**IACUC Training Exercise #4 – 2021 (What to Do About a Possibly Reportable Matter)**

The following exercise is a continuation of exercises #1-2021, #2-2021, and #3-2021, and may be useful in stimulating discussion regarding compliance with PHS Policy and VA Handbook 1200.07. To facilitate discussion, pages 1 and 2 of the exercise may be distributed to the IACUC members prior to a meeting. After a few minutes of discussion about the exercise during the meeting, the remainder of the exercise may be distributed to provide ideas for the committee’s consideration.

Recall: Matt Johnson, the lead technician for Dr. Carol Wang, an investigator at the Hometown VA Medical Facility, was cleaning and treating a surgical incision of an anesthetized cat with a newly developed agent designed to improve healing where the wound is subject to movement stress. Because the procedure is short, the cat had been anesthetized with an intramuscular (i.m.) injection of a mixture of ketamine and midazolam, which typically allowed plenty of time for the entire procedure and was less stressful on the cat than mask induction with isoflurane would be. The procedure took a little longer than usual, and Matt noticed a slight increase in the cat’s respiratory rate, suggesting the cat was in a lighter plane of anesthesia, which needed to be corrected. He asked his assistant, Jerry Kim (an undergrad student volunteering in the lab to gain some research experience), to administer a small supplemental dose of the ketamine/midazolam mixture. Jerry saw that there was not enough of the mixture left, and found that the bottle of midazolam they had used to make it up was empty, so he got out a new bottle, carefully made up more of the mixture, drew up the volume that Matt had said to give, administered it i.m., and recorded the dose on the surgical notes. Matt finished the procedure without incident, and the cat recovered uneventfully. A week later, Matt was cleaning the lab and noticed that several bottles of midazolam with the same lot number, including the one that Jerry had opened during the surgery on January 14, had actually expired three days earlier, on January 11. Matt used the required procedure to dispose of the expired midazolam so it could not mistakenly be used again. Matt provided a written report about this for the IACUC. The Chair had appointed the Attending Veterinarian to investigate, and put the matter on the agenda for the next IACUC meeting.

Next: After discussing all of the information provided by Matt and the Attending Veterinarian, the IACUC determined that the matter is reportable, so Anne Marie drafted the following description of the matter, based on the comments of the IACUC members during the meeting:

On January 14, 2021, Matt Johnson, the lead technician on the research staff of Dr. Carol Wang, administered a mixture of ketamine and midazolam to a cat according to an IACUC-approved protocol for cleaning and treating a surgical incision with a newly developed agent designed to improve skin healing. The cat was starved overnight, as specified in the protocol, in preparation for the anesthesia, and an appropriate plane of anesthesia was achieved, as expected. When it was noticed that the plane of anesthesia became lighter sooner than expected, Mr. Johnson instructed Jerry Kim, a student trainee in the lab, to administer a supplementary dose of the ketamine/midazolam. The cleaning and treatment procedure was completed, the cat recovered uneventfully, and the protocol is continuing until scheduled sacrifice 10 weeks post-operatively. It was discovered on January 21, 2021, that the bottle of midazolam used by Mr. Kim on January 14, 2021, for the supplementary dose expired on January 11, 2021. Mr. Kim maintained that he was unaware that he was expected to check the expiration date before administering the dose.

Subsequent investigation by the IACUC raised the possibility that the cat had been agitated when anesthesia was induced, which may have contributed to the need for a supplementary dose. It was not clear whether the induction dose had also contained expired midazolam, as the laboratory personnel failed to provide the IACUC with the vial from which that midazolam was drawn. The IACUC also noted that the approved protocol for this work did not include the option of administering a supplementary dose of anesthesia. The IACUC therefore determined that this is a reportable matter, involving (1) a failure to adhere to the IACUC-approved protocol, (2) the possibility that administration of expired midazolam in the induction dose may have been responsible for inadequate anesthesia and thereby jeopardizing the well-being of the animal, and (3) participation of an individual who was not appropriately trained, all of which are given in NOT-OD-05-034 as examples of reportable situations.

**For IACUC discussion (Question 1 of 1): Does this accurately describe the matter and the determinations of the IACUC? Is any of the information included in this draft actually extraneous to what ORO and OLAW require? Is there information needed that does not appear in this draft?**

Moderator:

Remember that language matters:

“Starved” inaccurately suggests a life-threatening lack of food, rather than the reality (for human and veterinary patients) of the clinically recommended standard withholding of food for 12-18 hours before induction of anesthesia, to reduce the risks of aspiration.

“sacrifice” in common use evokes misleading impressions of ritualistic exhibition. Other terms such as “killed off”, “put down”, and “sacked” likewise have connotations that do not apply in the scientific context but can nonetheless be exploited by those with interests in misrepresenting research with animals. “Euthanized” is recommended instead.

“failed to provide the IACUC with the vial” inaccurately suggests lack of cooperation, or even willful obstruction, rather than simply that the vial had been discarded before anyone realized that an investigation would be conducted.

“Mr. Kim maintained that” suggests a defensive attitude, which none of the information provided supports

“participation of an individual who was not appropriately trained” inaccurately portrays Jerry as unqualified to participate in the work on the protocol, when it was actually the case that no one in the lab recognized the need to monitor the expirations dates on the vials.

There is no requirement to identify by name any of the personnel involved. It is sufficient to indicate their roles in the work.

For the purposes of understanding what happened and how best to address it to prevent recurrence, the specifics of the procedure that Matt was conducting and the endpoints of the protocol are irrelevant, so there is no need to mention at all the pre-operative fasting or the endpoint at 10 weeks post-op.

Summary of steps to addressing a potentially reportable matter

Although VA programs of research with animals are subject to the reporting requirements of USDA, OLAW, AAALAC, and ORO, OLAW provides the most specific guidance about what information to include. So the following steps are based on OLAW’s requirements, with a few adjustments to address other applicable requirements as well. At each step of the process, the IACUC is encouraged to consult with the office of the CVMO, ORO, OLAW, and AAALAC as needed for guidance.

Step 1: Let the IACUC know that something has happened that might be reportable. ORO requires that this notification of the IACUC be documented in writing. It’s important to include the name of a contact person, so that the IACUC can respond – the contact person may be a member of the research staff involved, but may also be a member of the general public bringing a complaint to the attention of the IACUC, or any VA personnel who can tell the IACUC what the concern is. It is necessary to specify whether death or other serious harm to a human is involved, because the timeline for action specified by ORO is different for such matters. If a human death is involved, the notification of the IACUC must be within 1 day. Otherwise, the IACUC must be notified within 5 days.

Step 2: An IACUC investigation is initiated. Generally, the IACUC Chair appoints a subcommittee of IACUC members to conduct the investigation, but the subcommittee may consist of a single member, and the Chair may choose to investigate personally.

Step 3: Promptly provide preliminary pre-decisional notifications to ORO, OLAW, and the office of the CVMO that an investigation has been initiated. It’s important to also notify the Director of the local facility, and the local ACOS/R&D, so that they are also aware of the situation and can assist as needed in the investigation.

Step 4: The IACUC reviews the findings of the investigative subcommittee at the next scheduled meeting, or at an earlier emergency meeting, and at each subsequent meeting until the matter is resolved.

Step 5: The IACUC determines the appropriate corrective actions needed to bring the program back into regulatory compliance and reduce the risk of recurrence of noncompliance.

Step 6: The IACUC determines whether the matter is reportable to ORO and to OLAW.

Step 7: Within 5 days of making the determination of reportability, the IACUC communicates that determination to the Director. If the matter is reportable, the IACUC provides the Director with a report describing the matter, and the corrective actions required. The office of the CVMO is available to review draft reports and provide suggestions for making the language as accurate and unambiguous as possible.

Step 8: Within 5 days of receiving an IACUC’s determination of a reportable matter, the Director provides the report to ORO.