Jerald Silverman, DVM, Column Coordinator

Required modifications and designated member reviews

Larry Covelli, the chairman of the Great Eastern University IACUC, was unwinding in his office when Sandy White, the school's Attending Veterinarian, walked in and sat herself down. "You know, Larry," she said, "I'm still totally confused about the OLAW notice on how to use designated member reviews (DMRs) after full committee reviews in order to clean up loose ends on a protocol[1]. I thought that the IACUC already had the authority to use DMRs, to ask questions and to require modifications to a protocol to secure its approval."

"Well, yes," responded Covelli, "but the notice you're talking about refers to questions that the committee has about a protocol when important information is missing, not specific modifications requested by the IACUC. A required modification would be something like changing the dose of an anesthetic to one required by the committee or requiring the use of an IACUC-defined earlier study endpoint. If the Principal Investigator (PI) agrees to accept the required modification and revises the protocol to include it, the protocol can be administratively accepted. A question, on the other hand, is a simple query, like asking for a stronger justification for the number of animals requested. It still requires full committee or designated member review of the response."

"I understand that," said White, "and that's why I'm confused. The first thing the notice says is that the IACUC may have questions because some significant information is lacking in the protocol. You know as well as I do that happens quite often. But then the notice refers to using the DMR process to approve modifications made to the protocol as a result of the answers to those questions. It seems to me that having a question for a PI and requiring modifications to secure approval are not one and the same. Do you see why I'm confused? There is already a process for handling each of those issues. If the IACUC has questions, it can do one of the two things we already do. We table the protocol, send the questions to the PI and then discuss the protocol again at the next meeting after the PI responds. Or we withhold approval, send our concerns to the PI, let him clean up the protocol and then re-review it like it was a new protocol, using the DMR process."

Covelli thought for a moment, opened his personal "rules and regulations" book and re-read the National Institutes of Health (NIH) notice. After a minute, he turned to White and said, "You know, Sandy, we already have the authority to handle the situations you described, and the last part of the NIH notice actually says that we can continue to do what we've done in the past. My guess is that the whole idea of the notice is to make it easier to do a DMR without going through the process of notifying all the members and waiting to get their approval for using DMR. So maybe it's just a time-saver. But I do see your point. Getting an answer to a question is not the same as having a PI agree to an IACUC-required modification that's needed to secure approval. It's just confusing terminology, but I don't think we have to change the way we do business."

Is Covelli's explanation of what constitutes a required modification correct? Is White correct in claiming that OLAW notice NOT-OD-09-035 confuses questions with required modifications? Do you think that the notice simply expedites the protocol review process?

1. Office of Laboratory Animal Welfare. Guidance to IACUCs Regarding Use of Designated Member Review (DMR) for Animal Study Proposal Review Subsequent to Full Committee Review (FCR). Notice NOT-OD-09-035. (National Institutes of Health, Washington, DC; 8 January 2009). http://grants.nih.gov/grants/guide/notice-files/NOT-OD-09-035.html

RESPONSE

Expedite the process

F. Claire Hankenson, DVM, MS, DACLAM & Troy Hallman, MS, VMD, DACLAM

The casual conversation held between Covelli and White is probably not unusual for determining how to integrate NIH interpretations of Public Health Service (PHS) Policy requirements[1] into existing institutional methods. The new guidance under discussion (NOT-OD-09-035)[2] was developed in response to questions from the 'research community' and enumerates instructions for animal care committees, regardless of membership numbers and institutional approaches to protocol reviews.

In general, the mechanisms for review, whether designated member review (DMR), full committee review (FCR) or a combination thereof, are dictated by individual institutional needs and program scope. The language in PHS Policy[1] section IV.C.2 concerning FCR states that protocol approval may be granted 'only after review at a convened meeting of a quorum of the IACUC with the approval vote of a majority of the quorum present'. If a protocol reviewed by FCR is not approved owing to lack of information, the new guidance clarifies that every member of the IACUC must be present, or have otherwise signed a formalized proxy, to allow all opinions on a FCR to be heard or represented by designated committee members.

The change to IACUCs is in the formalizing of the proxy process, by having 'written standard procedures' that members have agreed to 'in advance and in writing' about deferring authority to their committee colleagues to make appropriate decisions on investigator responses to FCR requests.

We believe that the circumstance, described in NOT-OD-09-035 (section #2.a)[2], will serve to expedite the timeline for protocol approval in the periods between convened full committee meetings. The duties that IACUCs have—specifically, to facilitate institutional animal research programs while ensuring that thorough reviews of proposed animal care and use have been conducted—will be carried out in a more timely manner through the process of DMR subsequent to FCR. At no point does this guidance disallow any IACUC member from requesting to see correspondence for a particular animal protocol. The PHS Policy[1] maintains that 'any member of the IACUC may obtain, upon request, full committee review of research projects'.

Additionally, Covelli's assertion regarding approval of 'required modifications' is correct. If it is determined that a protocol requires very specific modifications before approval can be granted, the IACUC may handle the approval of these modifications or clarifications as administrative details that an individual, such as the Chair, could verify[3]. As with the formalization of DMR subsequent to FCR, this should be a 'written standard procedure'.

In conclusion, while many animal care and use committees, including that at Great Eastern University, may already have institutional and administrative mechanisms in place to handle DMR and FCR, the NIH guidance asks that a formal standard operating procedure, signed by all members, be maintained for those institutions who hold meetings with only a quorum (and not all members) present.

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. Office of Laboratory Animal Welfare. Guidance to IACUCs Regarding Use of Designated Member Review (DMR) for Animal Study Proposal Review Subsequent to Full Committee Review (FCR). Notice NOT-OD-09-035. (National Institutes of Health, Washington, DC; 8 January 2009). http://grants.nih.gov/grants/guide/notice-files/NOT-OD-09-035.html
3. Office of Laboratory Animal Welfare. *Institutional Animal Care and Use Committee Guidebook* 2nd edn. (US Department of Health and Human Services, Washington, DC, 2002).

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RESPONSE

A time-saver

Joseph O. Matu, DVM &
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Covelli and White are struggling over the meaning of "requires modification (to secure approval)[1]." This is demonstrated by White's statement: "It seems to me that having a question for a PI and requiring modifications to secure approval are not one and the same." They appear to be creating an artificial distinction between "required modifications" and "having questions," which does not exist within the regulation. PHS Policy[1] allows for only three possible responses by the IACUC during a protocol review: "… approve, require modifications in (to secure approval) or withhold approval of those components of PHS-conducted or supported activities related to the care and use of animals as specified in IV.C of this Policy."

More troubling is Covelli's statement: "If the PI agrees to accept the required modification and revises the protocol to include it, the protocol can be administratively accepted." As indicated in background section of NOT-OD-035, "PHS Policy does not allow for 'approved pending modification'[1] and does not recognize this approval designation." This is, in essence, what Covelli has described. Additional guidance on acceptable items for administrative review or acceptance can be found on the OLAW website FAQ page[2].

In the end, Covelli hits on the true benefit of NOT-OD-35: "Maybe it's just a time-saver." This notice outlines a process whereby the IACUC can establish a method to send a protocol directly from FCR to DMR without the delay caused by polling members to see if they wish to call for FCR.

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. Public Health Service. *Policy on Humane Care and Use of Laboratory Animals* – Frequently Asked Questions. Protocol Review, Question No. 9. (US Department of Health and Human Services, Washington, DC, 2006; revised 2009). http://grants.nih.gov/grants/olaw/faqs.htm#proto_9.

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RESPONSE

Not a shortcut

Katharine Connaughton, BS,
Javier Foronda, BS, LATG &
Douglas Lobner, PhD

We believe that Covelli's explanation of what constitutes a required modification is too narrow. Anytime the IACUC requires a PI to change what is written on the protocol form, it is essentially requiring a modification. Covelli is also incorrect in believing that the examples of modifications he describes can be accepted administratively. OLAW's FAQ #4 under 'Protocol review'[1] states that "requests for substantive modifications should result in the protocol coming back to the committee." The same FAQ also uses a contact telephone number as an example of a modification that may be verified administratively. Because Covelli's examples are substantive, they are not modifications that should be verified administratively. The IACUC encounters many scenarios during a protocol approval process; therefore, training members of the IACUC as well as administrators in what constitutes a substantive change is essential.

We also feel that the notice does not confuse questions with required modifications. The notice is intended to address both of these issues. The notice

is for anytime the "study protocol does not meet [the committee's] standards for approval."

The notice does suggest that protocol review by a designated member(s) may commence immediately after a meeting in which all members of the IACUC are present or, if the institution has a written policy in place allowing it, after a unanimous vote by the convened quorum. If OLAW was not intending to simplify the process of using DMR subsequent to FCR, there would be no need to distinguish between institutions with a policy for DMR after a meeting at which not all members of the IACUC are present and institutions that do not have such a policy.

The idea behind DMR subsequent to FCR is to expedite the protocol review process after a careful and well-documented FCR. OLAW states that "a DMR may be conducted only if all members of the committee have had the opportunity to request FCR and none have done so." At an IACUC meeting with all members present, all members of the committee are allowed that opportunity when they vote to send the protocol through DMR. At an institution with a written policy that allows a convened quorum to vote unanimously to use DMR, the committee members are aware that DMR of the protocol is a possibility and, if they have concerns, they may request that the protocol not undergo DMR after FCR. It is our belief that this is the reason the notice indefinitely extends the time frame in which a member can call for FCR of the revised protocol when DMR follows review of the protocol by a quorum of the committee.

1. Public Health Service. *Policy on Humane Care and Use of Laboratory Animals* – Frequently Asked Questions. Protocol Review, Question No. 4. (US Department of Health and Human Services, Washington, DC, 2006; revised 2009). http://grants.nih.gov/grants/olaw/faqs.htm#proto_4.

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A word from OLAW and USDA

In response to the issues raised 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:

Guidance to IACUCs Regarding Use of Designated Member Review (DMR) for Animal Study Proposal Review Subsequent to Full Committee Review (FCR)[1] was published in response to questions from IACUCs regarding allowable procedures when a protocol that has been considered at a convened meeting cannot be approved as written. Their questions focused on ways that IACUCs could use DMR as a follow-up to FCR when a protocol lacks substantive information.

Regarding the term "substantive information" in the context of proposals involving animal-related activities, IACUCs are required to evaluate proposals to ensure that they meet the following criteria: (i) conform with the institution's Animal Welfare Assurance and meet the requirements specified in the Public Health Service (PHS) Policy at IV.C.1 (ref. 2); (ii) provide the information described in the Policy at IV.D.1 (ref. 2); (iii) adhere to provisions of the *Guide for the Care and Use of Laboratory Animals*[3]; and (iv) as appropriate, are consistent with the USDA's Animal Welfare Regulations[4].

Should a proposal fail to address any of these items to the IACUC's satisfaction, the Committee may determine that the proposal lacks substantive information and require modifications to secure its approval.

OLAW and USDA note that if a protocol 'requires modifications to secure approval', then investigators must consider IACUC concerns (some of which may be expressed as questions) and address them to the Committee's satisfaction. It does not mean that IACUCs are authorized to dictate specific research methods in a protocol; for example, an IACUC should not require an investigator to use a specific analgesic, but rather should work with the investigator to ensure the animals are provided adequate pain relief[5]. Also, there are no provisions in the PHS Policy or the Animal Welfare Act for approval of proposals based on investigator responses to IACUC "questions."

Therefore, although the example in the scenario about inadequate justification for the number of animals requested may raise serious questions, it also represents a lack of substantive information that must be resolved by requiring an appropriate modification to the protocol from the investigator. There are no PHS Policy or AWA provisions for administrative acceptance (i.e., approval) of proposals.

Regarding the kinds of procedures that are allowable when an IACUC wishes to follow up on issues raised in a FCR by using the DMR process, the guidance contained in NOT-OD-09-035 describes the three options that are available[1]. OLAW also has an expanded Frequently Asked Question on this topic[6].

1. Office of Laboratory Animal Welfare. Guidance to IACUCs Regarding Use of Designated Member Review (DMR) for Animal Study Proposal Review Subsequent to Full Committee Review (FCR). Notice NOT-OD-09-035. (National Institutes of Health, Washington, DC; 8 January 2009). http://grants.nih.gov/grants/guide/notice-files/NOT-OD-09-035.html
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. Institute for Laboratory Animal Research. *Guide for the Care and Use of Laboratory Animals* (National Academies Press, Washington, DC, 1996).
4. Code of Federal Regulations, Title 9, Chapter 1, Subchapter A - Animal Welfare: Part 2 Regulations. [§2.31(d)].
5. U.S. Public Law 99-198 (1985), The Improved Standards for Laboratory Animals Act, Food Security Act of 1985, Subtitle F – Animal Welfare, [7 U.S. Code, Section 2143(a)(6)].
6. Public Health Service. *Policy on Humane Care and Use of Laboratory Animals* –Frequently Asked Questions. Protocol Review, Question No. 19. (US Department of Health and Human Services, Washington, DC, 2006, revised 2009). http://grants.nih.gov/grants/olaw/faqs.htm#proto_19.

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