

Jerald Silverman, DVM, Column Coordinator

Management of a holding protocol

For many years, the Great Eastern University IACUC had simply transferred animals from an expired protocol to a 'holding' protocol. The holding protocol had the same identification number as did the now-expired protocol, but the letter H was added as a suffix to indicate that it was in 'holding' status and that no further research was allowed on the protocol. The IACUC office sent out a notice to all IACUC members that unless the office was notified of a request for full committee review within 48 hours, the new holding protocol would be reviewed by the designated member review process. The protocol itself was quite basic. It listed the animal species, number of animals present on the day the protocol expired, any pertinent medical information or other special requirements for the welfare of the animals, and a statement that no research, breeding, teaching or other use of the

animals was to occur. The holding protocol would expire in one year for USDA-covered species and three years for all others.

The system worked well and was never questioned, until a new IACUC member asked simply, "Isn't it against federal regulations to have the animals placed on a holding protocol for 48 hours or more until the protocol is approved by the IACUC?"

"What do you mean?" asked Larry Covelli, the chairman of the committee.

"I mean that there's a gap of at least 48 hours during which the animals don't have any IACUC approval. Is that legal?"

"I assume it is," said Covelli. "Nobody has questioned it in the past."

"Well," said the new member, "I guess it's OK, but do you really allow animals to stay on a holding protocol for up to three years? That sounds really strange to me."

Covelli responded, "Don't worry about that. The investigators pay for the upkeep

of the animals so they usually respond very quickly."

"Okay. I have just one more question," said the new member. "Who becomes the Principal Investigator [PI] on a holding protocol, and is that person really responsible for the animals?"

"Actually," said Covelli, "there is no one person who is the PI. It's the IACUC. The IACUC as a whole has responsibility for the animals."

In your opinion, is the 48-hour (or longer) gap that is created while waiting for possible responses from IACUC members who might request a full committee review a legitimate concern for the Great Eastern IACUC, or is it just an administrative quirk that, for practical purposes, can be ignored for a holding protocol? Do you think that having the entire IACUC serve as the PI is appropriate? Would you approach the use of a holding protocol any differently than does Great Eastern University?

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RESPONSE

No delay

Amy J. Warshaw Funk, DVM, Diplomate ACLAM & Jan T. Orick, MLIS, AHIP

An Animal Holding Protocol exists to provide an immediate legal document for cases where a primary protocol is delayed or not in existence. These potential situations include the arrival of new faculty members that have animals imported before their protocols are approved, suspended protocols and expired protocols. These conditions necessitate a 'just-in-time' document to ensure that animal care is continuous despite uncontrollable events. It does not replace a timely renewal of a protocol, and an IACUC should safeguard against such uses. Furthermore, the purpose of a holding protocol is to identify a responsible person to oversee animal care and prohibit

any animal activity until administrative hindrances can be remedied.

The appropriate responsible entity to take the role of PI should be an attending, clinical or staff veterinarian. It is not suitable to assign responsibilities of animal care to a nonspecific group of people, such as those that function as an IACUC committee.

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RESPONSE

Holding protocol represents risk

Yasin Kokoye, BVMS, MPH & Ken Salleng, DVM, CPIA

Federal regulations require that all activities using animals for research must be

reviewed and approved by the IACUC. Assuming that Great Eastern University (GEU) receives NIH funding, a complete review of PHS-supported research projects is required at least once every three years¹. The USDA requires continuing reviews to be conducted no less often than annually². The NIH considers conduct of animal-related activities beyond the IACUC protocol expiration date as an example of reportable non-compliance³.

Given that the IACUC requires at least 48 hours to allow members the opportunity to request full committee review, the protocol will have been expired for 48 hours or longer before designated member (or full committee) review and approval is possible. Guidance from NIH specifies that the IACUC is not allowed to administratively extend the approval beyond the three years, but it appears that the GEU IACUC allows this extension to occur by at least 48 hours. The institution receiving the grant is required to report this non-compliance

directly to the granting NIH institute or center, as well as to the OLAW⁴. In this situation, the NIH has the authority to request itemized documentation of the charges no longer allowed due to expiration of the protocol⁴.

As a part of routine processing, GEU has labeled the protocol with the same number with the suffix 'H' added. This numbering system may lead to confusion as to whether or not the protocol allows procedures approved in the original

protocol. This point must be clarified to prevent additional non-compliance.

Given that the GEU IACUC would serve as the PI on the holding protocol, there are concerns related to conflict of interest in the review and approval process. Both the PHS *Policy on Humane Care and Use of Laboratory Animals* and the Animal Welfare Act and Regulations clearly indicate that no IACUC member may be involved in IACUC review or approval of a protocol for which there is a conflicting interest^{1,2}.

Responsibilities for the method of payment, provision of veterinary recommendations and euthanasia of animals would all need to be addressed before animals could be transferred to the holding protocol. In addition, the potential length of time that the animals could remain on the IACUC holding protocol should be clarified. Under the GEU IACUC's current practice, USDA-covered species could be maintained up to one year and other species up to three years; this seems an unreasonable amount

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:

In the described scenario, the PI's approved research protocol expired and a period of time passed before the animals were transferred to an approved holding protocol. APHIS and OLAW consider the intervening period as a lapse in IACUC approval. It is very important for IACUCs to have policies and procedures that prevent such lapses.

When IACUC approval expires, the research protocol is no longer valid. Continuation of research activities beyond the protocol expiration is a violation of both the Animal Welfare Regulations (AWRs)¹ and the PHS *Policy on Humane Care and Use of Laboratory Animals* (PHS *Policy*)². This noncompliance with PHS *Policy* must be promptly reported to OLAW³. Additionally, the Office of Management and Budget Cost Principles and the NIH Grants Policy Statement do not permit charges to grant awards for the conduct of animal activities after IACUC approval has lapsed; such charges are a violation of the terms and conditions of the grant award and must be reported to the NIH Institute or Center supporting the award⁴. (NIH expects grantees to continue to maintain and care for animals. NIH funding components may allow expenditure of grant funds for such maintenance and care on a case-by-case basis⁴.)

Specifically, in this scenario, the IACUC should develop a practice for handling protocols due for annual or triennial review prior to the expiration of the protocol.

IACUCs are empowered with the flexibility to develop methods that meet the needs of the institution. One option the IACUC could consider is to place the animals on an approved holding protocol prior to the expiration of the research protocol. Local institutional procedures may require the use of a holding protocol to ensure that the appropriate funding source is charged for maintaining the animals. Alternatively, the IACUC could choose to maintain the animals using IACUC-approved standard operating procedures (SOPs) for housing and routine animal care. Although the AWRs and the PHS *Policy* do not require holding protocols or SOPs, both options are permitted and are acceptable to APHIS and OLAW.

Additionally in the described scenario, the PI of the Great Eastern animal holding protocol is the entire IACUC, making it unclear who is responsible for the animals. APHIS and OLAW concur that the practice of appointing the entire IACUC as PI is not recommended. The *Guide for the Care and Use of Laboratory Animals* describes the PI as the individual "who has precise knowledge of both the objectives of the study and the proposed model"⁵. Should an institution choose to maintain the animals under a holding protocol, the PI position would be best served by an individual who takes responsibility for the animals, such as a veterinarian or animal facility manager, rather than the entire IACUC. Similarly, an SOP for holding animals should designate an individual with primary responsibility for the animals.

1. Code of Federal Regulations, Title 9, Chapter 1, Part 2, Subpart C, §2.31(c)(6)(7).
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). <<http://grants.nih.gov/grants/olaw/references/phspol.htm>>
3. Office of Laboratory Animal Welfare. Guidance on Prompt Reporting to OLAW under the PHS Policy on Humane Care and Use of Laboratory Animals. Notice NOT-OD-05-034. (National Institutes of Health, Washington, DC, 24 February 2005, updated 15 April 2010). <<http://grants.nih.gov/grants/guide/notice-files/not-od-05-034.html>>
4. Office of Laboratory Animal Welfare. Guidance Addressing the NIH Policy on Allowable Costs for Grant Activities Involving Animals when Terms and Conditions are not Upheld. Notice NOT-OD-07-044. (National Institutes of Health, Washington, DC, 26 January 2007) <<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-07-044.html>>
5. Institute for Laboratory Animal Research. *Guide for the Care and Use of Laboratory Animals* 8th edn. 27 (National Academies Press, Washington, DC, 2011).

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of time for animals to remain on a holding protocol. Animals would continue to age, and breeding would be stopped, with the potential consequences of loss of important lines of genetically engineered animals. This would also be a divergence from the principle of reducing animal numbers.

Institutions have many ways to handle holding protocols. One method is to have a single holding protocol, with a single PI (possibly a member of the veterinary staff) as the responsible entity. This method allows for animals to be transferred to the holding protocol from an expiring or suspended protocol before the expiration date, clarifies procedures included and standardizes responsibilities with respect to finances and care. Once the original PI has regained an approved protocol, the animals would then be transferred back to him or her. This method also allows for ease of transfer of animals for new investigators.

1. Public Health Service. *Policy on Human Care and Use of Laboratory Animals* (US Department of Health and Human Services, Washington, DC, 1986, amended 2002).
2. Animal Welfare Act Regulations. Code of Federal Regulations. Title 9, Chapter 1.
3. Office of Laboratory Animal Welfare. Guidance on Prompt Reporting to OLAW under the PHS Policy on Humane Care and Use of Laboratory Animals. Notice NOT-OD-05-034. (National Institutes of Health, Washington, DC, 24 February 2005, updated 15 April 2010). <<http://grants.nih.gov/grants/guide/notice-files/not-od-05-034.html>>
4. Office of Laboratory Animal Welfare. Guidance on Confirming Appropriate Charges to NIH Awards during Periods of Non-compliance for Activities Involving Animals. Notice NOT-OD-10-081. (National Institutes of Health, Washington, DC, 15 April 2010). <<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-10-081.html>>

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RESPONSE

One person is the PI

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The 48-hour gap could be a concern for the Great Eastern IACUC if they are holding animals covered by the Animal Welfare Act and Regulations (AWARs)¹ or the PHS *Policy on Humane Care and Use of Laboratory Animals* (PHS *Policy*)². Both documents require that the species that fall under their coverage be used in accordance with an approved protocol (sections §1.1, §2.31 of the AWARs and section II of the PHS *Policy*). If Great Eastern is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International, then it will likely be following the recommendations of the *Guide for the Care and Use of Laboratory Animals*, which require IACUC approval of animal activities³. If Great Eastern uses species that are covered by these regulations and guidelines, then their use would need to be governed by an approved IACUC protocol at all times. Great Eastern states that the PI will continue to pay for the upkeep of the animals while they are on a holding protocol. If the PI receives NIH funding, this would be a potential problem. The NIH Grants Policy⁴ (Part II 4.1.1.5) indicates that NIH grant awards are not allowed to be used when a protocol is expired. However, it further states that “ICs [Institute or Center] may allow expenditure of NIH grant funds for maintenance and care of animals on a case-by-case basis.”

It would not be appropriate for the entire IACUC to serve as the PI, because

each member would be involved with the protocol and therefore would have a conflict of interest in voting on the protocol. Both the AWARs (section §2.31(d) (2)) and the PHS *Policy* (section IV.C.2) state that “no member may participate in the IACUC review or approval of a research project in which the member has a conflicting interest (e.g., is personally involved in the project) except to provide information requested by the IACUC; nor may a member who has a conflicting interest contribute to the constitution of a quorum.”

For a holding protocol, we would identify one person as the PI who would maintain an active protocol. This person could be an IACUC member or one of the veterinarians at the institution; the latter choice would eliminate the potential for conflict of interest. Animals could be transferred as needed to this protocol without any gap in protocol coverage. Funding for the maintenance and care of the animals could come from a department general funds account. The protocol would be reviewed as required by the AWARs and the PHS *Policy*.

1. Animal Welfare Act Regulations. Code of Federal Regulations. Title 9, Chapter 1.
2. Public Health Service. *Policy on Human 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* 8th edn. (National Academies Press, Washington, DC, 2011).
4. National Institutes of Health. NIH Grants Policy Statement. Part II 4.1.1.5. (US Department of Health and Human Services, Washington, DC, 1 October 2011). <http://grants.nih.gov/grants/policy/nihgps_2011/index.htm>

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