University of Washington
August 15th , 2024 IACUC Meeting Minutes

| | | | | |
|---|---|---|---|---|
| Members Present: | AB | CC | JPVH | MB |
| | AP | GL | JS | RM |
| | AW | GW | JT | SF |
| | BE | JFI | | |
| Members Absent: | DM | KG | MRB | MK |
| | GS | | | |

**Opening Business**

- The Floor was opened for public comment at 2:31pm.
- The IACUC Chair called the meeting to order at 2:39 pm.

**Confirmation of a Quorum and Announcement**

- Quorum was confirmed by JS.

**Approval of the IACUC Meeting Minutes**

- The IACUC Chair called for the approval of the July meeting minutes.
  Motion was made and seconded: to approve the minutes as written.
  Further Discussion: *none*
  Vote: Approved with 12 members voting in favor, 0 against and 2 abstentions.

**Attending Veterinarian's Report**

I have checked with the leadership at all sites. I have two adverse events for the committee this month. One of them will be discussed during the Director's Report today.

The other event is a mouse death that occurred in June. During routine cage change by a member of our husbandry team, a 4-week-old mouse became trapped between the wired-top edge of the cage and the cage wall. Veterinary staff was contacted immediately, but death had occurred instantaneously. The mouse was otherwise healthy and experimentally naïve. The individual involved was properly trained. Retraining has also been performed.

**Protocol Monitoring Update**

There are currently 27 protocols on enhanced veterinary monitoring. One new protocol was added over the past month due to the novelty of proposed procedures. Of the 27 protocols on monitoring, 18 were placed on monitoring proactively, and the remaining 9 were placed on monitoring as the result of an unexpected outcome. A total of 11 protocols are currently performing the procedure for which they are on monitoring. All PIs on monitoring continue to work with their veterinary monitor.

University of Washington
August 15th , 2024 IACUC Meeting Minutes

**OAW Director's Report – JFI**

**IACUC metrics –** IACUC metrics are in the meeting folder

**Response to Letters**

At the June meeting, an adverse event was reported to the committee in which, during an intracranial injection surgery on a non-human primate, there was a software malfunction that caused the robotic arm holding the cannula to perform small uninstructed movements. The surgery was immediately suspended, the surgery site was closed, and the animal was allowed to recover from anesthesia. During recovery the animal had a seizure that responded to diazepam, and as recovery progressed, it was noted that the animal did not have full function of the left side of its body. Symptoms improved over the subsequent 2-3 weeks. The lab requested a 2nd surgery to complete the injections, at which time they were informed that they needed to submit an amendment to the protocol. An amendment was submitted and was approved by the IACUC to add the option to perform a 2nd surgery if an unexpected event such as an equipment failure precluded them from completing a planned surgery. During the review of this amendment, neither the specifics of the robot arm malfunction nor the animal's clinical condition were reported to OAW, the AV, or the IACUC. The second surgery was performed approximately 3 weeks after the 1st surgery, after the amendment was approved. While there was no malfunction of the robotic arm during that 2nd surgery, the animal did not recover from anesthesia and was euthanized. The IACUC voted to send a letter to both the PI and to WaNPRC veterinary staff seeking some additional information. Specifically, the letters asked if the report to the IACUC was consistent with their understanding of the incident, if they had additional relevant information, if they had any knowledge of conversations that occurred between vet staff and the group during the time of these events, what their understanding of the reporting chain was at the time of this incident, if that understanding has changed, and if they had any thoughts as to why this event was not reported appropriately.

Both parties responded to the letters. First, I'll summarize the PIs response. In their response, the PI had a few comments about what was reported to the committee. The PI felt that there was insufficient information to indicate that a "grand mal" seizure had occurred as reported. The PI also indicated that they do not know why the incident wasn't reported, and they referred to a WaNPRC SOP that states that "T*he veterinarian determines whether the problem constitutes an adverse event, and if so contacts the Associate Director of the Animal Resources Division and the UW attending veterinarian within 24 hours*". Based on this SOP, the PI assumed that the veterinarian would report any and all incidents as required. The PI also indicated it was their understanding that the Associate Director at that time did report this incident during an IACUC Records Review in October 2023. I want to note that our meeting minutes for that Records Review do indicate that this animal was reported as an unanticipated experimental euthanasia, although the minutes do not include any mention of the robotic arm malfunction or clinical symptoms following the 1st surgery. The PI in their response also emphasized that the surgeries were performed in accordance with their approved IACUC protocol, and risks were outlined in their protocol. Regarding conversations that occurred between the group and veterinary staff, the PI indicated that they were not heavily involved in those conversations, but to their knowledge the group was never informed by veterinary staff that the animal's clinical condition needed to be reported to OAW. The PI closed their letter by stating that they take both animal welfare and regulatory compliance very seriously.

As a side note, since the PI mentioned that risks were outlined in their protocol, I'll note that at the time, this surgery procedure in the protocol stated potential risks as including "infection and/or bleeding". I could not find any mention in the protocol of potential for seizure, paresis, or death. The group is currently working on an amendment that includes clarifying potential risks, and this protocol is due soon for Triennial Review.

Regarding the response from WaNPRC veterinary staff, after sending the letter, I and another member of the IACUC met with a member of the WaNPRC veterinary staff to discuss the questions in the letter, and that meeting was followed by a written response. The veterinarian indicated that although they weren't directly involved in the first surgery, they were aware of the subsequent seizure and approved the administration of diazepam. They were not aware of or could not recall any conversations at the time about reporting this as an adverse event. Regarding the reporting chain, they recall being instructed to inform the WaNPRC Associate Director about anything notable that occurred, and the Associate Director was then responsible for further reporting, although they did not recall receiving any specific or formal training about what constituted a reportable adverse event. The current AV met with the WaNPRC clinical vets earlier this year to review the process for reporting adverse events, and it became apparent at that time that this event may not have been reported as needed, and it was subsequently reported.

I also want to note that, unrelated to this specific incident, OAW did receive an anonymous concern that adverse events were possibly not being reported to the AV. We, including the AV, the IACUC Chair, and myself feel that the investigation of this incident has revealed a significant lack of clarity in the process, which has contributed to the current incident and potentially others not being reported appropriately. The AV has already taken several steps to improve communication and clarity around the reporting of adverse events, including monthly structured meetings between WaNPRC veterinary staff and the AV that will include discussion of any potentially reportable events, and a webinar that the AV will be providing to research staff about reporting requirements and the reporting process. If any other past adverse events are identified that have not yet been reported, those will be reported to the IACUC at a future meeting.

Discussion:

*The IACUC wants the SOP to be refined in order to enhance understanding and remove gaps in this process of reporting adverse events.*

*Regarding the anonymous concern, the Attending Veterinarian or Director will provide an update in 3 months.*

**Noncompliances**

**4534-01 -** Between the dates of May 14th and Jun 26th 2024, a non-human primate enrolled in a study that investigates the biomechanical and neurological mechanisms of feeding and drinking behavior underwent more frequent videofluoroscopy procedures than are approved on the protocol. Videofluoroscopy is a type of x-ray that allows collection of real-time moving images. As with standard x-ray, videofluoroscopy uses radiation to generate images. The protocol states that "recording sessions that require videofluoroscopy... will be limited to twice a week with an interval of at least 48 hours." Between the dates of May 14 and June

26, which covers a 7 week period, there were 5 weeks in which videofluoroscopy was performed, and in 4 out of those 5 weeks the animal underwent videofluoroscopy 3 times in a week, with the majority of those happening as sequences of 3 days in a row rather than sessions being 48 hours apart as stated in the protocol. These are typically set up as what the PI refers to as "triplets", with the first and 3rd session involving a nerve block, and the middle session being a control. The discrepancy in the protocol was noticed by the group on June 17th, and the group submitted an amendment to the protocol, but proceeded to perform 3 videofluoroscopy procedures that week. Additionally, the protocol indicates that animals wear anti-radiation goggles throughout the duration of radiation exposure, but those were not used.

This non-compliance was initially noted when the animal developed clinical signs that required veterinary intervention, so I'll ask Christina to fill us in on the adverse effect to the animal that occurred:

On June 20th, the lab reported abnormal oral and skin pigmentation as well as mild dry, flaky skin. These could be considered signs of superficial radiation toxicity but were considered very mild. The animal began supportive treatment, but the lab was allowed to proceed. The protocol discrepancy was not brought to the attention of vet staff at that time. On June 27th, after videofluoroscopy was performed, the animal was noted to be quiet, not eating, and grimacing when eating soft produce. The lab was instructed to stop imaging, and the animal has not been imaged since that time. The animal was started on additional supportive care, antibiotics, and analgesics at that time. Clinical signs continued to progress to include ocular and nasal discharge, significant skin reddening, generalized swelling of the face, eyelids, and lips, skin flaking, and intermittent edema - all considered likely impacts of radiation toxicity. The animal also experienced inappetance and constipation (likely secondary to opioid analgesics) and was noted to be unable to fully open his mouth for several weeks (cause unknown). Clinical signs waxed and waned for several weeks, and treatments included opioid analgesics, non-steroidal anti-inflammatory agents, antimicrobial agents, nutritional supplements, topical treatments, and various other supplements. At the time of this report, the animal's clinical symptoms are much improved – his demeanor and appetite have largely returned to normal, but he continues to exhibit some edema and ocular discharge. He has not undergone any further videoflouroscopy procedures at this time. He remains under veterinary care.

The approved protocol does include mention of the potential for adverse effects due to over-exposure to radiation and states the following: "The first indications of over-exposure are skin reddening, nausea, and leucopenia. Post experiment monitoring will include signs of skin reddening around the head and loss of appetite. If either of these are observed, a clinical blood cell count will be requested to check for leucopenia. This will be compared with a blood cell count to be taken during preparations for the first surgery.... Other symptoms such as skin redness and nausea generally do not last long (2-3 days) and the animal will be observed and treated as recommended by veterinarian (topical antibiotic ointments, different and more palatable diets)."

The PI's rationale for continuing to perform videofluoroscopy 3 times in a week after identifying the discrepancy in the protocol is that they perceived this to be an inconsistency in the protocol rather than a clear noncompliance. The approved protocol states "For the feeding task, the control feeding task will be performed a day before or after the nerve block session." In conversation with the PI, they explained that feeding tasks always involve fluoroscopy, so their intent of the language was to explain that the nerve block

procedures would occur at least 48 hours apart, but the control session would be in between. This is the "triplet" design that the PI used at their previous institution, and they intended to use the same design after coming to UW. However, the PI did acknowledge that the protocol clearly states in both the experiment description and the fluoroscopy procedure that fluoroscopy would only be performed up to two times per week.

Regarding the goggles, the PI indicated that the goggles were blocking the markers on this animal so they were not used. For the next animal they will change the position of the markers and customize the goggles so they can be used.

After observation of the symptoms, Radiation Safety personnel performed measurements and developed dose estimates. The protocol states the estimated maximum radiation dose is 2 Rem per 10-s trial, with a maximum of 60 trials per session. This totals to 120 Rem per session, or 240 Rem per week with 2 sessions per week. Skin dose estimates performed by Radiation Safety exceeded the per session limit in the protocol in 6 out of 14 sessions, and exceeded the per week limit in the protocol in 3 out of 5 weeks. Radiation Safety does want to stress that these are estimates. Radiation Safety personnel also emphasized that there is significant subject-to-subject variability in sensitivity to radiation.

Radiation Safety personnel have also met with the PI to discuss ways to potentially modify the procedures to reduce the risk of symptoms. These include spacing the procedures out so there is 48 hours between events and alternating active and inactive weeks (in other words, perform fluoroscopy on Mon/Wed/Fri one week, and no fluoroscopy the following week). Another option would be to reduce the duration of exposure per event (e.g., 300 seconds rather than 600 seconds). The PI plans to modify the experimental design via an amendment to the protocol to reduce the duration and/or frequency of sessions, monitor how the next animal tolerates that level of exposure, and then if they don't see any symptoms they could request to increase duration and/or frequency if needed for their science.

The PI has performed an in-depth review of the protocol and has reviewed the approved protocol with all staff. An amendment has been submitted, and the protocol is also coming due for Triennial Review.

This has been reported to OLAW and USDA.

Discussion:
*The IACUC discussed the nature of the deviations from the protocol, including the ignoring of the use of googles, and the time in between fluoroscopies.*

*The IACUC expressed concerns about the tone of the communication from the PI, which struck some as cavalier. The IACUC discussed the need to emphasize that UW has its own policies and standards, regardless of how previous experiments had been run at other institutions.*

*The IACUC also discussed if there would be a possibility to get a more accurate reading of the amount of radiation this animal is exposed to in real time. The IACUC had several questions about the long-term impact of cumulative exposure.*

*The IACUC suggested moving forward with a single pilot animal to be able to evaluate the revised study plan that will be described in a future amendment. The animal that is recovering will not be allowed to undergo any more radiation exposure until two weeks after full recovery. We will reach out to radiation safety for guidance on the lifetime exposure for this animal, and how that would factor into this plan.*

*The letter will ask the PI to explain how their planned amendment will address all of the concerns that the IACUC has brought for this.*

> Motion was made and seconded: To send a letter of Reprimand
> Further Discussion: *none*
> Vote: Approved with 14 members voting in favor, 0 against and 0 abstentions.

**2456-06 -** On the week of May 20th vet services received a report about one cage of mice that had significantly reduced hindlimb mobility. Some background on this study: This group studies a non-controllable model of Alzheimer's disease. These mice develop hindlimb paralysis due to the transgene expression in the spinal cord. The protocol notes that they are expected to show signs of hind limb paralysis at 9 months. They are not expected to survive beyond 10-12 months of age.

Upon evaluating this one cage of 5 mice, vet staff reported that one animal had a very low body condition score (1+/5), complete immobility of hind limbs, and no voluntary response to toe pinch. Euthanasia criteria in the protocol included weight loss >20% or loss of hindlimb activity by hindlimb clasping when picked up by the tail (body condition was not a monitoring or endpoint criteria). Based on the endpoint criteria described on the protocol it was determined that this animal had likely already met euthanasia criteria, and the animal was euthanized.

The monitoring on the protocol describes weekly weights starting at 3 months of age and increasing to 3x weekly once animals are phenotypic. In conversations with the group, vet staff determined that the animals were not receiving the monitoring outlined in their approved protocol. Specifically:

- Weekly weights were not being recorded, instead only some of the mice were being weighed as representative weights based on their age but not each individual mouse. This made it difficult for the group and vet staff to assess whether animals had met euthanasia criteria.
- It also appeared that the group was not evaluating hindlimb clasping, as no records were provided.

Following that initial report to vet services in May, the researcher called an emergency lab meeting to discuss the seriousness of the situation with her group, the required monitoring, and to make sure everyone was on the same page with the strategy moving forward. Veterinary staff also clearly stated to the group that each mouse had to have individual weight monitoring and hindlimb clasping tests, starting immediately. However, on June 11th, another sick animal report was submitted and the group had not yet started their individual weight monitoring. Five animals were again being reported for hindlimb weakness. The reason provided by the lab for not starting monitoring after the first incidence was staffing issues. Their colony manager had left the lab in March, leaving one person responsible for managing colonies for 4 different projects under that protocol. Following the first incident, the lead investigator assigned a grad student the responsibility of managing the colony, but that grad student had left the lab in early June.

Following the incident in June, the veterinary resident suggested they reach out to in vivo services for assistance with colony management. The lead investigator indicated that they had instituted a new phenotype scoring system, and would begin logging their monitoring on a spreadsheet that was shared with veterinary services.

Following those conversations, on July 23rd, sick animal reports were received for 2 underweight and paralyzed mice. Based on conversations with the group, 4 mice (2 mice in 2 cages) had been erroneously marked as sacrificed in their lab records, which led to a lapse in monitoring. The 2 animals that had been reported to vet services were euthanized. However, in conversation with the grad student it was identified that they had only been monitoring phenotypic mice once per week rather than the required three times a week as specified in the protocol. Vet services met in-person with the lead investigator and the grad student to review the protocol and discuss expectations in terms of monitoring and record-keeping. OAW remains in communication with the group and with veterinary staff and is working on amendment to the protocol to add a more robust monitoring strategy, including body condition scoring and a metric for evaluating hind limb paralysis.

This has been reported to OLAW.

Discussion:

*The IACUC discussed the circumstances under which these non-compliances have occurred. Including mentioning the egregiousness of repeated events after both veterinary staff attention, a scheduled emergency meeting and multiple appointments of individuals to care for this colony.*

*The IACUC specifically mentioned that a lack of staffing is not an acceptable reason for not monitoring animals appropriately. As possible actions were discussed by the IACUC, the committee discussed what might happen with the mice that remain on the protocol if the IACUC suspended protocol activity. The committee decided to require the research team responsible for monitoring these animals to email the IACUC Chair and the protocol liaison with an update every time the animals are monitored. The letters will ask specifically for a robust monitoring plan, including details about the staff that will perform the health checks.*

*Two separate letters were requested to be sent. One to the Protocol PI and one to the Lead Investigator.*

> Motion was made and seconded: To send two letters of reprimand, one to the Protocol PI and one to the Lead Investigator
> Further Discussion: *none*
> Vote: Approved with 14 members voting in favor, 0 against and 0 abstentions

**CLATR Update**

I wanted to present the results of the survey that was sent to IACUC members regarding IACUC member training and suggestions for training strategies.

70% of respondents reported they are satisfied with current training provided to IACUC members. It was also noted that training was perceived as relevant only ~60% of the time. And only ~50% of members feel

the training requirements & expectations are clearly communicated. These are both things we can (and will) work on.

On the upside, 100% of respondents felt that follow-up and support is readily available whenever it is needed so that's good.

CLATR will take this feedback into consideration and work with the IACUC chair to think critically about the relevance of required trainings. We are all busy so if there is training that is truly not relevant to committee functions, we definitely want to reconsider those requirements. If anyone is comfortable providing additional details about which trainings they found less relevant, please reach out!

There were a lot of good suggestions for future training topics as well so thank you to those who took the time to write in those suggestions. The administrative team has created a shared list we can access to keep track of requested topics so I'll make sure those suggestions get added to that list.

There was one request that the in-meeting training topics be published on a schedule for the year ahead so members can plan accordingly. I actually try to keep the in-meeting trainings tied to current, recent discussion topics so I personally like the flexibility of of being able to choose topics that fit with recent committee discussions. That said, I do understand the desire for members to be able to be more prepared and ideally to engage in more discussion during these sessions so I can work with our meeting coordinators to get training topics added to the agenda or included in the supporting docs in advance of each meeting, and I can work toward trying to announce 'next month's topic' at each meeting.

As mentioned previously, part of the goal of this survey was also as a bit of a test-run for creating a similar survey for researchers to solicit feedback about our available for staff. We did learn that some of our questions were confusing and didn't generate the type of information we had hoped so we are working on revising the manner in which the questions are asked before sending it out to researchers.

**Closing Business:**
The Meeting was brought to a close at 4:06 pm.