A3124-1C

UCONN
UNIVERSITY OF CONNECTICUT

May 9, 2018

Axel Wolff, M.S., DVM
Deputy Director, Division of Compliance Oversight
Office of Laboratory Animal Welfare
National Institutes of Health
Rockledge 1, Suite 360
6705 Rockledge Drive
Bethesda, MD 20892

RE: Animal Welfare Assurance #A3124-01

Dear Dr. Wolff:

I am writing to report the reinstatement of a suspended animal protocol A17-020 at the University of Connecticut/ Storrs campus. The protocol is linked to the following NIH/NINDS award #: R21NS098091-01. The decision to lift the suspension was made at a fully convened IACUC meeting on May 9, 2018, after confirmation of completion of the required actions outlined by the IACUC in its letter of suspension to the Principal Investigator dated April 26, 2018.

The IACUC has notified the Principal Investigator that she and listed protocol personnel may now regain access to the animals and resume all research activities described in the protocol. The appropriate personnel in the Animal Care Services (ACS) facility, as well as Sponsored Program Services (SPS) have received a copy of that notice. SPS staff will notify the sponsor of reinstatement.

This will be our final report on this incident. Should you have any questions regarding this report, please contact me or Dr. Holly Fitch, IACUC Chair (roslyn.h.fitch@uconn.edu; (b) (6)).
The University of Connecticut is committed to protecting the welfare of animals used in research and appreciates the guidance and assistance provided by OLAW in this regard.

Thank you for your assistance in this matter.

Sincerely,
Wesley G. Byerly, Pharm.D.
(b) (6)
Associate Vice President for Research Integrity and Regulatory Affairs/Institutional Official

c: R. Holly Fitch, Ph.D., Professor, Department of Psychological Sciences/IACUC Chair
(b) (6)
Laura Kozma, Executive Director, Sponsored Program Services and Faculty Services

Office of the Vice President for Research
438 WHITNEY ROAD EXTENSION, UNIT 1006
STORRS, CT 06269-1006
PHONE 860.486.3619
FAX 860.486.5381
research.uconn.edu

Morse, Brent (NIH/OD) [E]

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Thursday, May 10, 2018 10:16 AM
To: (b) (6) OLAW Division of Compliance Oversight (NIH/OD)
Cc: Fitch, Roslyn; (b) (6) Kozma, Laura; Byerly,Wesley (byerly@uchc.edu)
Subject: RE: A3124-01 Report of Reinstatement after Suspension

Thank you for this final information. We will add it to the case file.

Regards, Brent Morse

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

From: (b) (6)
Sent: Thursday, May 10, 2018 9:37 AM
To: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Cc: Fitch, Roslyn <roslyn.h.fitch@uconn.edu>; (b) (6) (b) (6) Kozma, Laura <laura.kozma@uconn.edu>; Byerly,Wesley (byerly@uchc.edu) <byerly@uchc.edu>
Subject: A3124-01 Report of Reinstatement after Suspension
Importance: High

Dear Dr. Wolff,
I have attached a written report from the UConn/Storrs Institutional Official (IO) documenting the reinstatement of a protocol after suspension that occurred at the University of Connecticut-Storrs.
If you have additional questions, please don't hesitate to contact us.
Sincerely,
(b) (6)

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) 402-7065

December 11, 2018

Re: Animal Welfare Assurance
#A3124-01 (OLAW Case 1L)

Dr. Wesley Byerly
Associate Vice President for Research Integrity and
Regulatory Affairs
University of Connecticut
263 Farmington Avenue, MC 1524
Storrs, CT 06030

Dear Dr. Byerly,

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your December 7, 2018 letter responding to my November 15, 2018 request for an update on a previously reported and closed case involving the suspension of an animal activity at the University of Connecticut. According to the information provided, OLAW understands the following:

1) An additional incident of noncompliance occurred on the study in question and was reported to OLAW on October 26, 2018 and the corrective actions were accepted by this Office.

2) The surgeries conducted under direct veterinary supervision were performed correctly and appropriate analgesia was given.

3) The study is now being conducted as described in the approved protocol.

4) The Principal Investigator (PI) and staff were retrained on proper administration of analgesia, record keeping, protocol compliance, and reporting protocol deviations. The protocol was placed on enhanced post-approval monitoring.

5) The matter of altering records was addressed via retraining as in #4 and enhanced post-approval monitoring.

6) The PI and staff are now contacting the veterinary staff frequently for advice and training before starting new protocol procedures.

Based on its assessment of this information, OLAW has a better understanding of the outcome and status of the corrective actions taken in response to the initial noncompliance. We appreciate having been informed about this matter and find no cause for further action by this Office.

Sincerely,

(b) (6)

Axel Wolff, M.S., D.V.M.
Deputy Director
Office of Laboratory Animal Welfare

cc: IACUC Chair

UCONN
UNIVERSITY OF CONNECTICUT

December 7, 2018

Axel Wolff, M.S., DVM
Deputy Director, Division of Compliance Oversight
Office of Laboratory Animal Welfare
National Institutes of Health
Rockledge 1, Suite 360
6705 Rockledge Drive
Bethesda, MD 20892

RE: Animal Welfare Assurance #A3124-01

Dear Dr. Wolff:

I am writing in response to your inquiry dated 11/15/18 requesting additional information on the corrective actions taken in response to a finding of non-compliance that occurred under approved animal protocol A17-020 utilizing mice at the University of Connecticut/Storrs campus. The protocol is linked to the following NIH/NINDS award #: R21NS098091-01. Please see below for additional information as requested:

1) **Have any new noncompliant items been identified?**
   Yes. An additional finding of non-compliance was reported to OLAW on October 26, 2018.
2) **Were the surgeries that were conducted under veterinary supervision carried out appropriately?**
   Yes. The surgeries and provision of analgesia were carried out appropriately under direct veterinary supervision as required by the IACUC as part of the reinstatement of this protocol. The last supervised surgery occurred on 5/29/18.
3) **Is the study now being conducted as described in the approved protocol?**
   Yes. No additional findings of non-compliance have been identified since the October 26, 2018 report.
4) **Has the matter regarding improperly directing students to withhold analgesia been appropriately addressed? What actions were taken to ensure that this does not happen on another protocol?**
   Yes. All listed personnel, including the Principal Investigator, received retraining on the proper administration of analgesia, record keeping, protocol compliance and reporting protocol deviations on 4/27/18. The IACUC in concert with Animal Care Services veterinary staff have increased the incidence of post approval monitoring of this protocol in order to ensure that another occurrence of this type does not happen.

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438 WHITNEY ROAD EXTENSION, UNIT 1006
STORRS, CT 06269-1006
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research.uconn.edu

5) **Has the matter regarding alteration of records been appropriately addressed? What actions were taken to ensure that this does not happen on another protocol?**
Yes. All listed personnel, including the Principal Investigator, received retraining on the proper administration of analgesia, record keeping, protocol compliance and reporting protocol deviations on 4/27/18. The IACUC in concert with Animal Care Services veterinary staff have increased the incidence of post approval monitoring of this protocol in order to ensure that another occurrence of this type does not happen.

6) **Have there been any additional developments, positive or negative, that are relevant to this case?**
Yes. The IACUC has noted an increased vigilance on the part of the Principal Investigator and her protocol personnel, as evidenced by frequent interactions initiated by those individuals with veterinary staff to request training, clarification, and consultation on protocol procedures prior to initiating unfamiliar activities.
In addition, the University was recently (11/8/18) contacted via email by Michael Budkie from Stop Animal Exploitation Now (SAEN) in connection to this incident. We reported this communication to OLAW by email on 11/8/18.

We hope that this addresses any outstanding questions regarding this matter. Should you have any questions regarding this response, please contact me or Dr. Randall Walikonis, IACUC Chair (randall.walikonis@uconn.edu; (b) (6)).

Sincerely,
Wesley G. Byerly, Pharm.D.
(b) (6)
Associate Vice President for Research Integrity and Regulatory Affairs/Institutional Official

c: Randall Walikonis, Ph.D., Associate Professor, Department of Physiology and Neurobiology/IACUC Chair

Wolff, Axel (NIH/OD) [E]

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Monday, December 10, 2018 12:06 PM
To: (b) (6) OLAW Division of Compliance Oversight (NIH/OD)
Cc: Byerly,Wesley (byerly@uchc.edu); Walikonis, Randall
Subject: RE: OLAW Case A3124-1L-Response

Thank you for providing this requested information. Doctor Wolff will send an official response soon.

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: Monday, December 10, 2018 11:54 AM
To: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Cc: Byerly,Wesley (byerly@uchc.edu) <byerly@uchc.edu>; Walikonis, Randall <randall.walikonis@uconn.edu>
Subject: OLAW Case A3124-1L-Response
Importance: High

Dear Dr. Wolff,
Attached please find a written response from the Institutional Official, Dr. Byerly, as requested in your communication dated 11/15/18.
If you have additional questions, please don't hesitate to contact us.
Sincerely,
(b) (6)

(b) (6)

DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

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FOR EXPRESS MAIL:
Office of Laboratory Animal Welfare
6700B Rockledge Drive, Suite 2500
Bethesda, Maryland 20817
Telephone: (301) 496-7163
Facsimile: (301) 402-7065

November 15, 2018

Re: Animal Welfare Assurance
#A3124-01 (OLAW Case 1L)

Dr. Wesley Byerly
Associate Vice President for Research Integrity and
Regulatory Affairs
University of Connecticut
263 Farmington Avenue, MC 1524
Storrs, CT 06030

Dear Dr. Byerly,

The Office of Laboratory Animal Welfare (OLAW) is contacting you to inquire about the status of the study at UConn Health which had been suspended by the Institutional Animal Care and Use Committee (IACUC) and subsequently reinstated. The purpose of our questions is to solicit responses to ensure completeness of the case file regarding the resolution of some of the corrective actions that had been proposed. The institutional protocol number is A17-020, supported by NIH grant #R21NS098091-01, and involved mice which had not received the required peri-operative analgesia. Since the reinstatement of this study, has the IACUC, during its post-approval monitoring, made any additional findings as follows:

1) Have any new noncompliant items been identified?

2) Were the surgeries that were conducted under veterinary supervision carried out appropriately?

3) Is the study now being conducted as described in the approved protocol?

4) Has the matter regarding improperly directing students to withhold analgesia been appropriately addressed? What actions were taken to ensure that this does not happen on another protocol?

5) Has the matter regarding alteration of records been appropriately addressed? What actions were taken to ensure that this does not happen on another protocol?

6) Have there been any additional developments, positive or negative, that are relevant to this case?

Please provide the additional requested information by **December 14, 2018**.

Sincerely,

(b) (6)

Axel Wolff, M.S., D.V.M.
Deputy Director
Office of Laboratory Animal Welfare

cc: IACUC Chair

Wolff, Axel (NIH/OD) [E]

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Friday, November 09, 2018 7:02 AM
To: (b) (6)
Cc: OLAW Division of Compliance Oversight (NIH/OD)
Subject: RE: Report of Correspondence on A3124-01

Thank you for this information, (b) (6) We will discuss this among OLAW staff and will contact UConn if more information is needed.
Axel Wolff

From: (b) (6)
Sent: Thursday, November 08, 2018 3:34 PM
To: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Cc: Byerly,Wesley (byerly@uchc.edu) <byerly@uchc.edu>; Walikonis, Randall <randall.walikonis@uconn.edu>; (b) (6)
Subject: Report of Correspondence on A3124-01
Importance: High

Dear Dr. Wolff,
I am writing on behalf of our Institutional Official, Dr. Wesley Byerly, to alert you to a recent communication the University of Connecticut received. This morning the President's Office was contacted by Stop Animal Exploitation Now (SAEN) in connection to a report of non-compliance from A3124-01 to OLAW in April 2018. We have forwarded that communication and it is captured below. Dr. Byerly wanted to be sure OLAW was made aware of the situation in case of additional media attention.
Please let us know if there are any questions.
Sincerely,
(b) (6)

From: Byerly,Wesley <byerly@uchc.edu>
Sent: Thursday, November 8, 2018 10:52 AM
To: (b) (6) Walikonis, Randall <randall.walikonis@uconn.edu>
Subject: Fwd: Request for Project Termination

(b) (6)

From: President Susan Herbst <president@uconn.edu>
Date: November 8, 2018 at 10:37:57 AM EST
To: (b) (6)
Cc: (b) (6) "Byerly, Wesley" <wesley.byerly@uconn.edu>
Subject: FW: Request for Project Termination

From: Michael Budkie <saen@saenonline.org>
Sent: Wednesday, November 7, 2018 4:08 PM
To: President Susan Herbst <president@uconn.edu>
Subject: Request for Project Termination

SAEN
Stop Animal Exploitation NOW!

Susan Herbst,
President
8
Office of the President
University of Connecticut
Gulley Hall UNIT (b) (4)
Storrs, Connecticut
Via Email: president@uconn.edu

11/7/1

President Herbst,

I am contacting you today because a specific Principal Investigator at the University of Connecticut (UCONN) has demonstrated a pattern of violating federal regulations regarding the use of animals in biomedical research. The malfeasance perpetrated by this Principal Investigator led to the suspension of a protocol.

UCONN correspondence with the Office of Laboratory Animal Welfare of the National Institutes of Health has delineated a long list of issues which indicate not only negligence and malfeasance but also falsification of records in an obvious effort to evade institutional and federal oversight. This correspondence discloses the scenario which revealed these serious incidents:

"During the period of March 2018 - April 2018, IACUC and ACS staff became aware of multiple incidents of failure to document analgesia administration on surgical/post-operative records associated with approved protocol A17-020. These findings arose during post approval monitoring, semiannual inspections, and daily rounds. The IACUC discussed the reports at a regularly convened April 11, 2018 meeting, at which time the Post Approval Monitor confirmed that he had visited the lab in response to initial reports (March 30, 2018). He confirmed that he had stressed the importance of analgesia administration and

documentation with the PI. Since additional incidents of failure to document analgesia had occurred after this visit, it was determined that further re-training was required."

The deliberate failure to utilize approved analgesia is heinous. This is nothing short of intentionally causing unnecessary pain and suffering in animals. This first mention of the research malfeasance indicates a clear unwillingness to change and comply with federal regulations. However, this PI's problems did not stop here:

"This issue rose to a higher level of concern when the IACUC office received several anonymous reports indicating that student surgeons had been directed to withhold analgesia in post-operative mice; specifically to withhold the pre-op dose altogether, and to provide "a small dose" of pain relief at 24/48 hours only if the mice appeared to be in pain. . . . the directives were non-compliant to the protocol as written. The complainants were concerned about the analgesia non-compliance and were unwilling to follow the directive to withhold pain relief being given by their PI (two in person, one phone and one email report; April 16 - 20, 2018). Two staff members subsequently left the lab."

The situation had become so scandalous that lab staff left the project. But the violations don't end there:

"An investigation followed, and during the course of investigation it became apparent that analgesia records from Feb - April 2018 had been retroactively altered. . . . In several of the revised records, the student performing surgery had stated clearly that the dose of Meloxicam was never given. Nonetheless the records were altered to show administration of full doses of Meloxicam, indicating they were retroactively falsified."

Apparently someone was trying to cover their tracks. The correspondence goes on to say:

"The PI's explanation was that in February 2018 she enacted a protocol change to withhold surgical and at times post-surgical doses of analgesia due to a series of unexpected deaths following intra-uterine surgery in pregnant mice, and in an attempt to improve survivability. She enacted these changes without an approved modification. . . . In addition to the withholding of analgesia, the PI admitted to instructing staff to eliminate the use of isoflurane to induce animals prior to injection with ketamine/xylazine anesthesia, again without a modification. Although the isoflurane would not normally be required for this surgical procedure, the failure to use it was a concern because subsequent inspection revealed that at least 3 surgeries performed in April 2018 without isoflurane or analgesia were also performed using expired ketamine."

Collectively, these incidents demonstrate willful and intentional violation of regulations, as well an effort to escape oversight by intentionally falsifying records. These incidents not only caused unnecessary pain and suffering for animals, but also demonstrate that either a flawed protocol was approved or unqualified staff were performing surgeries, because the withholding of analgesia was due to a "***series of unexpected deaths***."

However, this is not simply an animal welfare issue, this is also a scientific issue. If this PI not only intentionally made unapproved alterations to the protocol, but also falsified records to cover-up their malfeasance, how do you know that other falsifications didn't occur? How do you know that data was not altered? The approved protocol has become virtually meaningless because it has been demonstrated that not only was it not followed, but the PI lied about the

failure to follow the protocol. Additionally, the failure to report these unexpected deaths made the determination of the cause impossible. Were the animals being overdosed anesthetically? Were the surgeries botched? The facts of this situation cannot be determined because these deaths were hidden from UCONN research administration. This further compromises the validity of this experiment.

Through both violating research standards and lying about it, this PI has jeopardized the reputation and credibility of the entire research program at the University of Connecticut. While the temporary suspension of the protocol was necessary, it was by no means a sufficient response to these offenses. A temporary suspension might have been appropriate if the compliance issues had been accidental or based solely on competence -- but this was calculated and intentional behavior.

The withholding of pain relief was not accidental, it was **INTENTIONAL.** The falsification of records was not accidental, it was **INTENTIONAL.** And while the unexpected animal deaths may have been due to incompetence (thereby compromising this project further), the other issues of research misconduct were calculated and determined, going on for an extended period of time.

Therefore, I am calling upon your office to take administrative action to launch an independent investigation to determine if other incidents have occurred in relation to this project, as well how and why the unexpected deaths occurred.

However, the willful disregard for federal regulations as well as the authority of UCONN research administration and the welfare of the animals used in this project collectively require a much more serious penalty then temporary suspension of the project. If you are to restore the credibility of UCONN research you must:

1. Permanently terminate all animal protocols associated with this PI. These projects are forever questionable and must not move forward.

2. Prohibit the publication of the results of this research, because since the protocol was not followed, the data is meaningless.

3. Return all federal funding received for this project, which is approximately $424,000, to the federal government. The taxpayers of this country should not fund such shoddy experimentation.

I will await action from your office, and expect to receive a reply within five (5) business days.

Sincerely,

Michael A. Budkie, A.H.T.

Michael A. Budkie, A.H.T.,

Executive Director, SAEN

Attachment: University of Connecticut Correspondence

UCONN
UNIVERSITY OF CONNECTICUT

April 26, 2018

Brent Morse, DVM, DACLAM
Acting Director, Division of Compliance Oversight
Office of Laboratory Animal Welfare
National Institutes of Health
Rockledge 1, Suite 360
6705 Rockledge Drive
Bethesda, MD 20892

RE: Animal Welfare Assurance #A3124-01

Dear Dr. Morse:

I am writing to report a series of non-compliance events that lead to the suspension of an approved animal protocol A17-020 at the University of Connecticut/ Storrs campus. This decision was made at a regularly convened IACUC meeting on April 25, 2018. The protocol is linked to the following NIH/NINDS award #: R21NS098091-01. The timeline of events provided below was discussed by IACUC members, and resulted in the vote for suspension.

1. During the period of March 2018 – April 2018, IACUC and ACS staff became aware of multiple incidents of failure to document analgesia administration on surgical/post-operative records associated with approved protocol A17-020. These findings arose during post approval monitoring, semiannual inspections, and daily rounds. The IACUC discussed the reports at a regularly convened April 11, 2018 meeting, at which time the Post Approval Monitor confirmed that he had visited the lab in response to initial reports (March 30, 2018). He confirmed that he had stressed the importance of analgesia administration and documentation with the PI. Since additional incidents of failure to document analgesia had occurred *after* this visit, it was determined that further re-training was required. The IACUC also determined that regulatory notification was necessary, but that additional information was needed before formulating a report. A re-training session was planned with the lab for April 20, 2018.

2. This issue rose to a higher level of concern when the IACUC office received several anonymous reports indicating that student surgeons had been directed to withhold analgesia in post-operative mice; specifically to withhold the pre-op dose altogether, and to provide "a small dose" of pain relief at 24/48 hours only if the mice appeared to be in pain. It is not clear how student surgeons were instructed to assess pain in a heavily gravid post-surgical mouse, nor what the criteria for "low dose" represented. In either case, the directives were non-compliant to the protocol as written. The complainants were concerned about the analgesia non-compliance and were unwilling to follow the directive to withhold pain relief being given by their PI (two in person, one phone and one email report; April 16 - 20, 2018). Two staff members subsequently left the lab.

Office of the Vice President for Research
438 WHITNEY ROAD EXTENSION, UNIT 1036
STORRS, CT 06269-1036
phone 860 486 3619
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[illegible]

3. An investigation followed, and during the course of investigation it became apparent that analgesia records from Feb - April 2018 had been retroactively altered. On March 30 during his visit, the IACUC PAM representative had documented existing records. They were checked again when IACUC members met with the PI (April 20, 2018). In several of the revised records, the student performing surgery had stated clearly that the dose of Meloxicam was never given. Nonetheless the records were altered to show administration of full doses of Meloxicam, indicating they were retroactively falsified.

4. The PI's explanation was that in February 2018 she enacted a protocol change to withhold surgical and at times post-surgical doses of analgesia due to a series of unexpected deaths following intra-uterine surgery in pregnant mice, and in an attempt to improve survivability. She enacted these changes without an approved modification. The approved protocol states the PI will give a dose of 1-2 mg/kg Meloxicam at surgery and at 24 and 48 hours, per standard pain relief for a major survival surgery in rodents. She acknowledged that she continued to direct staff to withhold the analgesia without submitting a modification even after being alerted to this discrepancy through communication with ACS staff who noted the missing analgesia records (March 20 and again March 25, 2018), a lab visit from the IACUC Post Approval Monitor who emphasized the importance of following and recording prescribed analgesia administration (March 30, 2018), and notification of analgesia discrepancies identified during semi-annual inspection on (April 17, 2018). In addition to the withholding of analgesia, the PI admitted to instructing staff to eliminate the use of isoflurane to induce animals prior to injection with ketamine/xylazine anesthesia, again without a modification. Although the isoflurane would not normally be required for this surgical procedure, the failure to use it was a concern because subsequent inspection revealed that at least 3 surgeries performed in April 2018 without isoflurane or analgesia were *also* performed using expired ketamine.

In response to this series of events, the IACUC voted to suspend the protocol in question effective April 25, 2018. The suspension will last until the IACUC votes to approve reinstatement of the protocol at a fully convened meeting; that vote will not be considered until the PI has provided documentation of the completion of actions required by the IACUC, which are listed below:

1. **The PI must submit a modification of her protocol to describe the anesthesia and analgesia regime that will be used for the IUE surgery. The Appendix C (personnel) should also be updated to ensure that the list of personnel is current and exhaustive, and that the procedures each will be expected to perform, as well as their training, are described.**
2. **Each listed individual in Appendix C (including the PI) must complete the Biomedical Responsible Conduct of Research Training via the CITI training online module. The link to CITI is https://about.citiprogram.org/en/homepage/**
3. **Each listed individual in Appendix C (including the PI) must complete an in-person IACUC training.**

4. **Each listed individual in Appendix C (including the PI) must complete aseptic surgical training, anesthesia training and euthanasia training through ACS.**
5. **The PI must develop a written plan in consultation with the Attending Veterinarian describing the means by which she will secure veterinary oversight (from either a UConn vet tech or veterinarian) for the first six IUE surgeries to be performed after reinstatement, including the provision of analgesia. This plan should include details relating to how the surgeries will be scheduled, how vet oversight and observation of the surgeries will be secured and documented, and how the PI will ensure that vet oversight will be available to observe the provision of post-op analgesia for all six surgeries. The Attending Veterinarian should sign off on this plan, and a copy should be sent to the Department Head.**

In addition, we have referred the matter of altering surgical records, and issues of potential impropriety in supervisory directives to subordinates, to the Associate Vice President for Research for further investigation. In closing, I believe that we have taken appropriate corrective action. This will be my final report on this matter unless you request additional information or actions.

Sincerely,
Wesley G. Byerly, Pharm.D.
(b) (6)
Associate Vice President for Research Integrity and Regulatory Affairs/Institutional Official

c: R. Holly Fitch, Ph.D., Professor, Department of Psychological Sciences/IACUC Chair
(b) (6)
Laura Kozma, Executive Director, Sponsored Program Services and Faculty Services

DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

FOR US POSTAL SERVICE DELIVERY:
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Rockledge One, Suite 360
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Home Page: http://grants.nih.gov/grants/olaw/olaw.htm

FOR EXPRESS MAIL:
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Rockledge One, Suite 360
6705 Rockledge Drive
Bethesda, Maryland 20817
Telephone: (301) 496-7163
Facsimile: (301) 402-7065

April 30, 2018

Re: Animal Welfare Assurance
#A3124-01 (OLAW Case 1L)

Dr. Wesley Byerly
Associate Vice President for Research Integrity and
Regulatory Affairs
University of Connecticut
263 Farmington Avenue, MC 1524
Storrs, CT 06030

Dear Dr. Byerly,

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your April 26, 2018 letter reporting the suspension of an animal activity at the University of Connecticut. According to the information provided, OLAW understands that the Institutional Animal Care and Use Committee (IACUC) took this action after determining that mice undergoing surgery failed to receive pre-operative analgesia, were given insufficient post-operative analgesics and only when mice showed signs of pain, and that these practices continued after the Principal Investigator (PI) had been counseled. Furthermore, analgesia records had been retroactively altered, students conducting surgery were directed to withhold analgesia or under-dose animals, the protocol was not amended to reflect changes in analgesia, and expired analgesics were used.

In addition to the suspension, the corrective actions consisted of the Institutional Animal Care and Use Committee directing the PI to amend the protocol to include all analgesics/anesthetics, to include all personnel on the protocol, to ensure that the PI and all personnel have taken the required training, and to have veterinary staff oversee the first six surgeries following reinstatement of the protocol. The matter of altering records and improperly directing the students has been referred to the Associate Vice President for Research.

Based on its assessment of this explanation, OLAW understands that measures have been implemented to correct and prevent recurrence of this problem. OLAW concurs with the actions taken by the IACUC to comply with the PHS Policy on Humane Care and Use of Laboratory Animals. Please also inform the NIH funding component about the suspension of grant #R21NS098091-01. Thank you for informing OLAW about this matter.

Sincerely,

(b) (6)

Axel Wolff, M.S., D.V.M.
Deputy Director
Office of Laboratory Animal Welfare

cc: IACUC Chair
Tijuanna DeCoster, NINDS Chief GMO

UCONN
UNIVERSITY OF CONNECTICUT

April 26, 2018

Brent Morse, DVM, DACLAM
Acting Director, Division of Compliance Oversight
Office of Laboratory Animal Welfare
National Institutes of Health
Rockledge 1, Suite 360
6705 Rockledge Drive
Bethesda, MD 20892

RE: Animal Welfare Assurance #A3124-01

Dear Dr. Morse:

I am writing to report a series of non-compliance events that lead to the suspension of an approved animal protocol A17-020 at the University of Connecticut/ Storrs campus. This decision was made at a regularly convened IACUC meeting on April 25, 2018. The protocol is linked to the following NIH/NINDS award #: R21NS098091-01. The timeline of events provided below was discussed by IACUC members, and resulted in the vote for suspension.

1. During the period of March 2018 – April 2018, IACUC and ACS staff became aware of multiple incidents of failure to document analgesia administration on surgical/post-operative records associated with approved protocol A17-020. These findings arose during post approval monitoring, semiannual inspections, and daily rounds. The IACUC discussed the reports at a regularly convened April 11, 2018 meeting, at which time the Post Approval Monitor confirmed that he had visited the lab in response to initial reports (March 30, 2018). He confirmed that he had stressed the importance of analgesia administration and documentation with the PI. Since additional incidents of failure to document analgesia had occurred *after* this visit, it was determined that further re-training was required. The IACUC also determined that regulatory notification was necessary, but that additional information was needed before formulating a report. A re-training session was planned with the lab for April 20, 2018.

2. This issue rose to a higher level of concern when the IACUC office received several anonymous reports indicating that student surgeons had been directed to withhold analgesia in post-operative mice; specifically to withhold the pre-op dose altogether, and to provide "a small dose" of pain relief at 24/48 hours only if the mice appeared to be in pain. It is not clear how student surgeons were instructed to assess pain in a heavily gravid post-surgical mouse, nor what the criteria for "low dose" represented. In either case, the directives were non-compliant to the protocol as written. The complainants were concerned about the analgesia non-compliance and were unwilling to follow the directive to withhold pain relief being given by their PI (two in person, one phone and one email report; April 16 - 20, 2018). Two staff members subsequently left the lab.

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3. An investigation followed, and during the course of investigation it became apparent that analgesia records from Feb - April 2018 had been retroactively altered. On March 30 during his visit, the IACUC PAM representative had documented existing records. They were checked again when IACUC members met with the PI (April 20, 2018). In several of the revised records, the student performing surgery had stated clearly that the dose of Meloxicam was never given. Nonetheless the records were altered to show administration of full doses of Meloxicam, indicating they were retroactively falsified.

4. The PI's explanation was that in February 2018 she enacted a protocol change to withhold surgical and at times post-surgical doses of analgesia due to a series of unexpected deaths following intra-uterine surgery in pregnant mice, and in an attempt to improve survivability. She enacted these changes without an approved modification. The approved protocol states the PI will give a dose of 1-2 mg/kg Meloxicam at surgery and at 24 and 48 hours, per standard pain relief for a major survival surgery in rodents. She acknowledged that she continued to direct staff to withhold the analgesia without submitting a modification even after being alerted to this discrepancy through communication with ACS staff who noted the missing analgesia records (March 20 and again March 25, 2018), a lab visit from the IACUC Post Approval Monitor who emphasized the importance of following and recording prescribed analgesia administration (March 30, 2018), and notification of analgesia discrepancies identified during semi-annual inspection on (April 17, 2018). In addition to the withholding of analgesia, the PI admitted to instructing staff to eliminate the use of isoflurane to induce animals prior to injection with ketamine/xylazine anesthesia, again without a modification. Although the isoflurane would not normally be required for this surgical procedure, the failure to use it was a concern because subsequent inspection revealed that at least 3 surgeries performed in April 2018 without isoflurane or analgesia were *also* performed using expired ketamine.

In response to this series of events, the IACUC voted to suspend the protocol in question effective April 25, 2018. The suspension will last until the IACUC votes to approve reinstatement of the protocol at a fully convened meeting; that vote will not be considered until the PI has provided documentation of the completion of actions required by the IACUC, which are listed below:

1. **The PI must submit a modification of her protocol to describe the anesthesia and analgesia regime that will be used for the IUE surgery. The Appendix C (personnel) should also be updated to ensure that the list of personnel is current and exhaustive, and that the procedures each will be expected to perform, as well as their training, are described.**
2. **Each listed individual in Appendix C (including the PI) must complete the Biomedical Responsible Conduct of Research Training via the CITI training online module. The link to CITI is https://about.citiprogram.org/en/homepage/**
3. **Each listed individual in Appendix C (including the PI) must complete an in-person IACUC training.**

4. **Each listed individual in Appendix C (including the PI) must complete aseptic surgical training, anesthesia training and euthanasia training through ACS.**
5. **The PI must develop a written plan in consultation with the Attending Veterinarian describing the means by which she will secure veterinary oversight (from either a UConn vet tech or veterinarian) for the first six IUE surgeries to be performed after reinstatement, including the provision of analgesia. This plan should include details relating to how the surgeries will be scheduled, how vet oversight and observation of the surgeries will be secured and documented, and how the PI will ensure that vet oversight will be available to observe the provision of post-op analgesia for all six surgeries. The Attending Veterinarian should sign off on this plan, and a copy should be sent to the Department Head.**

In addition, we have referred the matter of altering surgical records, and issues of potential impropriety in supervisory directives to subordinates, to the Associate Vice President for Research for further investigation. In closing, I believe that we have taken appropriate corrective action. This will be my final report on this matter unless you request additional information or actions.

Sincerely,
Wesley G. Byerly, Pharm.D.
(b) (6)

Associate Vice President for Research Integrity and Regulatory Affairs/Institutional Official

c: R. Holly Fitch, Ph.D., Professor, Department of Psychological Sciences/IACUC Chair
(b) (6)

Laura Kozma, Executive Director, Sponsored Program Services and Faculty Services

Wolff, Axel (NIH/OD) [E]

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Friday, April 27, 2018 11:38 AM
To: (b) (6)
Cc: OLAW Division of Compliance Oversight (NIH/OD)
Subject: RE: A3124-01 Report of Suspension and Noncompliance

Thank you for this report, (b) (6) We will send a response soon. This letter is sufficient and no hard copy needs to be sent.

Axel Wolff, M.S., D.V.M.
Deputy Director, OLAW

From: (b) (6)
Sent: Friday, April 27, 2018 11:31 AM
To: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Cc: Fitch, Roslyn <roslyn.h.fitch@uconn.edu>; (b) (6) (b) (6) Kozma, Laura <laura.kozma@uconn.edu>; Byerly,Wesley (byerly@uchc.edu) <byerly@uchc.edu>
Subject: A3124-01 Report of Suspension and Noncompliance
Importance: High

Dear Dr. Morse,
I have attached a written report from the UConn/Storrs Institutional Official (IO) documenting a protocol suspension that occurred at the University of Connecticut-Storrs. If your office requires a hard copy of this letter in addition to the attached pdf version, please let me know.
If you have additional questions, please don't hesitate to contact us.
Sincerely,
(b) (6)

(b) (6)