



DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

FOR US POSTAL SERVICE DELIVERY:

Office of Laboratory Animal Welfare
Rockledge One, Suite 360
6705 Rockledge Drive B MSC 7982
Bethesda, Maryland 20892-7982
Home Page: <http://grants.nih.gov/grants/olaw/olaw.htm>

FOR EXPRESS MAIL:

Office of Laboratory Animal Welfare
Rockledge One, Suite 360
6705 Rockledge Drive
Bethesda, Maryland 20817
Telephone: (301) 496-7163
Facsimile: (301) 480-3387

December 3, 2021

Re: Animal Welfare Assurance
A3442-01 [OLAW Case 3H]

Matthew Hodgson
Vice President, Research Compliance
And Regulatory Affairs
Children's Hospital of Philadelphia
Roberts Center for Pediatric Research
2716 South Street, (b) (4)
Philadelphia, PA 19146

Dear Mr. Hodgson,

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your November 19, 2021 letter reporting the suspension of several animal activities at Children's Hospital of Philadelphia. According to the information provided, OLAW understands that the Institutional Animal Care and Use Committee (IACUC) took this action after determining that a pig on an approved surgical protocol experienced post-operative complications and required euthanasia. The research staff failed to adhere to the established humane endpoints and failed to contact the veterinary staff.

The corrective actions consisted of the IACUC suspending all ten related protocols, stopping additional animal orders, and stopping all survival surgeries. Following an extensive review by the IACUC, it was determined that the Principal Investigator must terminate protocols under which no active research was performed; develop a new non-survival protocol; combine similar protocols; consult the veterinary staff to develop a decision tree for swine surgical recovery protocols; and to amend the active protocols to refine the humane endpoints and post-surgical care. The laboratory staff was retrained, the internal staff training protocol was evaluated, and all research staff will participate in annual refresher training. The laboratory staffing, responsibilities, and supervisory channels were reorganized. The suspension on non-survival surgeries was lifted and the laboratory was placed under enhanced post-approval monitoring. Once veterinary staff is satisfied that survival surgery and post-operative care is being conducted correctly, these studies will also be allowed to resume under veterinary supervision. OLAW also understands that the funding components had been notified of the suspension, that pigs were the only animals involved in the suspension, and that the proposed corrective action plan was acceptable to the USDA inspector.

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. 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
Robert Gibbens, D.V.M., USDA-APHIS-AC

Matthew Hodgson
Vice President, Research Compliance & Regulatory Affairs
Roberts Center for Pediatric Research, Office 17121
2716 South Street
Philadelphia, PA 19146
267-426-8723

November 19, 2021

Brent Morse, DVM
Director, Division of Compliance Oversight
Office of Laboratory Animal Welfare (OLAW)
National Institutes of Health
6700B Rockledge Drive, Suite 2500, MSC 6910
Bethesda, MD 20892-7982

Dear Dr. Morse:

The Children's Hospital of Philadelphia (CHOP), in accordance with Assurance D16-00280 (A3442-01) and PHS Policy IV.F.3., submits this report of suspension and corrective and preventive actions that were taken by the IACUC of USDA-regulated activities for the following protocols:

- IAC 19-001236
- IAC 19-001327
- IAC 18-001304
- IAC 18-001318
- IAC 20-001121
- IAC 19-001206
- IAC 20-001261
- IAC 21-001373
- IAC 21-001408
- IAC 18-001303

On August 17 and 18, 2021, an animal welfare concern was brought to the attention of the Institutional Animal Care and Use Committee (IACUC) regarding a post-operative animal (IAC 19-001327) that experienced complications and required euthanasia. There were concerns about the condition of the animal, failure of research staff to contact Department of Veterinary Resources (DVR) veterinary staff, and adherence to approved humane endpoints.



**Children's Hospital
of Philadelphia**

Research Compliance & Regulatory Affairs

2716 South Street, 17th Floor • Philadelphia, PA 19104 • 267-426-8723

On August 19, 2021, the Attending Veterinarian, after consultation with the IACUC Chair and the Institutional Official, advised the research team that no animal orders could be placed, and no survival surgeries could be performed until the IACUC could discuss these concerns at a fully convened meeting. Both actions were adhered to by the research team.

On August 26, 2021, an off-cycle fully convened IACUC meeting was held to discuss the concerns with the research team. After meeting with the research team and discussions among the IACUC members, the committee voted unanimously to:

- suspend all research activities involving USDA species on the above- mentioned ten IACUC-approved protocols
- form an IACUC subcommittee to further review concerns that were raised specific to this incident and provide corrective and preventive actions
- report to AAALAC, Department of Defense (DOD), National Institutes of Health/Office of Laboratory Animal Welfare (NIH/OLAW), United States Department of Agriculture (USDA), and University of Pennsylvania (Penn) IACUC

On August 31, 2021, the Attending Veterinarian contacted our USDA Veterinary Medical Officer to provide a preliminary report of this incident and protocol suspensions. On September 1, 2021, the IACUC Administrative Director, contacted OLAW and DOD to provide a preliminary report of this incident and protocol suspensions. In addition, the Institutional Official contacted the Penn IACUC to provide a preliminary report of this incident and protocol suspensions.

A subcommittee of five IACUC members was formed and met beginning on September 2, 2021. These meetings included discussions regarding the timeline and summary of events for the post-operative animal, the IACUC protocol's language for post-operative care, and condition of the post-operative animal. The subcommittee interviewed 18 individuals from the veterinary and research teams, and reviewed survival surgery records for animals on IACUC protocol IAC 19-001327. The subcommittee provided a comprehensive report with recommendations. On October 12, 2021, the IACUC discussed the subcommittee's report at length. The IACUC voted to accept the subcommittee's recommendations as required directives and lift the protocol suspensions for all protocols pending approved amendments.

The required directives focused on the following areas:

- Protocol consolidations and revisions
 - Terminating protocols that have not had active research
 - Creation of a new non-survival protocol (approved October 9, 2021)
 - Consolidating protocols that have similar aims/procedures
 - Development of a rating system/ decision tree in collaboration with the DVR veterinary staff to be included for swine recovery protocols
 - Amendments focused on more robust humane endpoints, description, and care of post-operative animals

- Procedure refinements and amendments, where applicable
- Support personnel and training
 - All research staff who are listed as support personnel on swine protocols are to be retrained by the Office of IACUC Administration (OIA) and the DVR veterinary staff
 - The research team is to evaluate and revise their internal staff training program and submit to the IACUC for review
 - All research staff members will participate in an annual refresher training hosted by OIA and the DVR veterinary staff
- Continued PAM and DVR veterinary oversight of procedures until the IACUC determines that oversight by PAM and DVR is no longer necessary as demonstrated by competency and compliance by the research team
- Research team to submit monthly reports to the IACUC summarizing all swine procedures performed

Retraining of all research support personnel has been completed. Specific research staff have been assigned compliance and animal specific responsibilities. New roles were created within the research team, including a Large Animal Operations Manager and a Large Animal Personnel Manager. Initiation of non-survival procedures resumed on November 12, 2021, with representatives from OIA and the DVR veterinary staff observing the procedures.

Resumption of survival studies will depend upon approval of related protocols and a report from OIA and the DVR veterinary team that non-survival studies are being consistently conducted within parameters defined in accordance with the IACUC protocol for non-survival procedures. Resumption of survival studies will also be phased, beginning with short-term survival procedures, progressing towards longer-term survival procedures based on the research team's monthly summary reports and feedback from OIA and the DVR veterinary staff.

During the time of suspension, there were no swine being housed or used for research on the above-mentioned listed protocol numbers. Therefore, no grant funding was used to support swine research activities for the above-mentioned listed protocol numbers.

Brent Morse, DVM
November 19, 2021
Page 4

We believe that the above-described actions are appropriate to address the concerns that were identified. However, if you would like us to take any additional measures or desire additional information, please do not hesitate to contact me, our Attending Veterinarian (Laike Stewart, DVM, DACLAM), or our IACUC Chair (Laurence Eisenlohr, VMD, PhD).

Sincerely,

(b) (6)

CR Matthew Hodgson
Institutional Official

Cc:

(b) (6)

Laurence C. Eisenlohr, VMD, PhD, Chair, IACUC
Laike Stewart, DVM, DACLAM, Attending Veterinarian and Senior Director, Department of
Veterinary Resource

Wolff, Axel (NIH/OD) [E]

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Friday, November 26, 2021 8:14 AM
To: (b) (6)
Cc: OLAW Division of Compliance Oversight (NIH/OD)
Subject: RE: OLAW Assurance D16-00280 A3442-01_ - Report of Protocol Suspensions

Thank you for this report, (b) (6). Although we will send an official response soon, it is important to send us the following additional information at this time:

- The grant numbers for any involved projects supported by NIH, FDA, CDC, BARDA, NSF, NASA, or VA.
- Confirmation that the funding component(s) have been notified of the suspension.
- Confirmation that swine were the only species involved.
- Any additional subsequent communication from USDA regarding the acceptability of the corrective actions.

We will be sending additional questions following review of the report but will need to incorporate the responses requested above.

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

From: (b) (6)
Sent: Wednesday, November 24, 2021 1:00 PM
To: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Cc: Hodgson, Matthew <HODGSONM@chop.edu>; Eisenlohr, Laurence <eisenlc@pennmedicine.upenn.edu>; Stewart, Laike S <STEWARTL3@chop.edu>
Subject: OLAW Assurance D16-00280 A3442-01_ - Report of Protocol Suspensions
Importance: High

Dear OLAW,

Attached to this email please find a report of IACUC protocol suspensions. We look forward to your review of this matter.

Thank you,

(b) (6)

(b) (6)



OLAW Assurance D16-00280 A3442-01 - Report of Protocol Suspensions

- The grant numbers for any involved projects supported by NIH, FDA, CDC, BARDA, NSF, NASA, or VA.

IAC 19-001327	Improving Pediatric Cardiac Arrest Survival and Neurologic Outcome	Pigs	5R01HL141386-03	Improving Pediatric Cardiac Arrest Survival and Neurologic Outcome
IAC 18-001304	Mitochondrial Targeted Biofuels as Countermeasures Against Chemical Threats (CounterACT)	Pigs Rats	1R21ES031243-01A1	Mitochondrial-Directed Therapy in Carbon Monoxide Poisoning
IAC 18-001318	Intracranial Physiology and Treatment Options in a Pediatric Swine Model	Pigs	5R01NS113945-02	Diffuse Optics for Pediatric Hydrocephalus Management
			5R01NS119473-02	Novel Ultrasound Indices of Intracranial Pressure and Brain Ischemia in Neonatal Hydrocephalus
			5KL2TR001879-05	MTR and KL2
IAC 21-001373	Advanced Therapies in Mitochondrial Changes	Pigs	1R21ES031243-01A1	Mitochondrial-Directed Therapy in Carbon Monoxide Poisoning
IAC 18-001303	Therapeutics for Mitochondrial Disease	Pigs Mice	5R01NS114656-02	Superoxide-sensitive radiotracer as a predictive biomarker of Parkinson's disease progression

- Confirmation that the funding component(s) have been notified of the suspension.
 - Funding components were notified September 1-2, 2021.
- Confirmation that swine were the only species involved.
 - Swine were the only species involved
- Any additional subsequent communication from USDA regarding the acceptability of the corrective actions.
 - On November 24, 2021, following our report to USDA APHIS Animal Care, they acknowledged receipt of our report and informed us they were forwarding the report to our assigned inspector and their supervisor for review. However, we had previously informed our assigned inspector about the suspensions and during a recent facility inspection, the inspector commented on the corrective action plan as "fantastic and comprehensive" and added that the plan addresses the deficiencies from all of the right angles to ensure that such incidents do not occur again. We recognize that these comments do not represent an official response from the USDA but wanted to share this with OLAW.

Wolff, Axel (NIH/OD) [E]

From: [REDACTED] (b) (6)
Sent: Tuesday, November 30, 2021 9:28 AM
To: OLAW Division of Compliance Oversight (NIH/OD)
Subject: RE: [External]RE: OLAW Assurance D16-00280 A3442-01_- Report of Protocol Suspensions

Thanks so much!

(b) (6)

From: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Sent: Tuesday, November 30, 2021 6:12 AM
To: [REDACTED] (b) (6)
Cc: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Subject: RE: [External]RE: OLAW Assurance D16-00280 A3442-01_- Report of Protocol Suspensions

Thank you for your prompt and thorough response. I will carefully review all of this information and send a response to the IO soon.
Axel Wolff

From: [REDACTED] (b) (6)
Sent: Monday, November 29, 2021 12:52 PM
To: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Subject: RE: [External]RE: OLAW Assurance D16-00280 A3442-01_- Report of Protocol Suspensions

Good Afternoon,