

Jerald Silverman, DVM, Column Coordinator

## Amendment submitted; protocol reviewed?

Dr. Jan White submitted a protocol amendment to the Great Eastern University IACUC and patiently waited—seemingly forever—for feedback from the committee. Eventually she e-mailed the IACUC office and asked for an update. What she heard upset her and led to a series of less-than-pleasant interactions with the IACUC.

White's amendment proposed adding an open-field exploration test to an already long list of behavioral tests that were commonly done in her field of research. In the open-field test, a mouse is placed in the center of an enclosed area, and various observations are made without disturbing the animal. Unfortunately for White, the reviewer decided to review her entire protocol, not just the amendment, and was disturbed about how some of the other behavioral tests, such as the forced swim test, were being performed. When White learned of the

reason for the review's delay, she immediately complained to Dr. Larry Covelli, the IACUC chairman, saying that all of her other behavioral tests had been recently approved by the IACUC and that she hadn't asked for them to be reviewed again.

"I'm sorry," said Covelli, "but it's the prerogative of the reviewers to review any or all parts of the protocol in addition to your amendment. Sometimes they find important items that other reviewers have missed, and it's to the benefit of animal welfare and good research to have any perceived problems fully explored."

"And is it to the benefit of animal welfare and good science to have this drag on forever? You had a veterinary pre-review of my protocol, changes made by me in response to the pre-review, and then you had a full committee discussion about my protocol in which nobody found anything else that

needed changes. How many times does my protocol have to be reviewed and approved before I can get on with the science? Where in your rules and regulations book does it say that a protocol can be re-reviewed every time a person puts in an amendment?"

Covelli knew that during an initial full committee or designated member review, any member of the committee could request additional information or raise concerns about any aspect of a study. He also knew that at any time, any person could request that the IACUC consider re-reviewing all or part of an already approved protocol, but he wasn't entirely sure how to respond to White's question. When an amendment to a protocol is submitted by an investigator, does the reviewer have the authority under federal regulations to re-review sections of the protocol, in addition to the amendment? What is your opinion?

### RESPONSE

#### Unnecessary delays!

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It is unfortunate that White had to endure what many researchers face when dealing with their IACUCs: unnecessary delays. The amendment submitted was for a non-invasive behavioral observation procedure. For many IACUCs, a minor amendment like this could be reviewed through the designated member review (DMR) process. In most cases, the DMR process is faster than waiting for a full committee review. In this scenario, it appears that White's amendment was being reviewed by the DMR process.

Regardless of which process is used, the reviewers have the right to assess the amendment and how it fits with the procedures in the rest of the protocol. This may lead to concerns with parts of the

protocol that were already approved, and the IACUC should require the investigator to address those concerns. However, the IACUC should not require the investigator to wait "seemingly forever" or to contact the committee for a status report.

IACUCs should have deadlines for their reviewers to respond, just as they have deadlines for researchers to submit materials. The IACUC could inform the investigator of the review deadline, so that he or she would know when to expect a response. This would make the review process more objective and ensure a timely response to the investigator. If problems had been found in already-approved procedures and the reviewer had provided that information quickly, then White likely would not have had the same response for Covelli.

The designated member reviewer should also be questioned as to why he or she was not already comfortable with the recently approved protocol. Perhaps the reviewer did not attend the meeting where the protocol was initially discussed and was unable to review it and provide feedback

before that meeting, meaning that he or she is seeing the full protocol for the first time. In this situation, the reviewer can certainly raise concerns and ask for clarification regarding the approved procedures. Assuming there were no problems with this amendment, the IACUC, through the DMR process, could approve this amendment, allowing the researcher to collect data using the new procedure while addressing any concerns about the previously approved procedures.

IACUCs should adhere to the same standards that they expect from researchers. As the group responsible for the animal care program, the IACUC may become frustrated when researchers are delayed in responding to concerns. Likewise, IACUCs should be frustrated when their own processes cause delays in getting responses back to researchers.

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RESPONSE

Amendment necessitates re-review

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During the course of a research project, a need may arise for the investigator to submit to the IACUC an amendment to the animal research protocol for that project. This may occur when there is a significant change in the original protocol, to include but not be limited to the number of animals used, personnel changes and additional procedures or tests. According to the *IACUC Guidebook*<sup>1</sup>, “significant changes to an IACUC-approved protocol must be reviewed and approved before they occur (PHS Policy IV.C.1; and AWR §2.31[d][1])” or are implemented. The review can be done by the full committee or by a designated member.

White was questioning whether the submission of an amendment warrants a complete re-review of an already approved protocol. In response to this, the Public Health Service *Policy on Humane Care and Use of Laboratory Animals*<sup>2</sup> (PHS Policy) requires that a complete IACUC review of PHS-supported protocols be conducted at least once every three years beginning on the date of IACUC approval. The triennial review can be done by the full committee or by a designated member. On the other hand, the Animal Welfare Regulations (AWRs) require an annual review<sup>3</sup>. In either case, we know that all research activities must conform to the statutes of the Animal Welfare Act<sup>3</sup> and the guidelines of the PHS as described in the *Guide for the Care and Use of Laboratory Animals*<sup>4</sup> (the *Guide*). Depending on when White’s original protocol was approved by the Great Eastern University IACUC, and whether the approval was to comply with both the PHS Policy and the AWRs, it might be necessary to completely re-review her protocol.

The designated reviewer chosen by the IACUC thought it was necessary to review White’s entire protocol. Covelli understood the prerogative of a designated reviewer and

A word from OLAW and USDA

In response to the questions posed in this scenario, the Office of Laboratory Animal Welfare (OLAW) and the United States Department of Agriculture, Animal and Plant Health Inspection Service, Animal Care (USDA, APHIS, AC) offer the following clarification and guidance:

The question raised in this scenario is: “When an amendment to a protocol is submitted by an investigator, does the reviewer have the authority under federal regulations to re-review sections of the protocol, in addition to the amendment?”

Section IV.C.5. of the Public Health Service *Policy on Humane Care and Use of Laboratory Animals* (PHS Policy) authorizes the IACUC to conduct continuing review of previously approved ongoing activities<sup>1</sup>. This includes reviews conducted during designated member review of an amendment to a previously approved protocol. Section IV.C.1. of the PHS Policy also requires that the IACUC determine that the research project conforms to requirements for procedures to avoid or minimize discomfort, distress or pain unless justified for scientific reasons<sup>1</sup>. The reviewer is within his or her authority to re-review any sections of the protocol in addition to the amendment.

For those species under the jurisdiction of the USDA, section §2.31(d)(1) of the Animal Welfare Regulations (AWRs) give the IACUC authority to “conduct a review of those components of the activities related to the care and use of animals and determine that the proposed activities are in accordance with this subchapter”<sup>2</sup>. This authority includes designated member reviews and is not limited to just the activities described in a proposed amendment; it applies to all “components of the activities related to the care and use of animals.” In addition, all reviews are required to address the criteria listed in section §2.31(d)(1) of the AWRs, including the requirement to avoid or minimize discomfort, distress and pain to the animals<sup>2</sup>. The AWRs under section §2.31(d)(5) also allow the IACUC to “conduct continuing reviews of activities covered by this subchapter at appropriate intervals as determined by the IACUC, but not less than annually”<sup>2</sup>. Complete reviews conducted during a designated member review of an amendment to a previously approved protocol are well within the IACUC’s authority. It is also within the IACUC’s authority to determine the intervals at which such reviews are conducted.

1. Public Health Service. *Policy on Humane Care and Use of Laboratory Animals* (US Department of Health and Human Services, Washington DC, 1986; amended 2002).
2. Code of Federal Regulations. Title 9, Ch. 1, Part 2, Subpart C.

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the authority granted to him or her by the IACUC to make sound judgment for the benefit of animal welfare and good research. Therefore, in our opinion, it is fitting to re-review the entire protocol in addition to the submitted amendment if the entire IACUC or the designated reviewer determines that it will conform to the statutes of the Animal Welfare Act and the guidelines of the PHS as issued in the *Guide*.

2. Public Health Service. *Policy on Humane Care and Use of Laboratory Animals* (US Department of Health and Human Services, Washington DC, 1986; amended 2002).
3. Animal Welfare Act and Animal Welfare Regulations. 9 CFR Ch.1 §2.31[d][1].
4. Institute for Laboratory Animal Research. *Guide for the Care and Use of Laboratory Animals* 8th edn. (National Academies Press, Washington, DC, 2011).

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1. ARENA/OLAW. *Institutional Animal Care and Use Committee Guidebook* 2nd edn. (National Institutes of Health, Bethesda, MD, 2002).

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