

Misunderstanding of an MOU?

Great Eastern University received an NIH-funded grant to perform a study with deer mice (*Peromyscus sp.*). Although most of the work would be performed at Great Eastern, the school contracted out a small component of the study to Little Eastern College. The Memorandum of Understanding (MOU) between the two institutions stated that both schools were responsible for reviewing and approving the protocol for the work to be approved at Little Eastern College.

As the study progressed at Little Eastern it became obvious that the ketamine/xylazine anesthetic being used was unsatisfactory and that isoflurane would be a better choice. The principal investigator (PI) at Little Eastern submitted a request to his IACUC office to change the anesthetic. The office had an IACUC-reviewed and

approved policy on anesthetic use for rodents; therefore, using the veterinary verification and consultation process (VVC), the PI's request was forwarded to the attending veterinarian at Little Eastern. The veterinarian verified that isoflurane at the dosage requested by the PI was within the boundaries of the IACUC's policy and would be an acceptable anesthetic for the study. The PI's request and the veterinarian's subsequent concurrence were documented in the IACUC's meeting minutes.

Some time later, at a routine USDA site inspection at Little Eastern College, the inspector read the IACUC minutes and the MOU between the two schools and saw that the anesthetic change was made without the concurrence of Great Eastern University. She asked why this happened,

as the MOU clearly stated that both schools had to review and approve the protocol. The explanation provided by Little Eastern was that the protocol was approved by both schools, but the anesthetic change was made by using VVC and there was nothing in the MOU stating that a VVC request had to be approved by both schools.

What is your opinion? Did the Little Eastern College's IACUC overstep its authority in one or more ways or was it compliant with the MOU? □

Jerald Silverman

University of Massachusetts Medical School,
Worcester, Massachusetts, USA.

e-mail: Jerald.Silverman@umassmed.edu

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The More ≠ the merrier

In this scenario, both institutions must have a properly constituted IACUC in order to approve research activities in accordance with the Animal Welfare Act and Regulations¹ and the Public Health Service Policy on Humane Care and Use of Laboratory Animals². We assumed that both institutions were registered with USDA APHIS and that both had Assurances with OLAW.

OLAW states that inter-institutional collaborations “have the potential to create ambiguities. Therefore it is imperative that institutions define their respective responsibilities³.” The *Guide for the Care and Use of Laboratory Animals* recommends that “the participating institutions... have a formal written understanding (e.g., a contract, memorandum of understanding, or agreement) that addresses the responsibility for offsite animal care and use, animal ownership, and IACUC review and oversight⁴.” The formal written understanding between the two institutions in this scenario was a memorandum of understanding (MOU).

When Little Eastern College modified the protocol using the veterinary verification and consultation (VVC) process, it overstepped its authority with respect to the MOU. This is because, according to OLAW guidance, VVC is a review process for significant changes, though they are specific and may be handled administratively, with the veterinarian serving as a subject matter expert⁵, and

the MOU stated that both schools were responsible for reviewing and approving the protocol for the work to be performed at Little Eastern College. However, “OLAW and APHIS agree that review of a research project or evaluation of a program or facility by more than one recognized IACUC is not a federal requirement³.” Therefore, while Little Eastern College was incongruent with the MOU it established with Great Eastern University, no federal requirements or laws were violated.

The institutions may have been able to avoid this situation if the terms of their MOU had been different. “If both the awardee institution and the performance site institution have Domestic Assurances, they may exercise discretion in determining which IACUC reviews animal activities and under which institutional program the research will be performed. There is no requirement for dual review; IACUCs may choose which IACUC will review protocols for the animal activities being conducted,” according to OLAW guidance on inter-institutional collaboration³. Furthermore, “it is recommended that if an IACUC defers protocol review to another IACUC, documentation of the review should be maintained by both committees. Additionally, the IACUC conducting the review should notify the other IACUC of significant questions or issues raised during

a semiannual program inspection of a facility housing a research activity for which that IACUC bears some oversight responsibility³.”

We would advise both institutions to modify their MOU to delegate Little Eastern College as the IACUC responsible for reviewing protocols and animal activities at that institution, with the stipulation that Great Eastern University be provided a copy of all protocol documentation. Doing so would reduce regulatory burden as well as resolve such ambiguities as were observed by the USDA site inspector. □

Tom Chatkupt* and Odessa Reilly

Oregon Health & Science University, Portland, OR, USA.

*e-mail: chatkupt@ohsu.edu

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References

1. Animal Welfare Act and Regulations, 9 CFR, Chapter 1, Subchapter A.
2. Office of Laboratory Animal Welfare, National Institutes of Health. Public Health Service Policy on Humane Care and Use of Laboratory Animals, IV.C.1. (US Department of Health and Human Services, Bethesda, Maryland, USA, 2015).
3. Office of Laboratory Animal Welfare, National Institutes of Health. Frequently Asked Questions, PHS Policy on Humane Care and Use of Laboratory Animals, Section D, Question #8; <https://olaw.nih.gov/guidance/faqs#615>.
4. Institute for Laboratory Animal Research. Guide for the Care and Use of Laboratory Animals 8th Edition (National Academies Press, Washington, DC, 2011).
5. Office of Laboratory Animal Welfare, National Institutes of Health. Significant Changes to Animal Activities. <https://olaw.nih.gov/guidance/significant-changes.htm>

VVC doesn't override MOU

Per the inter-institutional agreements, the requested change in anesthetic delivery and drug should have received approval by both colleges before a change

in ACUP (Animal Care and Use Protocol) procedure was made. Despite the fact that the veterinary verification and consultation (VVC) process was used for approval, the

memorandum of understanding (MOU) between the two colleges clearly states that both colleges must review and approve changes to the protocol.

Per the NIH NOT-OD-126, Significant Changes to Animal Activities Previously Approved by the IACUC, point 2.aA. "The specific significant changes described in 2.a-c, may be handled administratively according to IACUC-reviewed and approved policies with a veterinarian authorized by the IACUC.... This includes changes in: a. anesthesia, analgesia, sedation or experimental studies." The change in anesthetic delivery constitutes a significant change that is out of the scope of a VVC and not within the MOU between institutions.

As this is an NIH-funded study, appropriate external reporting of the incident should be determined by the institutions' IACUCs.

Additional considerations for the change from injectable anesthetic drug to inhalant gas anesthesia may include the need for updates and changes to an administrative appendices for the ACUP, occupational health and safety concerns and possible need for staff training. As the use of inhalant anesthetic gases by mask administration carries increased risk to those involved, additional consultation and/or enrollment of those in contact should include their enrollment in the institutions occupational health and safety program.

As there is ongoing collaboration of research studies being conducted by the two institutions, a method for flagging collaborative studies where an MOU exists should be developed or (if exists) reviewed to help prevent future recurrences. This oversight falls on the shoulders of the IACUC chair and/or administrator.

Jill Murray

Oklahoma State University, Stillwater, OK, USA.
e-mail: jill.murray@okstate.edu

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A WORD FROM APHIS AND OLAW

In response to the issues posed in this scenario, the US Department of Agriculture- Animal and Plant Health Inspection Service (USDA-APHIS) and the National Institutes of Health- Office of Laboratory Animal Welfare (NIH-OLAW) provide the following clarifications:

In this scenario, two institutions are collaborating on research with deer mice under a Memorandum of Understanding (MOU). The MOU requires both Institutional Animal Care and Use Committees (IACUCs) to review and approve the protocol for the work. When a significant change is necessary, the IACUC where the work is conducted fails to inform the other institution's IACUC of the change made using veterinary verification and consultation (VVC).

USDA response

The review and approval of significant changes is an IACUC function^{1,2}. At least one IACUC that is party to the MOU must carry out the IACUC functions to meet the Animal Welfare Act regulatory requirements. Although USDA encourages research facilities that contract studies to determine and document which party is responsible for the functions of the IACUC, animal care and handling, and the reporting of animals on the Annual Report, there is no regulatory requirement that this occur. In the context of an animal welfare compliance inspection, USDA focuses on whether an IACUC carried out the necessary review and approval of the significant change as required by the regulations, not the division of

responsibilities described in the MOU. With that said, the implementation of the significant change by one IACUC without informing the other was not consistent with the MOU.

OLAW response

As noted by other reviewers, review of a research project by more than one recognized IACUC is not a federal requirement³. However, failing to inform the MOU partner of the significant change to the protocol is not in keeping with the MOU. OLAW does not consider the failure to follow the agreement in the MOU a reportable incident. Concerning the use of VVC in this scenario, if the IACUC's VVC policy allows changes in anesthetics which include inhalants and if the proper safety and training issues are considered, VVC is an acceptable option⁴.

Bernadette Juarez^{1*} and Patricia Brown^{2*}

¹Deputy Administrator, Animal Care, APHIS, USDA. ²Director, OLAW, OER, OD, NIH, HHS.

*e-mail: bernadette.r.juarez@aphis.usda.gov; BrownP@od.nih.gov

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References

1. Title 9 Chapter 1 Subchapter A Section 2.31(c)(7).
2. Title 9 Chapter 1 Subchapter A Section 2.31(e)(1-4).
3. Office of Laboratory Animal Welfare, National Institutes of Health. Frequently Asked Question D.8: PHS Policy on Humane Care and Use of Laboratory Animals. 2017. Found online at: <https://olaw.nih.gov/guidance/faqs#621>.
4. Office of Laboratory Animal Welfare, National Institutes of Health. Significant Changes to Animal Activities. 2018. Found online at: <https://olaw.nih.gov/guidance/significant-changes.htm>.

VVCs should be addressed in MOU

On its own accord, Little Eastern College appropriately applied the veterinary verification process (VVC) to change to a different anesthesia regimen that is supported in their approved IACUC

policy. OLAW and APHIS do not require that both institutions involved in the research perform an IACUC review of the project¹.

However, the Memorandum of Understanding (MOU) for this project states

that both schools must review and approve the protocol. Therefore, Little Eastern's decision to change the anesthetic protocol without notifying Great Eastern's IACUC of the action does not appear to align

with the MOU. Although the MOU does not specifically require VVC changes be reviewed by both institutions, the fact that Great Eastern University was not notified of the change in anesthetic means that the work being performed at Little Eastern College is not following the protocol as it was approved by Great Eastern. In addition to a communication breakdown, the change in anesthesia initiated by Little Eastern could have scientific impact as well. The work contracted to Little Eastern College is only a component of a larger project so presumably, any anesthetic

work done at Great Eastern is being performed using the same anesthetic that was listed in the initially approved protocol for Little Eastern (ketamine/xylazine). Now that research at Little Eastern is being done using isoflurane, the resulting data may no longer be comparable to results using ketamine/xylazine for anesthesia at Great Eastern.

Little Eastern College overlooked the MOU in changing the anesthetic used. The MOU should state the protocol review and approval process, including any changes needed post-approval, and

should clearly outline decision making authority and communication processes for both institutions. □

Melissa Dragon

Pfizer, Inc., Groton, CT, USA.

e-mail: Melissa.Dragon@pfizer.com

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References

1. Office of Laboratory Animal Welfare. Frequently Asked Questions. <https://olaw.nih.gov/guidance/faqs#D>