is a "reportable event." (Completed)

The IACUC reviewed this scenario at the 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 post-operative 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. They confirmed this was a serious noncompliance with the Guide, PHS policy and VHA regulations. An action plan was prepared and all survival surgeries were cancelled. (Completed).

The following letter was sent to the PI on 12/7/2015 (with a copy to the ACOS/R) detailing the corrective action plan:

(b)(6)

The IACUC met on 12/2/2015 to discuss events that occurred on 12/1/15 pertaining to protocol number 02002 "Autonomic Nerve Activity and Cardiac Arrhythmias". The committee determined you failed to provide adequate veterinary care post operatively which led to unanticipated harm to canine D2. After reviewing the details the committee unanimously decided that the incident represented a serious noncompliance with The Guide, PHS Policy and VHA Regulations and recommended the following corrective actions:

1. The IACUC has placed protocol 02002 "Autonomic Nerve Activity and Cardiac Arrhythmias" on veterinary hold. No initial survival surgeries may be conducted until this hold is lifted. If any second surgeries on existed animals or final non-survival surgeries are planned, a request must be sent to (b)(6) detailing what needs to be done and why it must be done to prevent animal wastage.

2. The IACUC requests that you submit a revised ACORP addressing the intraoperative pentobarbital dose and isoflurane removal and why this is necessary. This should be outlined in sections C.2.a, C.2.c and Appendix 5. Include how the animals are monitored during this time in Appendix 5. Additionally, update and expand on the post-operative monitoring procedures. You may submit the amendment to add the second procedure for sino-aortic denervation that was tabled at this meeting with this revision. The ACORP should be submitted to Ms. Stumpf by December 18, 2015.

3. The IACUC requests the PI submit a letter to the IACUC detailing the circumstances involved in this incident and what led to the reportable incident. Provide a plan stating what steps you will take to ensure this will not happen again. Explain why isoflurane needs to be removed during the surgery and how pentobarbital will be titrated differently to prevent overdose in the future. Finally, the letter should detail the proper emergency procedures to be used in the event of an incident in the future. This plan should be provided to the IACUC coordinator, (b)(6) by the submission date listed above.

4. A detailed intraoperative and post-operative record needs to be maintained for each

canine. This record sheet needs to contain the timing of anesthesia, amounts, IV monitoring/confirmation times as well as detailed post-operative recovery notes that contain temperature/pulse/respiration data every 30 minutes until the animal is fully sternal/responding to audible noises. These records will be sent to (b)(6) and the ARF supervisor the day after surgery for review and a copy signed by (b)(6) and (b)(6) (b)(6) These documents will remain in the animal's record. This will be in addition to the required monitoring records that are already maintained in the animal record.

5. The PI and technician will complete the CITI training modules for "Working with the IACUC" and "Working with Laboratory Dogs" again. This must be completed before the IACUC will lift the veterinary hold.

6. The technician must receive training on controlled substance/anesthesia agents and their side effects/contraindications as well as procedures to deal with dogs in distress post-operatively. This training will be provided by the VMU Supervisor.

7. All investigators will sign a form prepared by the IACUC coordinator stating they understand someone must be present to visually watch the canines while monitoring and recording temperature/pulse/respiration until the animal is sternal and responsive. The form will also verify they understand the 24 hour emergency procedures and have access to the contact information.

Once the IACUC have reviewed and approved all of the above documents and feel the other stipulations have been adequately met, your protocol hold will be lifted however the increased level of monitoring will remain for the duration of this protocol. Understand that any future serious violations may result in full suspension or termination of your animal protocol at the VA. The IACUC would like to stress that noncompliance could have implications beyond your research protocols and negatively impact the entire research program at this facility. If you have any questions regarding these corrective actions, please don't hesitate to contact me.
Sincerely,

(b)(6)

The Animal Handler competency form, completed by all research staff conducting any animal procedures, will be revised with a controlled substance safety section and a post operative care section. This will be reviewed and approved by the IACUC then sent to all research staff for completion. (To be completed January 2016)

All research staff using barbiturates or opiates will receive specialized training on the mechanisms of action, potential side effects and indications for use by the VMU Supervisor. The training will be reviewed and approved by the veterinarian. (Pending)

NOTIFICATION OF POTENTIALLY REPORTABLE ANIMAL SAFETY CONCERN

☒ Facility Director (Date: 12/3/2015) ☒ Attending VMO (12/2/2015)

☒ ACOS/Research (Date: 12/3/2015) ☒ R&D Chairman (12/3/2015)

This will be submitted to OLAW, AAALAC, and CVMO.

COMMITTEE REVIEW

☒ The event was reviewed by the convened IACUC (Date: 12/2/2015)

☒ The event will be reviewed at the next R&D meeting (Date: 12/8/2015)

(b)(6)

John A. Brandecker
Director

12/8/15
Date

Hunter Holmes McGuire VA Medical Center (652)
Report of Incident Involving Animals
OLAW Assurance #A4369-01
AAALAC #VA-061
USDA # 52-V-0003/681

Report Date: April 7, 2016 ☒ Initial Report (04072016) ☐ Follow-up Report
Report prepared by: VMU Supervisor/IACUC Coordinator

PROTOCOL INFORMATION

Project Title: 1016-02002 Autonomic Nerve Activity and Cardiac Arrhythmias
IACUC #: 02002
Sponsor: N/A
Funding Source: VCU

DISCOVERY INFORMATION

Discovery Source:
☐ Annual RCO Consent Form Audit
☐ Triennial RCO Regulatory Audit
☒ Other: VMU Supervisor

DESCRIPTION OF INCIDENT

CONCERN:
On March 2nd, 2016, the PI conducted an approved second survival surgery on Animal #7 (A7) in which catheter ablation of the sino-aortic afferent nerves was performed on both the left and right carotid sheaths. The immediate 24 hour post operative recovery was noted as normal (lack of appetite, pain relieved by analgesics is normal). On March 4th, it was noted A7 was not recovering and had significant nausea, weight loss, lethargy and anorexia. The veterinarian was consulted and did a full exam. At this point, A7 could not swallow oral medications without extreme nausea so IV anti-emetics, IV famotidine and IV fluids with dextrose were administered. These medications were continued twice a day on March 5th and 6th. On March 7th, it was evident A7 was not improving and had significant weight loss. The animal was scheduled for a non-survival surgery that evening. Prior to this terminal surgery, the technician performed the approved ventricular programmed stimulation on A7 and once this stimulation test was completed the animal developed ventricular fibrillation and sudden cardiac death as a result of the arrhythmia. This stimulation has been performed on 28 previous animals with no adverse effects so it can be assumed the ventricular fibrillation was due to the poor health of the animal. A necropsy was performed on A7 by the VMU supervisor and no significant issues were noted in the GI tract.

On March 3rd, prior to realizing the scope of A7's poor recovery, this same catheter ablation surgery was performed on Animal #9. A9 followed the same poor recovery as A7 and the same treatments were used leading to no improvement. The investigator conducted the approved terminal procedure on A9 on March 9th.

It was determined that there had been bilateral injury to the vagi nerves during this surgery due to excessive handling during the process of isolating the sino-aortic afferent branch of the vagus nerve.

With the Veterinarian's consent, he conducted this procedure again on A8 but did not conduct a bilateral ligation. He only used one side of the neck and used extreme caution in handling the nerves to prevent damage. A8 made a full recovery with no adverse effects noted.

ACTIONS TAKEN (OR TO BE TAKEN) TO ADDRESS EVENT

The VMU Director notified the IACUC chair of these events. (Completed)

ORO was notified of intent to investigate on 3/21/16. (completed)

A meeting of the convened IACUC was held on April 6, 2016 to discuss the concerns, determine what actions need to be taken, and to determine if this is a "reportable event." The Investigator submitted a letter detailing the events and what has been done to date to prevent this from happening in the future. (Completed)

A revised ACORP was submitted to request dividing the bilateral ablation survival surgery into two separate survival surgeries.

The IACUC reviewed this scenario at the convened meeting and determined this event led to unanticipated harm and loss of animal life. The committee did not approve the submitted ACORP amendment and devised a corrective action plan.
(Completed).

The following letter was sent to the PI on 4/7/16 (with a copy to the ACOS/R) detailing the corrective action plan:

"The IACUC met on 4/6/16 to discuss events that occurred on 3/2/16 pertaining to protocol number 02002 "Autonomic Nerve Activity and Cardiac Arrhythmias". The committee determined the bilateral procedure led to unanticipated harm and loss of animal life. After reviewing the details the committee unanimously decided that the incident represented serious noncompliance with The Guide, PHS Policy and VHA Regulations and recommended the following corrective actions:

1. The IACUC has placed protocol 02002 "Autonomic Nerve Activity and Cardiac Arrhythmias" on close veterinary supervision. A weekly log must be submitted to the VMU Supervisor and Veterinarian detailing what survival surgeries were done (if any), details on intra operative complications (minor or major) and post-operative recovery details. This will continue until further notice.

2. The IACUC did not approve the submitted ACORP revision and requests that you submit another revised ACORP for designated member review stating that you are approved to do unilateral surgery on four (4) animals. The committee did not approve the third survival surgery at this time. If these animals fully recover (3-4 weeks) and have shown no adverse effects from this second survival surgery, you may submit a revised ACORP requesting one (1) animal to conduct a third survival surgery for the bilateral denervation. The progress and recovery of this one animal must then be reported at the next convened IACUC meeting. If this one animal recovers well, you may submit a revised ACORP requesting to use a second animal for the third survival surgery.

3. If these two animals recover well, you must submit the data comparing unilateral to bilateral denervation and describe why the third survival surgery is essential to this protocol. The IACUC feels this timeline will adequately enable you to compare the two procedures and ensure unilateral will not suit the needs of this protocol.

4. You may continue with other approved components of this protocol with these initial 4 animals (i.e. exercise protocol, PVC, telemetry monitoring, etc)

5. The co-investigator with experience in this model must be present for all four of the denervation surgeries (second and, if approved, third survival surgeries). He must sign the intra operative records and denote any challenges or complications noted.

6. The VMU supervisor will be kept updated and will review/observe all surgeries, post-operative care procedures, intraoperative complications, etc.

Understand that any future serious violations may result in full suspension or termination of your animal protocol at the VA. The IACUC would like to stress that noncompliance could have implications beyond your research protocols and negatively impact the entire research program at this facility. If you have any questions regarding these corrective actions, please don't hesitate to contact me. "

The veterinarian sent a letter to the PI on 4/7/16 reinforcing the ethical responsibility held by the IACUC and PI when animals are used for research purposes. He stressed the importance of ensuring the safety and well-being of the animals while appreciating the complexity and importance of the research. Overall, he wanted to ensure the PI clearly appreciated the significance of the events and understood the importance of this action plan. (Completed)

The revised ACORP will be reviewed and approved by DMR prior to any surgeries being completed. (to be completed)

NOTIFICATION OF POTENTIALLY REPORTABLE ANIMAL SAFETY CONCERN

☒ Facility Director (Date:4/6/16) ☒ Attending VMO (3/4/16)

☒ ACOS/Research (Date: 3/21/16, 4/6/16) ☒ R&D Chairman (4/6/16)

This will be submitted to OLAW, AAALAC, and CVMO.

COMMITTEE REVIEW

☒ The event was reviewed by the convened IACUC (Date: 4/6/16)

☒ The event will be reviewed at the next R&D meeting (Date: 4/12/16)

(b)(6)

John A. Brandecker
Director

4/12/16
Date

OCT 19 2016

According to the Paperwork Reduction Act of 1995, an agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a valid OMB control number. The valid OMB control number for this information collection is 0579-0036. The time required to complete this information collection is estimated to average 2 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.

OMB APPROVED
0579-0036
Exp.: 10/31/2018

This report is required by law (7 U.S.C. 2143). Failure to report according to the regulations can result in an order to cease and desist and to be subject to penalties as provided for in Section 2150.

Interagency Report Control No. 0180-DOA-AN

Fiscal Year 2015

UNITED STATES DEPARTMENT OF AGRICULTURE
ANIMAL AND PLANT HEALTH INSPECTION SERVICE

ANNUAL REPORT OF RESEARCH FACILITY

(TYPE OR PRINT)

1. REGISTRATION NUMBER
52-V-0003 Customer number: 681

2. HEADQUARTERS RESEARCH FACILITY *(Name, address, and telephone number as registered with USDA, include ZIP Code)*
VA Medical Center (652)
1201 Broad Rock Blvd
Research Service 151
Richmond, VA 23249
(804) 675-5151

3. REPORTING FACILITY *(List all locations where animals were housed or used in actual research, testing, teaching, or experimentation, or held for these purposes. Attach additional sheets, if necessary.)*

FACILITY LOCATIONS *(Sites)*

001-Richmond VAMC (652)

REPORT OF ANIMALS USED BY OR UNDER CONTROL OF RESEARCH FACILITY *(Attach additional sheets, if necessary, or use APHIS FORM 7023A.)*

A. Animals Covered By The Animal Welfare Regulations	B. Number of animals being bred, conditioned, or held for use in teaching, testing, experiments, research, or surgery but not yet used for such purposes.	C. Number of animals upon which teaching, research, experiments, or tests were conducted involving no pain, distress, or use of pain-relieving drugs.	D. Number 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.	E. Number 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 on these animals and the reasons such drugs were not used must be attached to this report.)*	F. TOTAL NUMBER OF ANIMALS **(Cols. C + D + E)**
4. Dogs	6		12	11	23
5. Cats					0
6. Guinea Pigs					0
7. Hamsters					0
8. Rabbits					0
9. Non-human Primates					0
10. Sheep					0
11. Pigs					0
12. Other Farm Animals					
					0
13. Other Animals					
					0
					0
					0

ASSURANCE STATEMENTS

1.) Professionally acceptable standards governing the care, treatment, and use of animals, including appropriate use of anesthetic, analgesic, and tranquilizing drugs, prior to, during, and following actual research, teaching, testing, surgery, or experimentation were followed by this research facility.

2.) Each principal investigator has considered alternatives to painful procedures.

3.) This facility is adhering to the standards and regulations under the Act, and it has required that exceptions to the standards and regulations be specified and explained by the principal investigator and approved by the Institutional Animal Care and Use Committee (IACUC). **A summary of all such exceptions is attached to this annual report.** In addition to identifying the IACUC approved exceptions, this summary includes a brief explanation of the exceptions, as well as the species and number of animals affected.

4.) The attending veterinarian for this research facility has appropriate authority to ensure the provisions of adequate veterinary care and to oversee the adequacy of other aspects of animal care and use.

CERTIFICATION BY HEADQUARTERS RESEARCH FACILITY OFFICIAL

(Chief Executive Officer (C.E.O.) or Legally Responsible Institutional Official (I.O.))

I certify that the above is true, correct, and complete (7 U.S.C. Section 2143).

SIGNATURE OF C.E.O. OR I.O.	NAME AND TITLE OF C.E.O. OR I.O. *(Type or Print)*	DATE SIGNED
(b)(6)	John A. Brandecker, Institutional Official	12/14/16

APHIS FORM 7023
JUL 2013

Column E Explanation

Registration No: 52-V-0003/681

1. **Ten dogs used in this study A**

This study involves two procedures that are deemed Category E by the IACUC.

Ventricular Programmed Stimulation

Ventricular programmed stimulation (VPS) will be performed through the implanted cardiac device to determine ventricular effective refractory period (VERP) and test susceptibility of ventricular arrhythmias.. All animals will undergo VPS at baseline (2 weeks post-thoracotomy) and 1-7 days prior to final surgery. Animal may experience anxiety, cardiac arrest and weakness during arrhythmias. This may lead to heart failure which causes fluid retention, anorexia, lethargy and weight changes.
The use of sedatives must be avoided since it can interfere with induction of ventricular arrhythmias. The animals are closely monitored and resuscitation methods are immediately available.

Bilateral Afferent Denervation (part 1 and 2)

One group of animals will have complete bilateral sino-aortic denervation performed. This will be achieved via two survival surgeries in which the aortic depressor nerve and the carotid sinus nerve are ligated on each side (one side per surgery).
Post operative pain relief is provided and continued however this denervation causes significant side effects that can be treated symptomatically but not alleviated until they resolve on their own with 5-10 days. These side effects include significant nausea, drooling, anorexia, vomiting and weight loss. Since these side effect cannot be alleviated and cause distress to the animal, this procedure has been deemed a category E procedure.

2. **One Dog used in Study B**

This study involves one procedures that is deemed Category E by the IACUC

Myocardial Infarction

This project requires that we make a myocardial infarction. In order for this infarction to produce a reliable and reproducible ischemic cardiomyopathy it must be transmural (full muscle thickness). Unfortunately, the side effects of having a large myocardial infarction are chest pain, shortness of breath, and occasionally nausea. The animal will be fully anesthetized when the infarction occurs but pain will continue post operatively. We will administer medication to minimize continued pain and nausea after the animal recovers from the procedure. The

size and full muscle thickness of the expected myocardial injury will make the hearts electrically unstable. Myocardial infarction models with this magnitude of injury can cause ventricular tachycardia (VT), ventricular fibrillation (VF) and even death in up to 40% of animals. To minimize the chances of animal loss or suffering due to ventricular tachycardia and ventricular fibrillation, we will administer an amiodarone bolus before, during and after the surgery. In addition, lidocaine 1-2mg/kg bolus with 1-2mg/kg/hr infusion will be administered prior to, during, and after the procedure over the same timeline. This combination of medications has been shown to decrease incidence of VT and VF to 4.4%, and death to 2.2%. Furthermore, we will record telemetry on these animals, using our implanted DSI device for the first 24-72hours so that increased arrhythmia can be detected and treated. To prevent nausea and loss of appetite in the postoperative period we will administer famotidine 0.22mg to 0.44mg per pound and/or metoclopramide 100mg.

Some canines may experience acute cariogenic shock as a result of the myocardial infarction or subsequent PVC protocol. This may cause the animals to experience pain, nausea, dizziness, shortness of breath or even syncope. Due to the nature of this event, pain medications can not be given to pre-empt these events.

Analgesics will be given to help mediate the pain for 3 days post operatively but it is not felt this will completely remove the pain.

There is a chance that animals will develop an arrhythmia during the postoperative period that will require treatment with defibrillation by internal or external device. If this occurs the animals will be given analgesia after the procedure to help reduce the pain.

Since the arrhythmias, VT, VF, sudden death and cariogenic shock can occur without pain relief and the post operative period is known to cause extensive pain in humans, the IACUC deemed these procedures category E.

USDA Annual Report FY16

Authorized Personnel for Richmond VAMC (652) 52-V-0003/681

Institutional Official: John A. Brandecker

Research Associate (b)(6)

From: Petervary, Nicolette - APHIS
To: (b)(6)
Subject: [EXTERNAL] RE: Request for documents
Date: Friday, March 24, 2017 10:03:28 AM
Attachments: 681 column E explanation.pdf
681 form 7023 2016.pdf

Dear (b)(6)

Here is a copy of your facility's annual report as you requested.

Sincerely,

Nicolette Petervary, VMD, DACAW
Animal Care Specialist
USDA APHIS Animal Care
920 Main Campus Drive, Suite 200
Raleigh, NC 27606
(b)(6)

From: (b)(6) @va.gov]
Sent: Friday, March 24, 2017 9:54 AM
To: Petervary, Nicolette - APHIS (b)(6)
Subject: Request for documents

Good Morning,

I am writing to you as the Director for Research Safety and Animal Welfare in the Office of Research Oversight, Veterans Health Administration (VHA), Department of Veterans Affairs, to request a copy of the FY2014, FY2015, and FY2016 Annual Report of Research Facility submitted by the VHA Hunter Holmes McGuire VA Medical Center, registration #52-V-0003. As the principal office within VHA that is responsible for animal welfare research compliance and oversight and the Federal Agency that is the owner of these reports, this office is eligible to receive copies of said reports.

Please let me know if you need any additional information before you can provide the requested documents.

Sincerely,

(b)(6)

(b)(6)

Column E Explanation

Registration No: 52-V-0003/681

1. **Ten dogs used in this study A**

This study involves two procedures that are deemed Category E by the IACUC.

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One group of animals will have complete bilateral sino-aortic denervation performed. This will be achieved via two survival surgeries in which the aortic depressor nerve and the carotid sinus nerve are ligated on each side (one side per surgery).
Post operative pain relief is provided and continued however this denervation causes significant side effects that can be treated symptomatically but not alleviated until they resolve on their own with 5-10 days. These side effects include significant nausea, drooling, anorexia, vomiting and weight loss. Since these side effect cannot be alleviated and cause distress to the animal, this procedure has been deemed a category E procedure.

2. **One Dog used in Study B**

This study involves one procedures that is deemed Category E by the IACUC

Myocardial Infarction

This project requires that we make a myocardial infarction. In order for this infarction to produce a reliable and reproducible ischemic cardiomyopathy it must be transmural (full muscle thickness). Unfortunately, the side effects of having a large myocardial infarction are chest pain, shortness of breath, and occasionally nausea. The animal will be fully anesthetized when the infarction occurs but pain will continue post operatively. We will administer medication to minimize continued pain and nausea after the animal recovers from the procedure. The

size and full muscle thickness of the expected myocardial injury will make the hearts electrically unstable. Myocardial infarction models with this magnitude of injury can cause ventricular tachycardia (VT), ventricular fibrillation (VF) and even death in up to 40% of animals. To minimize the chances of animal loss or suffering due to ventricular tachycardia and ventricular fibrillation, we will administer an amiodarone bolus before, during and after the surgery. In addition, lidocaine 1-2mg/kg bolus with 1-2mg/kg/hr infusion will be administered prior to, during, and after the procedure over the same timeline. This combination of medications has been shown to decrease incidence of VT and VF to 4.4%, and death to 2.2%. Furthermore, we will record telemetry on these animals, using our implanted DSI device for the first 24-72hours so that increased arrhythmia can be detected and treated. To prevent nausea and loss of appetite in the postoperative period we will administer famotidine 0.22mg to 0.44mg per pound and/or metoclopramide 100mg.

Some canines may experience acute cariogenic shock as a result of the myocardial infarction or subsequent PVC protocol. This may cause the animals to experience pain, nausea, dizziness, shortness of breath or even syncope. Due to the nature of this event, pain medications can not be given to pre-empt these events.

Analgesics will be given to help mediate the pain for 3 days post operatively but it is not felt this will completely remove the pain.

There is a chance that animals will develop an arrhythmia during the postoperative period that will require treatment with defibrillation by internal or external device. If this occurs the animals will be given analgesia after the procedure to help reduce the pain.

Since the arrhythmias, VT, VF, sudden death and cariogenic shock can occur without pain relief and the post operative period is known to cause extensive pain in humans, the IACUC deemed these procedures category E.

USDA Annual Report FY16

Authorized Personnel for Richmond VAMC (652) 52-V-0003/681

Institutional Official: John A. Brandecker

Research Associate Chief of Staff: (b)(6)

OCT 19 2016

According to the Paperwork Reduction Act of 1995, an agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a valid OMB control number. The valid OMB control number for this information collection is 0579-0036. The time required to complete this information collection is estimated to average 2 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.

OMB APPROVED
0579-0036
Exp.: 10/31/2018

This report is required by law (7 U.S.C. 2143). Failure to report according to the regulations can result in an order to cease and desist and to be subject to penalties as provided for in Section 2150.

Interagency Report Control No. 0180-DOA-AN

Fiscal Year 2015

UNITED STATES DEPARTMENT OF AGRICULTURE
ANIMAL AND PLANT HEALTH INSPECTION SERVICE

ANNUAL REPORT OF RESEARCH FACILITY

(TYPE OR PRINT)

1. REGISTRATION NUMBER
52-V-0003 Customer number: 681

2. HEADQUARTERS RESEARCH FACILITY *(Name, address, and telephone number as registered with USDA, include ZIP Code)*

VA Medical Center (652)
1201 Broad Rock Blvd
Research Service 151
Richmond, VA 23249
(804) 675-5151

3. REPORTING FACILITY *(List all locations where animals were housed or used in actual research, testing, teaching, or experimentation, or held for these purposes. Attach additional sheets, if necessary.)*

FACILITY LOCATIONS *(Sites)*

001-Richmond VAMC (652)

REPORT OF ANIMALS USED BY OR UNDER CONTROL OF RESEARCH FACILITY *(Attach additional sheets, if necessary, or use APHIS FORM 7023A.)*

A. Animals Covered By The Animal Welfare Regulations	B. Number of animals being bred, conditioned, or held for use in teaching, testing, experiments, research, or surgery but not yet used for such purposes.	C. Number of animals upon which teaching, research, experiments, or tests were conducted involving no pain, distress, or use of pain-relieving drugs.	D. Number 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.	E. Number 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 on these animals and the reasons such drugs were not used must be attached to this report.)*	F. TOTAL NUMBER OF ANIMALS **(Cols. C + D + E)**
4. Dogs	6		12	11	23
5. Cats					0
6. Guinea Pigs					0
7. Hamsters					0
8. Rabbits					0
9. Non-human Primates					0
10. Sheep					0
11. Pigs					0
12. Other Farm Animals					
					0
13. Other Animals					
					0
					0
					0

ASSURANCE STATEMENTS

1.) Professionally acceptable standards governing the care, treatment, and use of animals, including appropriate use of anesthetic, analgesic, and tranquilizing drugs, prior to, during, and following actual research, teaching, testing, surgery, or experimentation were followed by this research facility.

2.) Each principal investigator has considered alternatives to painful procedures.

3.) This facility is adhering to the standards and regulations under the Act, and it has required that exceptions to the standards and regulations be specified and explained by the principal investigator and approved by the Institutional Animal Care and Use Committee (IACUC). **A summary of all such exceptions is attached to this annual report.** In addition to identifying the IACUC approved exceptions, this summary includes a brief explanation of the exceptions, as well as the species and number of animals affected.

4.) The attending veterinarian for this research facility has appropriate authority to ensure the provisions of adequate veterinary care and to oversee the adequacy of other aspects of animal care and use.

CERTIFICATION BY HEADQUARTERS RESEARCH FACILITY OFFICIAL

(Chief Executive Officer (C.E.O.) or Legally Responsible Institutional Official (I.O.))

I certify that the above is true, correct, and complete (7 U.S.C. Section 2143).

SIGNATURE OF C.E.O. OR I.O.	NAME AND TITLE OF C.E.O. OR I.O. *(Type or Print)*	DATE SIGNED
(b)(6)	John A. Brandecker, Institutional Official	12/14/16

APHIS FORM 7023
JUL 2013

(b)(6)

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From: Petervary, Nicolette - APHIS
To: (b)(6)
Cc: Goldentyer, Betty J - APHIS
Subject: [EXTERNAL] RE: Question on Annual Reports - Fiscal Year Dates
Date: Tuesday, April 25, 2017 8:22:06 AM

Hello (b)(6)

Your statement is correct. While program support sends the most up to date forms by mail, older versions of forms were available on the APHIS website. I can personally verify that this was the case for FY 16, because it was noted by a facility in October of 2016 and I reported the issue to program support so that they could work with the site webmaster.

Thank you.

Nicolette Petervary, VMD, DACAW
Animal Care Specialist
USDA APHIS Animal Care
920 Main Campus Drive, Suite 200
Raleigh, NC 27606
(b)(6)

From (b)(6) @va.gov]
Sent: Tuesday, April 25, 2017 8:06 AM
To: Petervary, Nicolette - APHIS (b)(6)
Subject: Question on Annual Reports - Fiscal Year Dates

Hi Dr. Petervary,

Thank you for your recent assistance in obtaining copies of annual reports submitted by one of our research facilities. We noted that the reports submitted for FY2016 and FY2015 were submitted on forms indicating Fiscal Year 2015 and Fiscal Year 2014, respectively, although the dates signed align with the correct reporting interval.

My team has been charged with investigation of events at this facility. As part of our response we will need to explain this apparent discrepancy in report dates. Based on conversations with our facility and with Drs. Fallon and Huang, we understand that the older forms were likely the only ones available on the USDA/APHIS website when these reports were filed.

Would it be possible for someone to provide an official statement for inclusion in our report regarding the use of these forms from previous years?

VA appreciates any assistance or insight you can provide regarding this matter.

Regards,

(b)(6)

Hunter Holmes McGuire VA Medical Center (652)
Report of Incident Involving Animals
OLAW Assurance #A4369-01
AAALAC #VA-061
USDA # 52-V-0003/681

Report Date: November 14, 2016 ☒ Initial Report (11142016) ☐ Follow-up Report
Report prepared by: VMU Supervisor/IACUC Coordinator

PROTOCOL INFORMATION

Project Title: Nanopartical Injection into Ganglionated Neural Plexi to Prevent Atrial Fibrillation
IACUC #: 02235
Sponsor: N/A
Funding Source: Center for Innovation Technology
Species: Canine

DISCOVERY INFORMATION

Discovery Source:
☐ Annual RCO Consent Form Audit
☐ Triennial RCO Regulatory Audit
☒ Other: VMU Supervisor

DESCRIPTION OF INCIDENT

CONCERN:

On 10/11/16, the PI and technician performed the second thoracotomy on D16 (first survival surgery was a thoracotomy and the second survival surgery involving a thoracotomy took place 3 weeks after as approved in the ACORP). D16 was the first canine to complete this procedure on this protocol. During the surgery, the animal had significant pleural adhesions that the PI released to visualize the heart. Once surgery was complete, blood was noted on the endotracheal tube upon removal. Following extubation the animal immediately became hypoxic and died shortly thereafter. Upon necropsy, it was noted that the lung had a substantial laceration and damage which likely led to the hypoxia and ultimate death of the animal.

The veterinarian stopped all new surgeries but allowed any animal already involved in the study to be completed. Two subsequent surgeries involving a second thoracotomy were conducted with no complications.

ACTIONS TAKEN (OR TO BE TAKEN) TO ADDRESS EVENT

The veterinarian must observe this surgery. (Completed on 10/20/16)

The Investigator must meet with the IACUC chairman. (completed on 10/21/16)

A meeting of the convened IACUC was held on November 9, 2016 to discuss the concerns, determine if what actions need to be taken, and to determine if this is a "reportable event." The Investigator submitted a letter detailing the event and a revised ACORP. (Completed)

A revised ACORP was submitted adding the risk of pleural adhesions as well as the pilot nature of this protocol which may lead to potential unexpected outcomes. The ACORP also included a more detailed post-operative monitoring plan. The committee reviewed this amendment and determined an action plan for this event. (Completed).

The following letter was sent to the PI on 11/14/2016 (with a copy to the ACOS/R) detailing the corrective action plan:

"The IACUC met on 11/09/2016 to discuss events that occurred on 10/11/206 pertaining to protocol number 02235 "Nanopartical Injection into Ganglionated Neural Plexi to Prevent Atrial Fibrillation". The committee determined the risk of pleural adhesions and subsequent lacerations with the adhesion release leading to loss of animal life was an unanticipated risk to the IACUC since it had not been detailed in the ACORP. After reviewing the details the committee unanimously decided that the incident represented a reportable event with The Guide, PHS Policy and VHA Regulations. The majority of the committee recommended the following corrective actions:

1. Update the post-operative monitoring section in Appendix 5 to include that the PI will remain with the animal until extubation and readily available until fully recovered (though he does not have to be in the same room). Additionally, please provide heart rate, blood pressure and oxygen saturation levels that are appropriate for this procedure for normal recovery. The committee realizes these parameters may be different from 'normal' and would like the investigator to use his experience to determine what normal recovery vital signs are.
2. You are limited to one survival surgery per week with this protocol.
3. The committee would like you to do some research by talking to other cardiac researchers who have conducted these procedures or similar ones to determine if other complications may occur including non-survival surgeries. Reviewing journals rarely discusses complications so contacting the investigator is the best way to achieve this. Please report your findings to the committee.
4. Ensure another surgeon is in the room during all surgical procedures.
5. The committee acknowledges and confirms that you have been counseled by the IACUC chairman and have had a subsequent surgery observed by the veterinarian.

Understand that any future serious violations may result in full suspension or termination of your animal protocol at the VA. A minority opinion was submitted from a voting member of the IACUC to terminate this protocol at this time. The IACUC would like to stress that noncompliance could have implications beyond your research protocols and negatively impact the entire research program at this facility. If you have any questions regarding these corrective actions, please don't hesitate to contact me. "

The following minority opinion was submitted by the non-scientist member of the committee. "The lack of foresight and preparation by the investigator prior to this surgery leads me to believe the investigator has a general sense of unintended reckless behavior. The investigator's actions threaten the integrity of this institution and I vote to close this study."

NOTIFICATION OF POTENTIALLY REPORTABLE ANIMAL SAFETY CONCERN

☒ Facility Director (Date:11/10/2016) ☒ Attending VMO (10/11/16)

☒ ACOS/Research (Date: 10/11/2016) ☒ R&D Chairman (11/10/2016)

This will be submitted to OLAW, AAALAC, and CVMO.

COMMITTEE REVIEW

☒ The event was reviewed by the convened IACUC (Date: 11/9/16)

☒ The event will be reviewed at the next R&D meeting (Date: 11/22/2016)

(b)(6)

John A. Brandecker
Director

11/15/16
Date

From: (b)(6)
To: (b)(6)
Cc:
Subject: [EXTERNAL] Re: Obligation to post projects
Date: Wednesday, May 03, 2017 1:18:00 PM

Hello (b)(6)

I am copying (b)(6) from VA's Rehabilitation R&D service, who has been a contact on the RePORTER and Federal RePORTER initiatives.

I am not aware of any mandate to post projects on the Federal RePORTER. Records on this website are supplied voluntarily by each participating agency, reflecting their own funded research programs (though some choose not to display funding amounts).

Some components of the VA voluntarily supply data for the RePORTER and Federal RePORTER web sites, allowing display of those projects alongside other biomedical or general research projects from other agencies

This is described on at least two VA pages:

- The Clinical Sciences R&D service: https://www.research.va.gov/services/csrd/finding_programs.cfm
- The Rehabilitation R&D service http://www.rehab.research.va.gov/staff/nihreporter.html

Posting of projects is straightforward for some components of the VA because they use parts of the NIH award administration IT systems to manage their programs.

If there is interest in posting additional types of projects from the VA, our Federal RePORTER team will be happy to discuss with representatives from the VA, as needed.

Thank you and best regards,
(b)(6)

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(b)(6)

From: (b)(6) @va.gov>

Date: Wednesday, May 3, 2017 at 6:58 AM
To: (b)(6)
Subject: Obligation to post projects

Good Morning (b)(6)

As the Director for Research Safety and Animal Welfare in the Department of Veterans Affairs, Office of Research Oversight, part of my responsibility is to investigate complaints against our research programs. We are currently working on a complaint that one of our facilities "failed to disclose … experimental projects in the Federal Reporter System". In reviewing information on the Federal RePORTER website, VA is clearly a participant in this effort. However, it is not clear to me what the specific reporting obligations are, and I am hoping that you can help me to understand the process or put me in contact with someone who can provide assistance.

Here are the questions that we're trying to answer:

1. Is reporting to Federal RePORTER mandatory for VA?
2. What research projects would be expected to be reported?
   For example:
   a. Would grants from private organizations (such as the American Heart Association) need to be reported?
   b. Would an NIH sub-award be reported and if so, would the primary awardee or sub-awardee be responsible for reporting the sub award?
3. Who within VA would be responsible for reporting? Is this at the level of the PI, the individual research facility, or is there an admin group that manages this?

I apologize for all the questions, but I am not familiar with Federal RePORTER requirements for reporting.

I appreciate your assistance as we look into this matter.

Regards,

(b)(6)

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