DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

FOR US POSTAL SERVICE DELIVERY:
Office of Laboratory Animal Welfare
6700B Rockledge Drive, Suite 2500, MSC 6910
Bethesda, Maryland 20892-6910
Home Page: http://grants.nih.gov/grants/olaw/olaw.htm

FOR EXPRESS MAIL:
Office of Laboratory Animal Welfare
6700B Rockledge Drive, Suite 2500
Bethesda, Maryland 20817
Telephone: (301) 496-7163
Facsimile: (301) 480-3387

March 4, 2021

Re: Animal Welfare Assurance
A3172-01 [OLAW Case K]

Dr. Morris Foster
Vice President, Research
Old Dominion University
4111 Monarch Way, (b) (4)
Norfolk, VA 23508

Dear Dr. Foster,

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt in this office on February 24, 2021 of your January 25, 2021 letter reporting an instance of noncompliance with the PHS Policy on Humane Care and Use of Laboratory Animals at Old Dominion University (ODU). Your letter supplements the information contained in the preliminary phone report to this office on October 21, 2020. According to the information provided, OLAW understands that on September 22, 2020 your office was notified of two rabbit deaths. The first rabbit did not recover from anesthesia following an experimental procedure (intratracheal instillation of an experimental substance) on September 21st, and the second rabbit was found dead during morning health checks on September 22nd. The IACUC requested that the PI temporarily halt research activity. It was suspected that the experimental substance was deposited into one lung, instead of both lungs as intended. On September 23rd, a third rabbit died subsequent to a fractured tibia and fibula. On September 24th, a fourth rabbit was found dead, due to expected findings for this model. In addition, due to a misunderstanding by the post-doctoral fellow, feeding of the rabbits was inconsistent. This activity was funded by the PHS.

Corrective and preventive actions included:

- An amendment was submitted to alter rabbit positioning during the procedure to improve the outcome.
- The feed log would be updated to also contain a start weight to record the amount of food given to the rabbit each day, as well as a place to initial the document by whomever feeds the animals.
- Feeding and weighing must occur in the mornings, so the animal care staff can check on the level of feed during afternoon health checks and notify the lab accordingly if more is needed.
- Feeding of rabbits, post-procedurally, is the research team's responsibility, and requests for animal care staff to feed and weigh the rabbits must be made via email the day prior.
- Post-approval monitoring must occur for the next scheduled procedure conducted by the post-doctoral fellow.

A Post-Approval Monitoring visit was initially scheduled for October 6th but was halted when it was discovered the post-doc was planning to replace Xylazine with Midazolam. This was not an appropriate substitution per the approved protocol and was halted by the compliance coordinator. The animal research privileges of the post-doc were suspended. An in-depth training session was conducted to discuss these issues with the post-doc and the supervising PI.

A second PAM was conducted on November 16, 2020. The post-doc was very attentive to detail and was well-versed on all aspects of the protocol when questioned by the compliance coordinator.

The IACUC determined at the December 2020 meeting that the post-doc could be reinstated on the protocol with initial close supervision and a more frequent PAM schedule. Since that time, the post-doc appears to be performing well and no further issues have been noted on this protocol.

It is further understood that this instance has led your program to remind your Principal Investigators of their oversight responsibilities and that technical competence is not the only measure that training has been internalized.

Based on the information provided, OLAW is satisfied that appropriate actions have been taken by Old Dominion University to investigate this incident and prevent recurrence. OLAW concurs that the incident warranted reporting. We commend your program for recognizing and addressing the root-cause of the issues. We appreciate being informed of this matter and find no cause for further action by this office.

Sincerely,

Brent C. Morse -S

Digitally signed by Brent C. Morse -S
Date: 2021.03.04 09:53:34 -05'00'

Brent C. Morse, DVM
Director
Division of Compliance Oversight
Office of Laboratory Animal Welfare

cc: IACUC contact
Dr. Robert M. Gibbens, USDA, APHIS, AC

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January 25, 2021

Brent Morse, D.V.M.
Director
Division of Compliance Oversight
Office of Laboratory Animal Welfare
National Institution of Health
RKL1, Suite 360, MSC 7982
6705 Rockledge Drive
Bethesda, Maryland 20892-7982

Re: Adverse Event Report

Assurance Number A3172-01

Dear Dr. Morse,

The purpose of this report is to provide a follow-up and final report regarding a series of events first reported to you this past October. These events involved rabbit deaths on a lung injury protocol that is PHS funded (NIEHS, 1U01ES030674-01A1). All of these events centered on a post-doctoral fellow on the project who had primary responsibility for the daily conduct of the project. The initially reported events and our subsequent actions are detailed in this letter.

On September 22nd, our office was notified of two rabbit deaths occurring on the aforementioned project. The first rabbit did not recover from anesthesia following an experimental procedure (intratracheal instillation of hydrochloric acid [HCl]) on September 21st, and the second rabbit was found dead during morning health checks on September 22nd. The IACUC requested that the PI temporarily halt research activity while the causes of death could be investigated. A necropsy could not be performed on the first rabbit, as the investigator had disposed of the body prior to notification of animal care staff and the Attending Veterinarian (AV). A necropsy on the second rabbit showed grossly hemorrhagic lung tissue unilaterally, with marked hemorrhage and edema of the tracheal mucosa. The AV suspected that all of the experimental substance (HCL) was deposited into one lung, instead of both lungs as intended, possibly leading to a cytokine storm or hypoxia from hypoperfusion. A plan was submitted via amendment to alter rabbit positioning during the procedure to improve the outcome as recommended by the AV, which was consistent with a pilot study that had been performed with no adverse animal outcomes. On September 23rd, a third rabbit was found in respiratory distress during morning health checks and was noted not to be using one of its hindlimbs. The AV was immediately contacted, but the animal expired before intervention could be initiated. On necropsy, it had a fractured tibia and fibula, which completely transected several major vessels in the leg, resulting in a large hematoma. There were no other abnormalities identified. The leg injury and resulting acute hypovolemia, in combination with lung tissue damage from the experimental procedure, likely resulted

Office of Research
4111 Monarch Way, Suite 203, Norfolk, VA 23508
Phone: 757/683-3460 • Fax: 757/683-5902 • www.odu.edu/research

in hypoxic hypoxemia. This incident was isolated and not directly attributable to the experimental procedures. On September 24th, a fourth rabbit was found dead, and a necropsy showed diffuse alveolar hemorrhage and lung edema, an expected finding for this model. All four of these rabbits had procedures performed prior to the requested halt. Rabbits #1, #2 and #3 had procedures on September 21st, and rabbit #4's procedure date was September 16th.

The IACUC met on September 24th for a regularly scheduled meeting and was informed of the adverse events. At that time, the full investigation had not yet been completed. The committee agreed that the investigation would continue, that a subcommittee of members would meet again as information was available after which the future of the project would be discussed.

Discussions occurred between the AV, compliance coordinator, and animal care staff from Sept 24-25. It was suspected that the rabbits had not been fed consistently, stemming from a series of miscommunications and misunderstandings on the part of the research staff, as to which animals they were to be feeding and which animals the animal care staff was to be feeding. A meeting was held on September 25th with the lab group, the AV, facility manager, and compliance coordinator to discuss who was responsible for feeding and weighing the rabbits. During this meeting, it was determined that the rabbits had not been fed for at least one day, possibly up to 3 days (though not consecutively) since the protocol began on September 16th. It is the AVs opinion that these animals, which were subjected to experimentally induced lung injury, did not have adequate nutritional support to aid in recovery and likely contributed strongly to the deaths of 3/4 of these animals. The protocol clearly stated that the rabbits and their feed were to be weighed daily for the first 7 days after a procedure, and an email was sent that this responsibility was that of the lab staff. Additionally, yellow cage card tags had been placed on each cage stating, *"PI responsible for feed from X date to X date"*. Unfortunately, the post-doctoral fellow misunderstood, and had been recording the weight of the feed that was left in the feeder each morning, most of the time recording 0 grams, and not refilling the feeder. On a few occasions, animal care staff would notice that the feeder was empty and ask the post-doc if he wanted them to provide food and was told to do so when asked. Based on the rabbit body weight log, the experimental rabbits had not gained any substantial weight since their procedures, whereas the rabbits who had not had procedures performed yet, who were still under the feeding care of the animal care staff, had gained weight consistently.

The subcommittee of IACUC members met on September 29th, and the AV and compliance coordinator briefed the group on the findings and plan moving forward for this protocol. The subcommittee agreed the project should be allowed to continue under the following conditions:

- The feed log should also contain a start weight to record the amount of food given to the rabbit each day, as well as a place to initial the document by whomever feeds the animals.
- Feeding and weighing must occur in the mornings, so the animal care staff can check on the level of feed during afternoon health checks and notify the lab accordingly if more is needed.
- Feeding of rabbits, post-procedurally, is the research team's responsibility, and requests for

animal care staff to feed and weigh the rabbits must be made via email the day prior.

- Post-approval monitoring must occur for the next scheduled procedure conducted by the post-doctoral fellow.
- Continue with the amended procedure to modify the position of the rabbit during HCL instillation and slow the rate at which the HCL is instilled.

A Post-Approval Monitoring visit was initially scheduled for October 6th but was halted when it was discovered the post-doc was planning to replace Xylazine with Midazolam. This was not an appropriate substitution per the approved protocol and was halted by the compliance coordinator. The IACUC subcommittee met the same day and determined that the post-doc should be temporarily removed from working on the protocol until the reason behind these protocol deviations could be determined.

At this point, the IACUC began to strongly believe that the miscommunications with the post-doctoral fellow and his belief he could alter the protocol without amendment resulted from language and cultural differences stemming from his international status. The post-doctoral fellow in question moved here from Russia a few years ago. While his written English is excellent, we soon discovered that his spoken English was not at the same level. We believe that misunderstandings between him and the animal care staff resulted from this. Additionally, he was a credentialled veterinarian in Russia and believed that he had authority to make changes from the written protocol based upon his background. While this is obviously counter to the training provided at ODU, it explains the mindset that we discovered in further discussion with the post-doc.

An in-depth training session was conducted to discuss these issues with the post-doc and is supervising PI. This training focused upon the expectations of the IACUC, the post-doc's responsibility to follow a protocol exactly as it is approved, and the responsibility of the PI to more closely monitor the actions taken on the project. Those involved in the training indicated that the post-doc appeared to understand the information being presented when asked to explain it himself and was truly remorseful about not fully comprehending his responsibilities. In addition to the training intervention, the post-doc started conversational English classes to improve his communication skills.

A second PAM was conducted on November 16th. The post-doc was very attentive to detail and was well-versed on all aspects of the protocol when questioned by the compliance coordinator.

Based upon the details surrounding this matter, the intervention that took place, and the results of the second PAM, the IACUC determined at the December meeting that the post-doc could be reinstated on the protocol with initial close supervision and a more frequent PAM schedule. Since that time, the post-doc appears to be performing well and no further issues have been noted on this protocol.

While our procedures allowed these incidents to be detected soon after they occurred, we believe this serves as a lesson to the IACUC and investigators regarding assumptions on how training is comprehended. In this case, both online and in-person training was conducted in accordance with our

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policies. However, this instance has led us to remind our Principal Investigators of their oversight responsibilities and that technical competence is not the only measure of training being internalized.

Please feel free to contact me by e-mail (mfoster@odu.edu) or phone (b) (6) should you have any questions or require additional information.

Sincerely,

(b) (6)

Morris W. Foster, Ph.D
Vice President for Research

Cc: (b) (6)
Dr. Stephen Beebe, IACUC Chair
Dr. Nicole Compo, ODU Attending Veterinarian

Morse, Brent (NIH/OD) [E]

From: Morse, Brent (NIH/OD) [E]
Sent: Wednesday, February 24, 2021 12:04 PM
To: (b) (6)
Subject: RE: OLAW report? A3172-K

Follow Up Flag: Follow up
Flag Status: Flagged

Thank you (b) (6) I will send an official response within a couple of weeks.

Best regards, Brent Morse

Brent C. Morse, DVM, DACLAM
Director, Division of Compliance Oversight
Office of Laboratory Animal Welfare
National Institutes of Health

From: (b) (6)
Sent: Wednesday, February 24, 2021 11:50 AM
To: Morse, Brent (NIH/OD) [E] <morseb@mail.nih.gov>
Subject: RE: OLAW report? A3172-K

Hello, Dr. Morse,

It appears that the report was completed but never forwarded for signature. I'm extremely sorry about this oversight. The letter signed by our IO is attached. Please let me know if you have any questions or would like to discuss this matter further.

Best regards,

(b) (6)

From: Morse, Brent (NIH/OD) [E] <morseb@mail.nih.gov>
Sent: Wednesday, February 24, 2021 9:33 AM
To: (b) (6)
Subject: RE: OLAW report? A3172-K
Importance: High

Hello (b) (6)

We don't have a record of receiving this. Please let me know if you sent it or if you'll be sending it soon. Thank you.

Best regards, Brent Morse

Brent C. Morse, DVM, DACLAM
Director, Division of Compliance Oversight
Office of Laboratory Animal Welfare
National Institutes of Health

From: (b) (6)
Sent: Tuesday, January 19, 2021 9:59 AM
To: Morse, Brent (NIH/OD) [E] <morseb@mail.nih.gov>
Subject: Re: OLAW report? A3172-K

Good Morning, Dr. Morse,

My apologies for the delay. Our IACUC wrapped up the investigation of this issue right before the holiday break. I should have had the final report sent to you after the new year but got sidelined with some COVID related planning issues for the new semester. I will have the final report sent within the next day or two.

Best regards,

(b) (6)

Sent from my iPad

> On Jan 19, 2021, at 9:50 AM, Morse, Brent (NIH/OD) [E] <morseb@mail.nih.gov> wrote:
>
> Hello (b) (6)
>
> On October 21st you notified our office of the euthanasia of unexpected mortality and protocol noncompliance involving rabbits. Our office has no record of receiving further information regarding this issue. Is there a final, or interim, report you can submit to us? Your cooperation is appreciated.
>
> Best regards, Brent Morse
>
> Brent C. Morse, DVM, DACLAM
> Director, Division of Compliance Oversight
> Office of Laboratory Animal Welfare
> National Institutes of Health

Morse, Brent (NIH/OD) [E]

From: (b) (6)
Sent: Wednesday, February 24, 2021 9:36 AM
To: Morse, Brent (NIH/OD) [E]
Subject: RE: OLAW report? A3172-K

Good Morning, Dr. Morse,

I thought this had been sent. I'll check with my IACUC coordinator and be back in touch shortly.

Best regards,

(b) (6)

From: Morse, Brent (NIH/OD) [E] <morseb@mail.nih.gov>
Sent: Wednesday, February 24, 2021 9:33 AM
To: (b) (6)
Subject: RE: OLAW report? A3172-K
Importance: High

Hello (b) (6)

We don't have a record of receiving this. Please let me know if you sent it or if you'll be sending it soon. Thank you.

Best regards, Brent Morse

Brent C. Morse, DVM, DACLAM
Director, Division of Compliance Oversight
Office of Laboratory Animal Welfare
National Institutes of Health

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(b) (6)

Sent from my iPad

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Best regards, Brent Morse

Brent C. Morse, DVM, DACLAM
Director, Division of Compliance Oversight
Office of Laboratory Animal Welfare
National Institutes of Health

Morse, Brent (NIH/OD) [E]

From: Morse, Brent (NIH/OD) [E]
Sent: Tuesday, January 19, 2021 10:03 AM
To: (b) (6)
Subject: RE: OLAW report? A3172-K

Thank you (b) (6) The delay is understandable. We look forward to receiving the report.

Sincerely, Brent Morse

Brent C. Morse, DVM, DACLAM
Director, Division of Compliance Oversight
Office of Laboratory Animal Welfare
National Institutes of Health

From: (b) (6)
Sent: Tuesday, January 19, 2021 9:59 AM
To: Morse, Brent (NIH/OD) [E] <morseb@mail.nih.gov>
Subject: Re: OLAW report? A3172-K

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Best regards, Brent Morse

Brent C. Morse, DVM, DACLAM
Director, Division of Compliance Oversight
Office of Laboratory Animal Welfare
National Institutes of Health

A3172-K

Office of Laboratory Animal Welfare

OLAW

Initial Report of Noncompliance

By: (b) (6)

Date: 10/21/2020 Time: 10:05

Name of Person reporting: (b) (6)
Telephone #: (b) (6)
Fax #:
Email: (b) (6)

(copy USDA)

Name of Institution: Old Dominion U.
Assurance number: A3172

Did incident involve PHS funded activity? Yes
Funding component: NIEHS
Was funding component contacted (if necessary): _____

What happened? Rabbit did not recover from surgery. Second rabbit dead on 9/22/20 due to unilateral distribution of HCl instead of bilateral. 4th rabbit found dead as result of research.*

Species involved: Rabbit
Personnel involved:
Dates and times: 9/21/20 & 9/22/20
Animal deaths: Yes

Projected plan and schedule for correction/prevention (if known): _____
Changing positioning of rabbits during Sx.

Projected submission to OLAW of final report from Institutional Official:
Told to notify USDA

OFFICE USE ONLY
Case #_____

- * Rabbits also were not fed by post. Acc due to misunderstanding.
- Oct 6, 2020 - Post-doc using Midazolam instead of approved Xylazine.