

The Pain and Distress of VVC

In 2017, Great Eastern University's (GEUs) IACUC deliberated^{1,2} on the limits of the application of OLAW's *Guidance on Significant Changes to Animal Activities*³ and learned that the veterinary verification and consultation (VVC) process cannot be used for the addition of new procedures that are not previously approved on the protocol. OLAW's *Guidance* describes specific significant changes that may be handled (i.e., approved) by the VVC process; they are:

- anesthesia, analgesia, sedation or experimental substances;
- euthanasia to any method approved in the AVMA Guidelines for the Euthanasia of Animals; and

- duration, frequency, type or number of procedures performed on an animal.

Dr. Jerry Silverman, GEUs most preeminent faculty member, is constantly submitting amendments to change previously IACUC-approved activities. Because GEUs IACUC has an overly specific application form that requests so much detail, amendments are required for even the smallest change which are reviewed via Designated Member Review (DMR). This process can take up to 2 weeks for approval, which negatively impacts all research timelines. It wasn't surprising that Jerry was ecstatic to learn about the VVC

process and how it would reduce the burden related to submitting amendments.

With extreme delight, Jerry called Dr. Bernie Rollin, the area veterinarian, to request modifications via VVC. Specifically, Jerry wanted to:

- Add a strain of a transgenic *Peromyscus* (newly created model from a collaborator at GEU),
- Add a retro-orbital route for blood collection (which is approved on Jerry's other deer mouse protocol),
- Add cervical dislocation without anesthesia as a method of euthanasia (which is approved on Jerry's other deer

A WORD FROM OLAW AND USDA

A Word from OLAW

On August 26, 2014, NIH released Notice NOT-OD-14-126, *Guidance on Significant Changes to Animal Activities*¹, with the concurrence of USDA, APHIS, Animal Care. According to this Notice, specific significant changes may be handled administratively by Veterinary Verification and Consultation (VVC), as long as they are described in a pre-existing IACUC-reviewed and -approved policy. The IACUC should have an approved VVC policy that lists VVC-eligible significant changes accompanied by IACUC-approved policies/references for each that set allowable parameters for use by the IACUC-authorized veterinarian for verification. A veterinarian authorized by the IACUC may review and verify that the proposed significant changes are consistent with the policy. An institution may choose to further restrict the use of VVC, as is the case here with GEU. The IACUC-authorized veterinarian(s) handling significant change requests may refer any request to the IACUC for review for any reason and must refer any request that does not meet the parameters of the IACUC-reviewed and -approved policies for IACUC review by Designated Member Review (DMR) or Full Committee Review (FCR). A significant change "resulting in greater pain, distress, or degree of invasiveness"¹ does not qualify for VVC and must be reviewed by FCR or DMR. Also, the description of a procedure on one IACUC-approved protocol does not qualify it for inclusion on another protocol

and cannot be used as an IACUC-approved reference for verification by the veterinarian by VVC. Each proposed significant change must be considered for the animals in the context of their specific protocol. Therefore, Dr. Rollin correctly referred the addition of a potentially adverse phenotype and the proposed use of retro-orbital blood collection (due to GEU's policy) to the IACUC. The GEU IACUC requirement for review of scientific justification for the use of cervical dislocation without anesthesia also precludes review via administrative handling, such as VVC. The proposed increase in the number of rounds of glucose testing (via tail blood draw) may have qualified for VVC as a significant change in the "number of procedures performed on an animal"¹, provided the procedure met the requirements of the IACUC-approved policies/references.

A Word from USDA

USDA concurs with OLAW's *Guidance on Significant Changes to Animal Activities*, including the IACUC's discretion to allow the administrative handling of some significant changes to approved animal activities following veterinary verification of IACUC-reviewed and -approved policies¹. Furthermore, USDA emphasizes the veterinarian's authority to refer any request to the IACUC for review for any reason and the requirement that the veterinarian refer any request that does not specifically meet the parameters of the IACUC-reviewed and -approved policies or

that may result in greater pain, distress or degree of invasiveness. While the AVMA Guidelines on Euthanasia describe humane methods of euthanasia that are compliant with the AWR, the AWR themselves define the regulatory standard by which methods of euthanasia are evaluated for compliance². In this case, Dr. Silverman's request for significant changes to his previously approved activities does not specifically align with GEU's IACUC-reviewed and -approved policies, adds procedures not previously approved on the protocol, and the additional procedures proposed will result in greater pain and distress. Thus, Dr. Rollin's referral to the IACUC is warranted, and IACUC review and approval through one of the two methods described in the AWR (DMR or FCR) is required³. □

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- NIH/OLAW. *Guidance on Significant Changes to Animal Activities*. Notice NOT-OD-14-126 <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-126.html>
- Animal Welfare Regulations. 9 CFR § 1.1
- Animal Welfare Regulations. 9 CFR § 2.31(d)(2)

- mouse protocol and includes the same personnel), and
- Increase the number of rounds of glucose testing (via tail blood draw) from 3 to 4.

These changes also involved an increase in animal numbers, but not more than 10% of the originally approved value (and thus, they could be administratively approved). Rollin wasn't certain that VVC was appropriate for all of these changes and called the amendment to Full Committee Review, leaving Jerry anything but ecstatic.

During the IACUC discussion, Rollin communicated the following concerns:

1. Although the transgenic deer mouse strain is approved under a different protocol at GEU, it is new to Jerry's lab and the mice develop dermatitis that needs

2. Per GEUs IACUC policy, retro-orbital blood collection requires anesthesia (thus, this is increased pain/distress for the protocol);
3. Per the AVMA, cervical dislocation without anesthesia is conditionally acceptable (i.e., personnel must be proficient), but GEUs IACUC requires scientific justification for its use and the IACUC would need to review this justification; and
4. Increasing the number of rounds of glucose testing is increasing the pain/distress for the animals.

How would you/your IACUC respond to Rollin's concerns?

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2. Silverman, J. *Lab Anim (NY)* **47**, 9–11, https://olaw.nih.gov/sites/default/files/lab47_01_0118.pdf (2018)
3. NIH/OLAW. *Guidance on Significant Changes to Animal Activities*. Notice NOT-OD-14-126 <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-126.html>

The Appropriate Use of the Veterinary Verification and Consultation (VVC) Process

Dr. Jerry Silverman learned that the new VVC process should result in his protocol amendments being quickly approved. Consequently, Jerry asked his veterinarian, Dr. Bernie Rollin to authorize his protocol modifications through the VVC process. Except for the request to increase the animal numbers by less than 10%, Dr. Rollin felt that the other modification requests did not qualify for the VVC process and had to be reviewed using either the DMR or FCR process.

1. The addition of the newly created genetic strain of *Peromyscus*, which is under the purview of the USDA's definition of an animal¹, is approved under another protocol at GEU; but since this is a new strain for Dr. Silverman's lab, he must provide additional information within the adverse consequences section of the protocol. Dermatitis requires additional monitoring and potential veterinary oversight because of the potential increase in pain and distress associated with the dermatitis. The IACUC review will provide the necessary assurance that the animals will be monitored and treated, if necessary, and veterinarians will be made aware in the event other adverse consequences are present².

2. Dr. Silverman wishes to use the retro-orbital method of blood collection. According to GEU's IACUC Policy for Blood Collection, retro-orbital blood collection requires anesthesia. Although this is approved on Jerry's other protocol, he must confirm on this protocol that the Policy will be followed by using necessary anesthesia for this method³. If Jerry provides scientific justification for not using anesthesia, he must also provide confirmation of proficiency of trained staff using retro-orbital bleeding⁴. This will ensure that animals will not endure additional pain and distress created by what appears to be a painful blood collection technique. Along with this new technique, Jerry wishes to add a 4th collection event. Clarification must be provided to ensure that the total blood volume does not exceed 1% of the animal's body weight in 14 days. If it does, then fluid therapy may be necessary. This clarification is required because the new details were not previously approved.
3. The method of euthanasia, described, is approved with conditions in the 2020 AVMA Panel on Euthanasia⁵. To add cervical dislocation without anesthesia,

- which can cause additional pain⁶, Jerry must describe why it is scientifically necessary³. Also, if anesthesia cannot be used for this method, then Jerry must confirm proficiency of trained staff⁴.
4. It is important to remember that no amendment that results in an increase of animal pain and distress can be added by the VVC process. All work funded through PHS Agencies, the PHS Policy IV.C.1., "Review of PHS-Conducted or Supported Research Projects" requires review of all new modifications to approved protocols by the IACUC. "...the IACUC shall confirm that the research project will be conducted in accordance with the Animal Welfare Act insofar as it applies to the research project, and that the research project is consistent with the *Guide* unless acceptable justification for a departure is presented. Further, the IACUC shall determine that the research project conforms with the Institution's Assurance" and ensures that procedures with animals avoid or minimize discomfort, distress, and pain (consistent with sound research design)⁷, by providing appropriate sedation, analgesia, or anesthesia unless scientifically justified³ and that euthanasia methods are consistent with the

AVMA Panel on Euthanasia⁵. It would be in the best interest of the GEU staff to provide additional training opportunities to help the research community understand how to use the VVC process appropriately. □

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2. Public Health Service. *Policy on Humane Care and Use of Laboratory Animals*, IV. C.1.e. page 14

3. Public Health Service. *Policy on Humane Care and Use of Laboratory Animals*, IV. C.1.b. page 13.
4. Public Health Service. *Policy on Humane Care and Use of Laboratory Animals*, IV. C.1.f. page 14.
5. American Veterinary Medical Association. *AVMA Guidelines for the Euthanasia of Animals* (2013 Edition or succeeding revised editions).
6. NIH/OLAW. *Guidance on Significant Changes to Animal Activities*. Notice NOT-OD-14-126.1.b
7. Public Health Service. *Policy on Humane Care and Use of Laboratory Animals*, IV. C.1.a. page 13.

COMPLIANCE CONSIDERATIONS

The Protocol Review coordinators offer the following compliance considerations:

1. Types of changes to IACUC-approved activities:

OLAW's *Guidance on Significant Changes to Animal Activities*¹ defines the flexibility afforded to IACUCs in the review and approval of changes to animal activities; specifically:

- a. Significant changes are those “that have, or have the potential to have, a negative impact on animal welfare” and a few others that don't have such an impact (e.g., change in Principal Investigator (PI)) – these require IACUC review and approval via the FCR or DMR method. However,
- b. “The IACUC has some discretion to use IACUC-reviewed and -approved policies to define what it considers a significant change...” Consequently,
- c. IACUCs may make some significant changes using “IACUC-reviewed and -approved policies in consultation with a veterinarian authorized by the IACUC”. Lastly,
- d. Administrative changes to protocols can occur without IACUC review (e.g., editorial).

2. Is there a threshold for VVC vs FCR/DMR?

The critical distinguishing factor, according to OLAW¹, in the application of VVC vs

FCR/DMR is when a change can result in “greater pain, distress, or degree of invasiveness” (P/D/I). In other words, any change that is expected to increase P/D/I requires FCR/DMR.

Additionally, VVC is intended to only change previously approved animal activities or procedures, i.e., those that are already described in the protocol. Adding a new activity/procedure (regardless of the pain or distress level for that procedure) is, generally, not appropriate for VVC.

3. What about Jerry's amendment?

- a. The transgenic animals have been evaluated by the IACUC; and over the course of veterinary care for those animals (under the second GEUs PI), it has been determined that there is no pain or distress associated with dermatitis. However, unless GEUs IACUC Policy specifically states that any animal activity previously approved by the IACUC and documented to not to involve P/D (i.e., no pain management or palliative care is required) is eligible for VVC, this change cannot be added to Jerry's protocol via VVC.
- b. Although all staff are trained/proficient in the performance of retro-orbital blood collection, a procedure that requires the use of anesthesia or analgesia, it increases P/D and appears beyond the threshold for VVC. However, what if GEUs IACUC requires anesthesia

to stabilize the animal and avoid injury and not because the IACUC considers the procedure to involve P/D? It is the responsibility of GEUs IACUC to determine if this procedure increases P/D/I.

- c. Adding cervical dislocation without anesthesia would be acceptable for VVC (provided that all personnel are proficient in the method); however GEUs self-imposed burden of requiring scientific justification for the method precludes the use of VVC.
- d. Increasing the number of rounds of glucose testing is most likely acceptable for VVC, but this determination is accomplished by the consultation between the veterinarian and PI (i.e., does it increase P/D/I for this specific animal?). □

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What a tangled web of reviews we weave

The issue at hand pertains to the selection between using VVC, DMR, or FCR for the review and approval of Dr. Silverman's amendment. VVC is suitable for making significant changes to animal activities that are part of a previously approved protocol. The VVC process may not be used to add new procedures to a previously approved protocol¹. All Dr. Silverman's additional procedures will bring greater pain, distress or degree of invasiveness for the animals. Per PHS Policy IV.C.2., significant changes that result in greater pain, distress or degree of invasiveness must be approved by one of the valid IACUC methods, FCR or DMR². Therefore, both the retro-orbital blood collection and cervical dislocation without anesthesia fall under this category. Dr. Silverman also intends to introduce a new mouse strain, but it's important to note that deer-mouse strains are subject to USDA-regulations³. The question arises: does the USDA recognize VVC as an

appropriate method? If so, could it be used in this case? To add, cervical dislocation without anesthesia is not permitted by the USDA without using FCR. It may be wise to consult the APHIS Veterinary Medical Officer (VMO) for GEU in this matter. One could argue that these same procedures were previously approved in another protocol; and if the amended procedures align with the principles of the 3Rs, then VVC could be used, or at the very least, DMR. I stand with Dr. Rollin's decision to bring this amendment to FCR review, as there are far more questions than answers. It is better to proceed with caution than to risk non-compliance.

It appears that this scenario presents a good opportunity for GEU to revisit their VVC policy or guidelines. GEU should establish an inclusive IACUC-approved policy and/or guidance document that clearly outlines when the VVC process is appropriate. This would not only minimize confusion but also decrease regulatory

and administrative burdens on both the IACUC and the Principal Investigator (PI), ultimately decreasing the lengthy review and approval process. To boot, it would help to avoid human pain and distress in the future...particularly, Jerry's! □

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3. Animal Welfare Act and Animal Welfare Regulations. https://www.aphis.usda.gov/animal_welfare/downloads/AC_BlueBook_AWA_508_comp_version.pdf