Jerald Silverman, DVM, Column Coordinator

Managing a pending IBC approval

"I don't know how many times I've said this, but I'll say it again. There is no such thing as a conditional or limited approval. We can't approve a protocol based on something that may happen in the future, even if we're almost sure it's going to happen." With that, Dr. Larry Covelli, chairman of the Great Eastern University IACUC, began to discuss the next protocol on his list.

"Hold on, Larry," said Seth Gordon, "I think we used the wrong wording, but the concept isn't wrong. We want to approve this protocol in its entirety. We're saying that Dr. Francis can't start her biocontainment work with rats until her IBC [Institutional Biosafety Committee] approval comes through, but she can start all of her non-biocontainment mouse work in the meantime."

"I'm not worried about the wording, Seth," said Covelli. "It's the concept of a limited approval that you and the others are promoting that I think is plainly wrong, but I can easily check that." Covelli went online to the OLAW website, and under 'Frequently Asked Questions' he found the following statement:

"If the IACUC determines that a protocol is approvable, contingent on receipt of a very specific administrative modification or clarification (e.g., a contact telephone number), the Committee may handle the issue as an administrative detail that an individual (e.g., IACUC Chair or Administrator) may verify. Requests for substantive modifications should result in the protocol coming back to the Committee. Protocols that lack substantive information necessary for the IACUC to make a judgment (e.g., justification for withholding analgesics in a painful procedure) should be considered incomplete and the IACUC should defer review until the requisite information is provided by the investigator."

"So I'm right," said Gordon. "The IBC approval is just an administrative detail we're waiting for, and whenever it arrives, the rat part of the research can start because we've already approved all of the actual animal work."

"No, I don't think so," said Covelli. "The IBC approval is a substantive piece of information that's missing. Even though the work with rats has been approved by us, we can't give Dr. Francis approval for moving ahead with only part of her study. But I have an idea. What if we ask her to delete the rat segment of the study, and we can approve the protocol for the mouse work only? When we get the IBC approval, Dr. Francis can amend her protocol to add the rats. Is that a good compromise for everybody?"

"Not really," Seth Gordon replied. "The IBC is slow enough, and now you're suggesting a major amendment to add a new species. That can delay things at least a couple of weeks more. I have a better idea. Since the IACUC has already discussed and approved all the rat work, why can't the addition of the rats be a minor amendment and you can give it immediate IACUC approval when Francis submits it? Is that okay with you?" Covelli thought about it for a few moments and agreed with Gordon's suggestion. With that understanding in place, Covelli finally moved on to the discussion of the next protocol.

Was Covelli right when he said that the IACUC could not let Dr. Francis begin any work on her protocol until the IBC approval arrived for the segment that used rats? Was he right in agreeing with Gordon that amending the protocol with an additional species of animals can be considered a minor amendment if the IACUC had already discussed and approved the use of the animals? Would you have done anything differently?

RESPONSE

Communicate with the PI

Shan Yan, PhD & Yvette Huet, PhD

The PHS *Policy on Humane Care and Use of Laboratory Animals* (PHS *Policy*)[1] allows an IACUC to review protocols with three possible outcomes: approval, requiring modifications in (to secure approval) and withholding approval. Covelli's initial point that there is no option for conditional or limited approval is consistent with the PHS *Policy*. In our opinion, the IBC approval is an administrative approval as long as the IBC approves the protocol without modifications. Francis, the Principal Investigator (PI), cannot start to work on animals until the administrative approval from the IBC is provided and the protocol is officially approved by the IACUC. Allowing Francis to start her mouse work without an IACUC protocol approval, as suggested by Gordon, is an apparent violation of the PHS *Policy*[1] and the *Guide for the Care and Use of Laboratory Animals*[2].

The compromise suggested by Covelli is a more practical approach. The IACUC can require the PI to remove the rat segment to secure the approval of mouse work. Then the PI can start her mouse work under the approved IACUC protocol. Once the IBC approval is provided, the PI can submit the rat work as an amendment to the approved protocol. We believe that such an amendment should be considered a major amendment, not a minor one, and must be reviewed by the IACUC again. The IACUC can decide whether this amendment will receive Full Committee Review or Designated Member Review (DMR). The DMR method may allow the amendment to be approved more quickly, because it does not require a convened meeting of a quorum of the IACUC members.

When Covelli and the IACUC discussed how to proceed with this protocol, they did

not include one important participant in the whole process: the PI. The IACUC should communicate the two choices to the PI: (i) wait for protocol approval until IBC approval is provided, or (ii) remove the portion of the protocol that requires IBC approval so that the mouse protocol can be reviewed and approved first, then add a major amendment for the rat procedures once IBC approval is available. If the PI wants to starts her mouse work as soon as possible, she can choose the second option. If the PI doesn't mind waiting, the IACUC can choose the first option and approve the protocol pending the IBC approval.

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. Institute for Laboratory Animal Research. *Guide for the Care and Use of Laboratory Animals* 8th edn. (National Academies Press, Washington, DC, 2010).

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RESPONSE

PI must wait

Eva B. Ryden, PhD, DVM, DACLAM, Lois Laemle, PhD & Sharron Kirchain, DVM, DACLAM

This situation is not uncommon. The IACUC wants to assist the Principal Investigator (PI) in obtaining approval for the protocol so that she can start research while also assuring compliance with all applicable laws and policies, both federal and institutional. Both Covelli and Gordon are trying to find a way to obtain protocol approval expeditiously.

Covelli is correct in stating that there is no such thing as conditional approval. But the PHS *Policy on Humane Care and Use of Laboratory Animals* (PHS *Policy*) recognizes that a protocol can be 'approved pending modifications' (APM)[1]. In our experience, many or even most IACUC protocols are APM at the time of Full Committee Review (FCR). In these cases, the protocol is not approved, and animal research cannot start until the modifications requested by the IACUC have been received[2].

IBC approval may or may not be an administrative matter. The IBC approval number itself may be technically regarded as simply a number in the IACUC protocol, similar to a phone number. Once the missing number is received in the IACUC office, the protocol can be approved administratively by the Chair or an IACUC Administrator[3]. In our judgment, IBC review and approval is a substantive part of the protocol. If the IBC requires changes in procedures, such as the use of a biosafety cabinet that is not readily available to the PI, thus entailing 'substantive modification' prior to approval, then these changes may require modification to the IACUC protocol as well. This would necessitate a re-review of the amended protocol by the IACUC. This repeat review could be assigned to either FCR or Designated Member Review (DMR), as approved by the IACUC and in accordance with the policies described in the institution's PHS Assurance.

Can the IACUC give the PI permission to move ahead with the part of her study that does not involve IBC procedures? Although we would like do so, in agreement with the Great Eastern University IACUC, the answer is 'no'[2]. If there were some assurance that the PI could not start the IBC studies before obtaining IBC approval (e.g., if the experimental compounds that required IBC approval could only be ordered though the IBC), then this option could be considered. But Covelli is correct that the IACUC cannot give approval for Francis to move ahead with only part of her study. The idea that the rat segment can be removed and added later as a minor amendment is unacceptable. The PI cannot remove the rats without also revising the protocol, eliminating procedures, doses, experimental groups, etc. pertaining to the rats, essentially making it a new protocol. Subsequently adding rats and rat procedures to the protocol would be a major amendment requiring either DMR or FCR according to institutional policies. Although OLAW does not specify exactly what is a minor versus major amendment, it is suggested that addition of a species be considered a significant change[4]. Finally, first deleting and then adding rats and rat procedures would entail substantial amounts of extra work for the PI as well as for the IACUC. Both revisions would require either FCR or DMR review as determined by the IACUC.

In summary, the protocol should not be revised to exclude the rat work pending IBC approval. The PI must await IBC approval before her IACUC protocol can be approved and animal work started.

1. Public Health Service. *Policy on Humane Care and Use of Laboratory Animals – Frequently Asked Questions.* Protocol Review, Question No. D-3. (US Department of Health and Human Services, Washington, DC, 2006; revised 2010). <http://grants.nih.gov/grants/olaw/faqs.htm#d3>
2. Public Health Service. *Policy on Humane Care and Use of Laboratory Animals – Frequently Asked Questions.* Protocol Review, Question No. D-5. (US Department of Health and Human Services, Washington, DC, 2006; revised 2010). <http://grants.nih.gov/grants/olaw/faqs.htm#d5>
3. Public Health Service. *Policy on Humane Care and Use of Laboratory Animals – Frequently Asked Questions.* Protocol Review, Question No. D-4. (US Department of Health and Human Services, Washington, DC, 2006; revised 2010). <http://grants.nih.gov/grants/olaw/faqs.htm#d4>
4. Public Health Service. *Policy on Humane Care and Use of Laboratory Animals – Frequently Asked Questions.* Protocol Review, Question No. D-9. (US Department of Health and Human Services, Washington, DC, 2006; revised 2010). <http://grants.nih.gov/grants/olaw/faqs.htm#d9>

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RESPONSE

IBC approval not substantive

Quynh T. Tran, DVM, PhD, Cynthia R. Lockworth, DVM & Suzanne L. Craig, DVM, DACLAM

Covelli's opposition to conditional or limited approval of protocols is valid. But there are other options available that will not place unnecessary restrictions on the investigators and the IACUC process. Therefore, we do not completely agree with Covelli that the IACUC could not let Francis begin any work on her protocol until the IBC approval was received.

IACUCs can approve, require modifications (to secure approval) or withhold

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:

Although this scenario involves rodents, which are not USDA-covered species, it is important to consider how the USDA/APHIS/AC requirements would apply to a similar scenario involving USDA-covered species.

There are three questions asked at the conclusion of the scenario that we will address. May the IACUC allow work to start on a protocol while portions of the study are pending IBC approval? The Animal Welfare Act and Regulations and the Public Health Service *Policy on Humane Care and Use of Laboratory Animals* do not allow IACUCs to grant conditional approval for animal use protocols. Committees may only approve, require modification (to secure approval) or withhold approval of a protocol[1,2]. We highly recommend using this unambiguous language when communicating with the principal investigator (PI)[3,4]. The phrase 'approved pending modifications' is confusing, and IACUCs should avoid using it[4].

Is the addition of another species to the protocol considered a minor amendment? We consider the addition of a second species of animals to the protocol to be a significant change[5]. A significant change must be reviewed and approved by the IACUC by either full committee or designated member review.

Is there a different approach for the IACUC to consider? One option is to include the work that requires IBC approval in the protocol and delay notification to the PI of IACUC approval until after the IBC has conducted its review and approval. The approval date of the protocol should be on or after the date of the IBC approval as determined by the IACUC's operating procedures[6]. Another option is to submit the work that requires IBC approval as an amendment to the protocol after IBC review and approval has been obtained. A third option is for the PI to submit one protocol for the mouse study and another for the rat study. After review and approval by the IACUC, the research on the mouse protocol may then proceed without delay, while the rat protocol awaits IBC approval of the safety issues.

In our experience, many IACUCs conduct protocol review in parallel with IBC review. This expedites the process as long as both committees effectively communicate their actions and decisions. If the safety committee reviews and approves the work without modifications, the IACUC may document this approval administratively without further IACUC review. IBC approval may be indicated by, for example, a check box, an IBC protocol approval number or a safety committee representative's signature. Any of these methods are acceptable for documentation of IBC approval.

1. Code of Federal Regulations, Title 9, Chapter 1, Subchapter A - Animal Welfare: Part 2 Regulations (§2.31).
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. Garnett, N.L. & DeHaven, W.R. So much work, so little time. OPRR and USDA commentary. *Lab Anim. (NY)* **27**, 18 (1998).
4. Wolff, A., Garnett, N., Potkay, S., Wigglesworth, C., Doyle, D. & Thornton, V. Frequently asked questions about the Public Health Service Policy on Humane Care and Use of Laboratory Animals. *Lab Anim. (NY)* **32**, 33–36 (2003).
5. Public Health Service. *Policy on Humane Care and Use of Laboratory Animals –Frequently Asked Questions.* Protocol Review, Question No. D-9. (US Department of Health and Human Services, Washington, DC, 2006; revised 2010). <http://grants.nih.gov/grants/olaw/faqs.htm#d9>
6. Office of Laboratory Animal Welfare. Guidance to Reduce Regulatory Burden for IACUC Administration Regarding Alternate Members and Approval Dates. Notice NOT-OD-11-053. (National Institutes of Health, Washington, DC, 18 March 2011). <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-11-053.html>

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approval of proposed activities related to the care and use of animals[1,2]. If the IACUC determines that a protocol is approvable contingent upon receipt of a very specific administrative modification or clarification, then it may handle the issue as an administrative detail that is verifiable. IACUCs should avoid using the term 'conditional approval' of a protocol, even when they determine that no major revisions or clarifications are required, because use of the term may cause confusion[3]. Because IBC approval may not be considered a major revision or clarification, the IACUC can approve Francis' protocol with the contingency that the IBC must review and approve the biocontainment work on the rats. This modification is an administrative detail that an individual, such as the IACUC Chair or IACUC Administrator can verify[3]. Once the IBC approves Francis' biocontainment work and she updates her protocol to reflect the approval, the contingency can be lifted and she can begin the biocontainment research on rats. No substantive information (e.g., justification for withholding analgesics in a painful procedure), as required in the PHS *Policy on Humane Care and Use of Laboratory Animals*[1] or the *Guide for the Care and Use of Laboratory Animals*[4], is missing from Francis' protocol; therefore, the IACUC can make a judgment on the animal work. We disagree with Covelli's viewpoint that the IBC approval is a substantive piece of information missing from her protocol. The protocol contains all the required information and should be accepted and approved by the IACUC.

We believe that Covelli was incorrect in agreeing with Gordon that adding a species to the protocol can be considered a minor amendment, even though the IACUC has already discussed and approved the use of animals. The justification for the use of each species must be included in the protocol. Removal and subsequent addition of the rats would both need to be reviewed. This could

easily be accomplished using the Designated Member Review process.

Another option would be to request that Francis submit two different protocols for IACUC review, as there are two different species being used (mice and rats), along with two different experiments (non-biocontainment work and biocontainment work, respectively). The mouse non-biocontainment work could be approved so that Francis could begin that study while waiting for IBC approval for the rat biocontainment work. Having separate protocols would help to avoid potential conflicts during IACUC review pertaining to limited and conditional approvals.

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. Animal Welfare Act. 9 CFR, Chapter 1, Section 2.31.
3. Silverman, J., Suckow, M.A. & Murthy, S. *The IACUC Handbook* 2nd edn. 130 (CRC Press, Boca Raton, FL, 2007).
4. Institute for Laboratory Animal Research. *Guide for the Care and Use of Laboratory Animals* 8th edn. (National Academies Press, Washington, DC, 2010).

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