



DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

FOR US POSTAL SERVICE DELIVERY:

Office of Laboratory Animal Welfare
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Bethesda, Maryland 20817
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February 8, 2017

Re: Animal Welfare Assurance
A3143-01 [OLAW Case O]

Dr. Camille P. Wicher
Vice President, Corp. Ethics and
Research Subject Protection
Roswell Park Cancer Institute
Elm & Carlton Streets
Buffalo, NY 14263

Dear Dr. Wicher,

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your January 31, 2017 letter reporting the suspension of an animal activity at Roswell Park Cancer Institute. According to the information provided, OLAW understands that the Institutional Animal Care and Use Committee (IACUC) took this action after determining that mice were not being adequately monitored, several were unhealthy or moribund and one had died, there was no documentation present, and frequency of monitoring was not increased as clinical signs deteriorated. The laboratory staff was inadequately trained in identifying sick mice and did not understand the protocol documentation requirement. Also, the IACUC failed to identify the problems in a timely manner.

The corrective actions consisted of suspending the protocol and moving the animals to a holding protocol. The Attending Veterinarian retrained the staff on animal distress and scoring criteria, the health scoring sheets were revised and staff was trained on their use, health monitoring reports will be sent to the IACUC to ensure compliance, the Principal Investigator (PI) and staff were trained on the cage health flagging system, the laboratory staff read the protocol and certified understanding, the PI will ensure staff receives ongoing training, and the protocol was revised to reflect the increased monitoring and documentation. The PI will inspect the animal rooms to ensure appropriate health monitoring and documentation.

The IACUC will review the health monitoring sheets quarterly and will review the flagging frequency of cages monthly. Laboratory animal staff will notify the IACUC of any increase in mortality for any high dose radiation study and the IACUC will review such protocols closely during the semiannual review. The study was subsequently reinstated by the IACUC.

Based on the information provided, OLAW is satisfied that appropriate actions have been taken to investigate, correct, and prevent recurrence of the noncompliance. In future reports please indicate whether the protocol involved was PHS-supported and provide the relevant grant number(s) if so. Also, if this study was PHS-supported please notify the funding component of the suspension. We appreciate having been informed about this matter and find no cause for further action by this Office.

*Page 2 -- Dr. Wicher
February 8, 2017
OLAW Case A3143-O*

Sincerely,

A handwritten signature in cursive script, appearing to read "Axel Wolff, M.S., D.V.M.", followed by a horizontal flourish.

Axel Wolff, M.S., D.V.M.
Director
Division of Compliance Oversight

cc: IACUC Chair



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A3143-0

Obtained by Rise for Animals. Uploaded 07/09/2020

January 31, 2017

Axel Wolff, DVM.
Director, Division of Compliance Oversight
Office of Laboratory Animal Welfare
National Institutes of Health
Rockledge 1, Suite 360, MSC 7982
6705 Rockledge Drive
Bethesda, MD 20892-7982

RE: Report of Non-Compliance

Dear Dr. Wolff,

Please accept the enclosed report as required by 9 CFR 2.31 (c) (3) and (d) (7) Subchapter A of the Animal Welfare Act, as well as PHS Policy IV.F.3. Please accept my apologies in the delay in this report. When completing our annual AAALAC report, I realized that although I had started this report, I did not email it to your attention. It was reported to me in a timely manner, so the oversight is mine.

Corrective action has been instituted. Roswell Park Cancer Institute is committed to protecting the welfare of animals used in research and appreciates the guidance and assistance provided by OLAW in this regard. Should you have any questions, please do not hesitate to contact me at [redacted] telephone # [redacted].

Thank you in advance for your cooperation in this matter.

Sincerely,

Camille P. Wicher, PhD., Esq., RN, MSN
Vice President
Institute Official
OPRR Assurance #A-314301.
USDA Regis. #21-R-032

OPRR Assurance #A-314301.
USDA Regis. #21-R-032

Please accept the following (revised) final report in accordance with 9 CFR 2.31 (c) (3) and (d) (7) Subchapter A of the Animal Welfare Act:

ISSUE: Non-compliance with protocol led to animal welfare issues.

SUMMARY:

The IACUC conducted a random inspection on August 2, 2016 and found several instances of serious noncompliance with protocol 1143M. The findings were discussed and the IACUC deliberated as a full committee and voted to suspend 1143M. The IACUC determined that because of the protocol non-compliance and animal welfare issues it was necessary to stop research on protocol 1143M until appropriate actions were taken by the PI to correct this non-compliance.

To briefly summarize; during the random inspection animals in 2 rooms were determined to be unhealthy or moribund and there was no required documentation indicating that the animals were being closely monitored as required by the protocol (1143M). In fact one of the mice was found dead in the cage after it had been flagged by LASR veterinary services on July 26th. The PI's laboratory response to the flag was "monitoring daily". However there was not a health monitoring sheet in the room indicating the health condition of the animal or that any monitoring was in fact taking place. The other cage with a moribund mouse had been flagged by LASR veterinary services on July 29th and the labs response to that flag was "not bad will monitor daily". Again there was no monitoring sheet for this animal, cage, or protocol.

Protocol 1143M states that increased monitoring will be required for "...ruffled fur, ocular discharge, lethargy, hunched back, inappetite, ataxia, tremors, ulcerated tumors, diarrhea, and huddled appearance, and respiratory rate change. In addition, mice will also be weighed at least 2-3x/week. Animals found to demonstrate any of these clinical signs and/or greater than or equal to 10% weight loss will not be further treated or manipulated and will have their monitoring for morbidity/moribund state increased to 3 times per day to determine recovery versus clinical worsening."

The response of "not bad will monitor daily" was not an appropriate response and there should have been increased monitoring and documentation of that monitoring.

Investigation

LASR records were checked in an effort to determine if the instances found during inspection on August 2nd were anomalies and could not have been foreseen. However, records show that this was not the case. Three other mice had been found dead in the week preceding the inspection. These losses should have resulted in increased monitoring and documentation and appropriate action for animal welfare.

Review by the IACUC of flagging by LASR veterinary services for the month of July 2016 listed that 45 flags were issued for animals found dead, and only 6 of the flags for unhealthy animals had a response from the investigator of "will monitor". These flagged

cages should have resulted in increased monitoring and documentation of the increased monitoring.

At the monthly IACUC meeting (08/02/2016) (the afternoon of the random inspection) the committee discussed these findings and determined this failure to increase and document the monitoring of unhealthy animals as written in the approved protocol was serious non-compliance with protocol 1143M and was an animal welfare issue. The IACUC voted unanimously to suspend all animal research on protocol 1143M. Animals on protocol 1143M were transferred to LASR's holding protocol and the investigator and his laboratory staff did not have access to these animals until the IACUC was assured that corrective and preventative plan of action (CAPA) was appropriate and could be instituted.

The PI provided a corrective and preventative plan of action to address how to prevent a recurrence of this non-compliance. To summarize the CAPA:

Root Cause of the Non-Compliance – A misunderstanding of lab members regarding the monitoring of health and documentation of that monitoring. The lab members mistakenly thought that LASR veterinary staff was to write comments/messages on the monitoring forms. The PI stated that the lab members were actually taking rotations to monitor the sick mice three times per day as per protocol 1143M. Dr. Cao also determined that a new post-doc who had just finished his lab's internal training and was performing independent experiments was responsible for the "not bad will monitor daily". The lab staff did not understand the protocol documentation provisions.

Corrective Plan – Laboratory staff along with the PI met with LASR Attending Veterinarian to revise and review the criteria for the health scoring sheets. The Attending Veterinarian also trained all the lab staff on the scoring criteria and how to recognize animal distress and how to interpret the signs of distress. The lab staff will resume posting and filling out the revised health monitoring sheets. Quarterly copies of the health monitoring reports will be sent to LASR and IACUC, to be reviewed for compliance.

The Attending Veterinarian also reviewed with the PI and his laboratory staff LASR's health cage flagging system, its purpose to communicate any concerns regarding an animal in that cage and how to address the concerns. In addition, the importance of appropriate contact information on the cage was reviewed, including why the contact person should be the individual responsible for the experiment as well as why LASR veterinary services needs to have this contact information.

All laboratory personnel on the protocol read the animal protocols 1143M (experimental) and 1140M (breeding) and documented they understood the protocols. The PI met with his laboratory staff and reviewed laboratory training processes and experimental procedures and methods for improvement. All Laboratory personnel have access to electronic versions of the IACUC protocols and this access will be included in training of new personnel. All laboratory personnel are to have received retraining on IACUC protocols, experimental procedures checklist and scoring system on a semi-annual basis.

An amendment to 1143M was submitted (and approved) that clearly outlines the increased monitoring procedure and the documentation of that procedure

Monitoring CAPA – the PI will patrol the animal rooms twice a week to monitor the health monitoring process and documentation and any of issues that might arise.

A subcommittee of the IACUC charged with the investigation and review of 1143M suspension and the power to rescind the suspension reviewed the CAPA provided by the PI and voted to approve the CAPA and rescind the suspension (unanimous; 5 yes).

The IACUC subcommittee after review of this serious non-compliance developed its own CAPA.

Root Cause of the Non-Compliance – In addition to root causes identified by the PI, the IACUC determined there were additional causes that led to the non-compliance. The PI had a research associate leave the lab in November of 2015, a new post-doc added to the protocol December 2, 2015, and a post-doc left the laboratory on February 12, 2016. The IACUC believes the loss of senior personnel (a research associate and a post-doc) contributed to the non-compliance. The IACUC believes that the PI did not provide sufficient training to the new post-doc nor provided retraining of existing personnel. Another cause may have been a lack of adequate oversight of the animal research experiments on his protocol 1143M. The IACUC agrees there was a misunderstanding of the laboratory personnel as to documentation, however due to the number of mice found dead there was also insufficient training of laboratory personnel regarding the scoring system and the appropriate signs and severity indicative of a moribund condition.

Although, the IACUC did provide oversight and review of protocol 1143M apparently it was insufficient to prevent the non-conformance. The IACUC had included 1143M in the recent annual inspection as well as the semi-annual inspection in May 2016, but the oversight in May was not sufficient to prevent or identify the non-compliance sooner. Although the health monitoring sheets were examined during the semi-annual inspection in May there were no animals showing signs that required increased monitoring so when the monitoring sheet was examined there were no required entries that would have initiated concern. However, the IACUC did not closely monitor veterinary services daily bed checks and flagging of mice on protocol 1143M which could have identified the non-conformance sooner.

Corrective Plan for IACUC – In agreement with the PI's CAPA the IACUC will receive and review copies of health monitoring sheets from the protocol on a quarterly basis. The IACUC will review flagging frequency of cages enrolled on 1143M in which mice receive lethal doses of radiation at each monthly convened meeting of the IACUC for the next year to monitor for any issues with 1143M. To prevent any monitoring concerns or oversight of animal protocol's in which increased monitoring is required and documented the IACUC will request that LASR brings to the attention of the IACUC at the monthly convened meetings any unusual increase in flagging for animals found dead for any IACUC protocols in which animals receive high dose radiation treatment. The IACUC during random inspections for the next year will always include protocol 1143M. In addition, all protocols for which IACUC requires an increased monitoring due to high dose lethal radiation treatment will be checked for health monitoring and documentation of monitoring compliance during semi-annual review.

Monitoring CAPA – The metrics to be measured will include: 1.) the number of animals found dead following treatment with lethal doses of radiation as part of the experimental design in protocol 1143M (A decrease in the number of animals found dead following radiation treatment (~1-7 days) under protocol 1143M will be an indicator of a successful CAPA); 2.) The completion of health monitoring sheets by the laboratory staff for mice that received lethal doses of radiation; 3.) The elimination of IACUC of major and minor non-compliance (s) by this PI and his laboratory staff during semi-annual and random inspections.

The IACUC subcommittee believes that the PI's CAPA as well as the IACUC's CAPA address sufficiently the root causes, the corrective plans needed and the preventative processes to prevent a recurrence of this serious non-compliance.

If you have any additional questions, require clarification or further action by the IACUC please feel free to contact me.

Respectfully submitted,

Camille P. Wicher, Ph. D. Esq. RN MSN
Institutional Official
Vice President
Roswell Park Cancer Institute