Department of Veterans Affairs

Memorandum

Date: October 25, 2019

From: Chairman, Institutional Animal Care and Use Committee (IACUC), CAVHS

Subj: Initial Report of Unanticipated Mortality and Suspension of Protocol #1378872, entitled "PCSK9, Inflammation and Infarct Size", conducted under Principal Investigator (PI) b6, MD, PhD

To: Medical Center Director, Central Arkansas Veterans Healthcare System, CAVHS (00)

1. On September 26, 2019, during a Combined Program Review site visit, the Office of Research Oversight (ORO) informed the IACUC Chair, Veterinary Medical Unit Supervisor, Veterinary Medical Officer, and the IACUC Coordinator that a review of surgery records for protocol #1378872 resulted in allegations of non-compliance that require reporting to the IACUC for a determination.

2. During a review of the surgical records, ORO noted that study personnel performed a total of 44 murine surgeries, noted on three separate occasions, from July 9, 2019 to September 11, 2019 resulting in 19 deaths (43% mortality rate). This mortality rate is more than twice the anticipated mortality rate of 20%, per the approved ACORP.

3. The Institutional Animal Care and Use Committee (IACUC) reviewed this information at their October 9, 2019 meeting. The committee was not made aware of any report or other evidence of specific actions on the part of the project's personnel that constituted mistreatment or negligence toward the animals; likewise, the committee was not made aware of any specific deviation from the procedures outlined in the ACORP. The committee determined that since the mortality reached a rate higher than the anticipated mortality rate stated in the ACORP (20%), the project's personnel should have taken action to address the elevated mortality rate. The improvement in mortality rate between August 9, 2019 and September 11, 2019 was considered *prima facie* evidence that the unexpected mortality rate did not constitute evidence of consistent mistreatment or negligence. The committee also noted that the only local policy addressing such unanticipated events stipulates that they be reported to the IACUC at the time of Annual Request for Continued Approval of Animal Use; such a request was not due for this protocol during the relevant time period.

4. The IACUC decided to determine that the conditions rose to the level of mandatory reporting specified in PHS Policy, section IV.F.3. or in NIH Guide Notice NOT-OD-05-034: a) serious or continuing noncompliance with PHS policy; b) serious deviation from the provisions of the Guide for the Care and Use of Laboratory Animals; or c) suspension of an activity by the IACUC. Indeed, the situation would seem consistent with a specific example provided in NOT-OD-05-034 of an event not typically reported: "animal death or injuries related to manipulations that fall within parameters described in the IACUC-approved protocol."

5. Although the conditions were not deemed explicitly consistent with reportable events, the IACUC considered the elevated mortality rate a grave matter and evidence of a threat to animal welfare. Pursuant to these concerns, the committee voted to report the situation to OLAW.

6. Since September 11, 2019, no surgeries have been performed for this protocol. Plans for corrective action agreed upon at the meeting included implementation of a policy requiring that such unanticipated incidents be promptly reported to the IACUC by the PI. This policy will be disseminated to each PI at the time of initial protocol approval and will be displayed in the animal facility. The IACUC also agreed to implement and abide by a post-approval monitoring mechanism (PAM) to detect such unanticipated events more readily. Specific provisions of this PAM will include random selection of one protocol per month, which will be subjected to examination of animal-use records and interviews with the PI and other project personnel.

7. On October 17, 2019, the above information was then forwarded by email in a Memorandum to the Facility Director and ACOS/R. After receiving the email, the Facility Director requested additional information on the following concerns:

1). -*"Was it the same study personnel performing the surgeries for each of these three periods (any variation in primary versus secondary operators)?"*

2). -*"Was there any deviation from protocol or process (medication, technique, pre or post-operative steps) during these three timeframes?"*

The IACUC Coordinator responded, and stated, *"At our IACUC follow-up meeting w/ORO during their site visit last month, as well as, the exit interview notes, it was not mentioned about multiple personnel staff performing the reported surgeries nor any deviations from the protocol or process. The IACUC will follow-up with a thorough investigation of the lab, records and personnel (if needed, after record investigation) on Monday, October 21, 2019 to gather and provide adequate details of these occurrences".*

8. On October 21, 2019 an IACUC Subcommittee met to review the surgical records of the approved protocol, "*PCSK9 inflammation and infarct size."* We also met with two research staff members listed on the approved protocol, one listed as performing surgeries after being trained and one listed as the person providing the training, who provided additional information regarding the specific procedures being performed. As a result of this investigation, we discovered the following areas of non-compliance:

- Experimental procedures being performed that are not listed on the approved protocol
- Staff member being trained to perform surgical procedures by an individual not listed on the approved protocol, instead of the one listed as the trainer.
- Not following the measures for maintaining sterility as listed on the approved protocol

9. With the allegations presented, the Subcommittee has decided to suspend access for the two research staff members from entering the VMU, by temporarily deactivating their badges until this matter can be discussed at our next convened IACUC meeting on October 28, 2019. For now, the VMU staff will provide animal husbandry for these mice.

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Department of Veterans Affairs

Memorandum

Date: November 4, 2019

From: Chairman, Institutional Animal Care and Use Committee (IACUC), CAVHS

Subj: Reportable Event Cont'd. of Protocol #1378872, entitled "PCSK9, Inflammation and Infarct Size", conducted under Principal Investigator (PI), [redacted], MD, PhD

To: Medical Center Director, Central Arkansas Veterans Healthcare System, CAVHS (00)

1. On October 21, 2019, an IACUC Subcommittee met to review the surgical records of the Approved protocol, "PCSK9 inflammation and infarct size." We also met with two research staff members listed on the approved protocol, one listed as performing surgeries after being trained and one listed as the person providing the training, who provided additional information regarding the specific procedures being performed. As a result of this investigation, we discovered the following areas of non-compliance:

   - Experimental procedures being performed that are not listed on the approved protocol.
   - Not following the measures for maintaining sterility as listed on the approved protocol.

2. As a result, the Subcommittee decided to suspend access to the Veterinary Medical Unit (VMU) for the two research staff members, by temporarily deactivating their badges until this matter could be discussed with the IACUC Committee at the next convened meeting.

3. The Principal Investigator was notified of the suspension and responded with a letter of apology.

4. The Committee acknowledged the response letter and once again met with the research staff members at the October 28, 2019 IACUC meeting; the PI was unable to attend. The research staff members answered the Committee's concerns and expressed sincere apologies regarding the areas of non-compliance. The research staff members stated that the reason they were conducting the unapproved research was to obtain preliminary data.

5. After deliberation the Committee unanimously agreed that this is a reportable event of non-compliance and that the suspension of access to the VMU would continue until the research staff members provided the IACUC with a written document outlining the procedures that they are allowed to perform as stated on the approved ACORP.

6. Once this document is reviewed by the IACUC Chair, and accepted by the members of the IACUC, the suspension of access to the VMU will be lifted.

7. In an effort to avoid future noncompliance issues, the IACUC Committee agreed unanimously that all personnel listed on this ACORP would be placed on a six-month probation period starting the date when VMU access is again granted. During which time the VMU Supervisor and the IACUC will closely monitor the use of animals and procedures. This will allow the PI to continue animal

research while at the same time sending a clear message that further noncompliance must be prevented.

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