

Jerald Silverman, DVM, Column Coordinator

Tackling investigator noncompliance

In a never-ending quest for perfection, the Great Eastern University IACUC modified its annual progress report form (used by investigators with ongoing animal research) to include a summary of the past year's activity and a projection of future activity. While reviewing the form submitted by Dr. Steven Wright and comparing it to Wright's IACUC-approved protocol, the reviewer began to suspect that Wright had performed some unapproved procedures. The approved protocol allowed for recovery major surgical procedures in nonhuman primates (NHPs), however, the type of surgery approved by the IACUC and that performed by Wright appeared to be significantly different. A phone call to Wright confirmed the reviewer's suspicion. Wright had indeed performed survival surgery, but not the surgery approved by the IACUC. Wright was apologetic and agreed to submit an amendment to his protocol. Even though all animals were doing well post-surgery, and even though Wright

quickly submitted the amendment, the issue was brought before the full IACUC. A relatively short discussion, with Wright present, confirmed that the surgical procedures were on an entirely different organ system than described in the approved protocol. Although he repeated his apologies, Wright also added that if he could not continue his work, the data already collected would be worthless. In an executive session, the IACUC determined that it had the following options:

1. Process and review the amendment like any other protocol amendment, allowing work to continue, reminding Wright that in the future all research procedures must be conducted as described in the approved protocol;
2. Suspend any additional surgeries until the amendment is reviewed and potentially approved, but allow non-surgical parts of the study to continue;
3. Suspend the entire study for a specified period of time; or

4. Suspend the entire protocol permanently.

It was obvious that Wright would consider the first option ideal under the circumstances, but would possibly agree to the second. Moreover, some IACUC members who were familiar with Wright's work agreed with Wright's position that the third and fourth options would effectively stop valuable research, invalidate the already completed parts of that research (since the nonsurgical aspects of Wright's studies were directly linked to recording post-surgical data), and result in the animals' having needlessly undergone surgery and recovery.

Can the Great Eastern IACUC suspend selected parts of Wright's protocol? Are there other options to consider that are not listed above? How would you manage this problem? Based on your experience, do you think that an IACUC would approach this problem differently if rats were involved rather than NHPs?

RESPONSE

Suspend the surgeries

Kathy Wadsworth, BS

The investigator clearly violated Animal Welfare Act Regulations (AWARs) and the Public Health Service *Policy on Humane Care and Use of Laboratory Animals* (PHS *Policy*) by conducting unapproved surgical procedures. However, the IACUC is correct to consider Wright's concern that complete suspension of his work would invalidate his research, which in turn would mean that animals would have undergone surgical manipulations needlessly.

The AWARs¹ and PHS *Policy*² grant IACUCs the authority to suspend previously approved activities, but are silent as to

whether the IACUC has the authority to suspend selected parts of a previously approved protocol. As such, it can be inferred that an IACUC may suspend portions of a protocol, depending upon the nature and circumstances involved in the noncompliance.

Since the surgical procedures conducted without IACUC approval involved a completely different organ system, the noncompliance would likely be deemed serious, regardless of species. Additionally, many institutions have Assurances with the Office of Laboratory Animal Welfare (OLAW) that apply the same policies and regulations governing the use of USDA-covered species to non-USDA covered species. Therefore, those IACUCs would likely approach any noncompliance in the same manner regardless of species involved.

The third and fourth options described in the scenario are, of course, the most

punitive and conservative approaches to this noncompliance. However, as the investigator appears to be cooperating with the IACUC's investigation, these options may be unnecessarily severe, given the potential loss of valuable research and subsequent need for additional surgery to replace the lost data. The first option would allow the research to continue unimpeded, but does not address the cause of the noncompliance. Given the seriousness of the noncompliance, it is important to take all measures necessary to avoid future violations.

In light of these concerns, I would recommend that the IACUC consider the second option: suspend surgeries until the amendment is reviewed and approved, but allow previously approved nonsurgical portions of the study to continue. In addition, the IACUC should require that the investigator

submit a corrective action plan detailing procedures to avoid future noncompliance. The IACUC may also wish to initiate a protocol review of the investigator's other approved studies to determine whether the noncompliance is limited to the one protocol or extends to other protocols.

Although the scenario did not mention funding, PHS *Policy* requires IACUC approval of those components of the proposal(s) related to animal care and the use of animals. If Great Eastern's Assurance does not distinguish between federally funded and non-federally funded research, a re-review of the documents would be required to verify consistency between the grant and protocol, regardless of funding. Any inconsistencies would need to be addressed prior to approval of the amendment.

Of course, had the animals not fared as well as they did in the scenario, the IACUC's deliberations would likely be quite different.

1. 9 CFR, 2.31(c)(8).
2. Public Health Service. *Public Health Service Policy on Humane Care and Use of Laboratory Animals* IV.B.8 (US Department of Health and Human Services, Washington, DC, 1986; reprinted 2002).

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RESPONSE

Decide now

Todd A. Jackson, DVM, DACLAM

In this scenario, Wright has implemented a significant change to a protocol without prior IACUC approval as required by section IV.B.7 of PHS *Policy*. This is a serious infringement of animal welfare regulations and requires immediate attention from the IACUC and the Institutional Official (IO).

Of the four choices presented, options three and four are permissible under the regulations. Certainly the IACUC has the authority to suspend the protocol, either temporarily or permanently. However, suspension may not be the most appropriate action as it would invalidate the completed work and result in some animals having undergone needless surgery. The first option, allowing additional

surgeries while the amendment undergoes review, is inappropriate. Animal activities must receive IACUC approval before they begin. Option two is the best choice, striking a tenuous balance between good stewardship of the animals and meeting regulatory requirements. Allowing data collection from already operated-upon animals prevents the previously collected data from becoming worthless, circumventing the possibility that the project would need to start over with additional animals. Unfortunately, this option does not meet “the letter of the law,” in that non-IACUC-approved animal procedures would continue until review of the amendment is completed.

To meet both the letter and the spirit of the law, the IACUC should act on the amendment by full review. Although meeting in executive session (*i.e.*, behind closed doors for privacy) the text indicates that the full committee is present. If the IACUC has questions about the amendment as written, Wright could be called back into the meeting to provide answers. Once the committee has all the information it needs, it should act on the amendment by approving or withholding approval. If approval is granted, the project would be back in regulatory compliance. If approval is withheld, all work would cease immediately, and the IACUC should determine what to do with the animals already on study.

The IACUC should also discuss what programmatic lapses allowed this problem to happen in the first place. Does the training program adequately train Principal Investigators (PIs) and their research staff about what changes to previously approved procedures require IACUC approval before implementation? Do the Attending Veterinarian (AV) and his or her staff have adequate oversight of the surgical program? Are they involved in the planning of surgical procedures (or any procedures that might involve more than momentary pain or distress)? If so, how is their involvement coordinated with the IACUC review process? The programmatic issues that allowed the incident to happen should be fixed to prevent it from happening again. Because the incident was a serious violation of PHS *Policy*, the IACUC, through the IO, should promptly provide OLAW with a full explanation of the circumstances related to the problem and the actions taken to resolve it.

As to the last question (about whether the situation should be handled differently if rats are involved instead of NHPs), the answer is no. Although rats are not covered by USDA's animal welfare regulations, they are treated the same according to the *Guide for the Care and Use of Laboratory Animals* and PHS *Policy*.

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RESPONSE

Cooperation counts

Marc Breedlove, PhD, Sally Light, BA, Chris Parks, DVM, PhD & Molly Greene, BA

The Great Eastern IACUC's executive committee (Chair, Administrator, and AV) should meet and take the following into consideration in determining a course of action:

- Although off-protocol, the procedures were conducted properly and the PI has no history of non-cooperation or non-compliance. The PI is willing to temporarily discontinue all surgeries, not just the non-compliant portion, while the IACUC reviews his case.
- A major goal of the IACUC is to promote voluntary compliance and cooperation. When this kind of protocol drift happens, it needs to be addressed. Criminalizing the drift and punishing PIs who admit to it would be counterproductive, however; in a case involving a PI who is cooperative and apologetic, a cooperative approach will send a positive message to other faculty that problems can be addressed in a collegial manner for those PIs willing to work with the IACUC. A strong arm approach may be viewed negatively by other faculty and possibly damage the rapport between researchers and the IACUC.
- It is unclear whether the AWARs and PHS *Policy* allow for ‘suspension’ of part of a protocol. PHS *Policy* states that IACUCs are “authorized to suspend an activity involving animals¹,” but the definition of ‘activity’ (“those elements of research, testing, or teaching procedures that involve the care and use of animals²”) does not use the term ‘protocol’. This

may be an important distinction that gives an IACUC the authority to suspend an un-approved activity. Moreover, just because the IACUC has the authority to suspend a protocol does not mean it must. We believe that suspensions should be reserved for willful and/or egregious noncompliance and/or refusal to cooperate.

- Suspending Wright’s research may cause a loss of valuable data and the need to replicate the experiments (using more animals) or risk invalidating all the previous work, thereby ‘wasting’ the animals already used.

Based on these considerations, we would suggest that the IACUC’s executive committee propose the following recommendations to the full Committee:

- Because of the PI’s willingness to cooperate in a timely manner, a formal suspension of the protocol does not seem warranted. Nevertheless, Wright’s agreement to discontinue all surgeries pending a satisfactory review and approval of the amendment should remain in force.
- Wright must agree in writing with the requirement that all research procedures be conducted as described in the approved protocol unless and until an amendment has been reviewed and approved.
- Wright and his staff must repeat the applicable training requirements.
- An IACUC member and/or representative of the IACUC should conduct post-approval monitoring of Wright’s lab at six-month intervals.
- A note should be sent to all PIs reminding them that all research procedures must be conducted as described in the approved protocol unless a modification is approved in advance for any new procedures. Investigators would be reminded that federal regulations allow for permanent suspension of the use of animals in activities and/or procedures not covered by a protocol approved by the IACUC.
- The executive committee should also recommend that this be the IACUC policy for all future similar infractions regardless of species, funding source, or type of activity (teaching or research); that the IACUC determine if it effectively communicates requirements to the faculty; and that the IACUC deter-

mine if amendments and modifications are reviewed in a timely manner to allow research to move forward.

Finally, it should be noted that if the study is PHS-funded research, the IACUC would be required to send an incident report to OLAW in compliance with its February 2005 directive³. If privately funded (and the protocol is not suspended), notification of either OLAW or USDA is not required.

1. Public Health Service. *Public Health Service Policy on Humane Care and Use of Laboratory Animals* IV.B.8 (US Department of Health and Human Services, Washington, DC, 1986; reprinted 2002).
2. 9 CFR Subchapter A—Animal Welfare, Section 1.1.
3. Office of Laboratory Animal Welfare. NOT-OD-05-034. Guidance on Prompt Reporting to OLAW under the PHS Policy on Humane Care and Use of Laboratory Animals. (24 February 2005). <http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-05-034.html>.

Breedlove is IACUC Chair, Light is IACUC Administrator, Parks is Interim Attending Veterinarian, and Greene is IACUC Advisor, Michigan State University, East Lansing, MI.

RESPONSE

Stop and investigate

Anthony McMickle, BS, ALAT & Roger Buchanan, PhD

The Great Eastern IACUC must send a message to Wright and all other researchers that no animal procedures will be allowed without an approved protocol. While his cooperation after the fact would be considered in his favor, it in no way excuses knowingly embarking on unapproved surgeries. Since IACUC members familiar with Wright’s previous research might be hesitant about stopping his work, we would suggest that the following steps be taken:

- The IACUC immediately report a serious noncompliance to OLAW. The aspects of Wright’s research program that require use of the affected animals will be temporarily suspended. The suspension would remain in effect until Wright prepares a relevant animal protocol proposal and that proposal is approved by the IACUC. Because of the critical nature of his research, the

IACUC would expedite review of this protocol with the expectation that this suspension could be lifted within a few days. Wright would also be placed on probation for a specified amount of time (e.g., one year). During that time, his use of animals would be closely monitored by animal care personnel and the IACUC. If it is discovered during the course of that year that he was again performing unapproved surgeries, his animal-based research would be suspended. A supervised probation would allow Wright to continue his research while at the same time send a clear message that further noncompliance would result in serious consequences.

- The IACUC immediately begin an investigation to determine if students and post-docs working with Wright were aware that the surgeries were not approved. This would emphasize to all that, although Wright (as PI) bears the burden of responsibility for noncompliance, all persons using animals at Great Eastern are responsible for reporting violations of animal care policies. If this investigation determined that Wright instructed those under him to disregard animal use and care policies, the IACUC would have no choice but to suspend his animal-based research until the situation is resolved. If this investigation did not find evidence of intentional violations, then his cooperation with the IACUC and the probationary period would be considered sufficient to prevent recurrence.

If Wright’s research was funded by a grant or contract from an extramural funding source, then the funding agency’s policies governing animal use must also be considered. Those policies might require additional responses by the Great Eastern IACUC.

As far as the IACUC is concerned, the species of animal should make no difference. However, every researcher should be sensitive to how their work would be viewed by the general public. We cannot imagine that public revelation of unapproved surgeries on NHPs would be very favorable for Wright or for Great Eastern University.

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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. This commentary assumes that the research project in question was PHS-supported.

The primary questions posed in the scenario are whether an IACUC can suspend selected parts of an investigator’s protocol and whether provisions of the PHS Policy are applied differently depending on the animal species involved. The column also asks whether the institution has other options not addressed in the scenario.

OLAW has defined ‘suspension’ as any IACUC intervention that results in the temporary or permanent interruption of an animal activity¹. USDA, APHIS, AC and OLAW have also stated that the “PHS Policy, USDA Regulation, and the Guide language presume that all ongoing animal activities have received prospective review and approval. Accordingly, the IACUC’s authority to suspend unauthorized activities is always implied, if not explicit².”

Regarding options available to the institution other than those described in the scenario, OLAW has previously indicated that “while the PHS Policy does not contain specific sanctions other than suspension, most institutions have developed procedures for disciplining individuals.... Institutionally imposed sanctions vary from counseling, temporary suspensions of privileges, and imposition of monitored probation to permanent withdrawal of animal-use privileges and the termination of employment³.”

Provisions of the PHS Policy apply to all live vertebrate animals used or intended for use in research, research training, experimentation, biological testing, or related purposes. These provisions do not distinguish between species.

IACUCs and IOs are expected to follow their promises to adhere to provisions of the PHS Policy contained in their Assurances of Animal Welfare. They are required to assess the research facility’s animal program and procedures, and legally commit the research facility to compliance with the Animal Welfare Act and Regulations. While collegiality is important in attaining this goal, IACUCs and IOs should not enable or condone unacceptable behavior. OLAW and USDA have addressed this issue in comments on scenarios posed in past Protocol Review columns and reiterate them here:

- “Regardless of the issues of investigator intent, history, or subsequent harm to animals, circumvention of institutional animal welfare oversight mechanisms for prospective IACUC review constitutes serious noncompliance with the PHS Policy⁴.”
- “No amount of rationalization about lack of harm done can erase the fact that the PI knowingly violated the protocol⁵.”

- “The IACUC’s willingness to accept such behavior is [unacceptable], given the potential consequences for the institution that include violations of PHS Policy, NIH Grants Policy (including possible disallowance of charges against the grant), and the federal False Claims Act (31 U.S.C. §§ 3729–3730)⁵.”

OLAW has elaborated further on the potential effects of violations, stating that “[a]lthough certain changes in funded scientific research programs are allowable, some require prior notification of NIH grants management or program staff. Also, compliance with the PHS Policy, including prior IACUC approval of significant changes, is a term and condition of award. Failure to satisfy these commitments exposes the institution to potential disallowance of charges against the grant and other more serious sanctions⁴.”

Arguments that previously unauthorized work should be allowed to continue so as not to waste animals must be critically evaluated. These arguments may be moot when it is understood that data from activities not conducted in compliance with applicable federal regulations may not be publishable. From that perspective, the animals as well as all of the other institutional resources used to support the unauthorized work may already have been wasted. Along these lines OLAW has cautioned that “Publication of articles in many refereed journals requires conformity with certain editorial or professional society animal welfare policies. Most are clear about accepting only those studies conducted under fully compliant conditions. Therefore, the integrity of the investigator and the institution could be damaged by misrepresentation of the conditions under which...animal work was conducted⁴.”

1. Office for Protection from Research Risks. Requirements for prompt reporting of problems to OPRR. OPRR Reports (12 January 1994). <http://grants.nih.gov/grants/olaw/references/dc94-2.htm>.
2. Garnett, N.L. & DeHaven, R.W. The view from USDA and OPRR. *Lab Anim. (NY)* **27(9)**, 17 (1998).
3. Potkay, S. & DeHaven, W.R. OLAW and APHIS: common areas of noncompliance. *Lab Anim. (NY)* **29(5)**, 32–37 (2000).
4. Garnett, N.L. A word from OLAW. *Lab Anim. (NY)* **31(5)**, 21 (2002).
5. Garnett, N.L. & Gipson, C.A. A word from OLAW and USDA. *Lab Anim. (NY)* **32(9)**, 19 (2003).

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