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Revisiting approved protocols

IACUC member Mark Wilson and researcher Carrie Ross did not like each other, a fact that was no secret to the other members of the Great Eastern University IACUC. The issue came to a head when Wilson asked Larry Covelli, the IACUC chairman, to reopen a discussion on one of Ross's recently approved protocols. "Why?" asked Covelli, already dreading the answer. "Because she obviously asked for more animals than she needs," said Wilson. "When I was working with her she did the same kind of experiment with half that number of animals." "Maybe that was true then," Covelli responded, "but now she's asking different questions and the IACUC was satisfied with her justification of animal numbers. It's approved and I don't see any need to reexamine it. You know, Mark, you and Carrie split up years ago. You got to move on with your life."

But Wilson was not about to move on. If his informal request to Covelli did not work, he would pursue the matter formally. In fact, the next day Covelli received a formal request from Wilson to reopen the review of the Ross protocol based on three assertions. First was that Ross used twice as many animals as was needed. Wilson referenced a previous Ross protocol that had essentially the same type of assay but with half the number of animals. Wilson's second assertion was that the protocol was approved through the Designated Member Review (DMR) process while he was out of town and that he did not have the opportunity to request a full committee review. The final assertion was that as a member of the IACUC, he had a right to have any protocol re-reviewed if he believed a re-review was necessary. Nevertheless, Covelli denied the request, saying that the IACUC had sent Wilson the

same e-mail notice that all other members had received about the DMR and that it was simply unfortunate that he did not check his e-mail in the allotted time. Covelli also said that the reviewers were satisfied that the justification provided by Ross for the number of animals requested was scientifically sound and, lastly, that IACUC members do not have any special right to have a protocol re-reviewed simply as a consequence of their service on the committee. The Great Eastern policy was that the IACUC chair would review any complaint and make a decision about the need for further investigation. "I'm sorry, Mark," said Covelli, "but I reviewed the facts and I don't think reopening the discussion on Carrie's protocol is warranted. I'm closing the file on this."

Do you think that Covelli acted within the word and spirit of existing federal regulations?

RESPONSE

Approval should stand

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The 3Rs, originated by Russell and Burch in 1959 (ref. 1), include replacement of animal models (with non-animal systems or computer simulations), refinement or elimination of unnecessary pain and distress in animals, and reduction of the number of animals used.

The Public Health Service (PHS) *Policy on Humane Care and Use of Laboratory Animals*² and the Animal Welfare Regulations (AWRs)³ require institutions to ensure that investigators consider in essence the 3Rs; this case focuses on reduction. The *Guide for the Care and Use of Laboratory Animals*⁴ states that "justification of the species and numbers of animals requested" should be considered in the preparation and review of animal

care and use protocols and that "whenever possible, the number of animals requested should be justified statistically."

Reduction in the number of animals necessary for a particular project is often accomplished by carrying out pilot studies to assess variability, by standardizing procedures, by carrying out a power analysis, by tissue sharing and by refining experimental design. US Government Principle II (ref. 5) states that "procedures involving animals should be designed and performed with due consideration of their scientific relevance to ...the advancement of knowledge."

It is apparent that Ross has met the burden of all federal regulatory expectations, including provision of acceptable justification for the increase in animal numbers since her previous protocol, presumably based on her elucidation of a different hypothesis.

The regulations are virtually standardized in regards to proposals including appropriate justification of requested number of animals.

The AWRs³ and the PHS *Policy*² both state that proposals to use animals must include "identification of the species and the approximate number of animals to be used" and "a rationale for involving animals and for the appropriateness of the species and numbers of animals to be used."

Federal regulations do not speak to IACUC members having the authority to demand post-approval re-reviews. Wilson was given the opportunity to review the protocol and to request full committee review if he felt the protocol lacked appropriate justification of animal numbers. The PHS *Policy*² and the AWRs³ both require that each member of IACUC receive animal use proposals for review. Both regulatory documents recognize Designated Member Reviews (DMRs) as an acceptable method for proposal review after all members receive the opportunity to send the protocol to full committee. These requirements were met in this case.

Wilson's failure to respond in a timely manner does not negate the fact that the protocol was approved with the justification of animal numbers. The AWRs³ and the PHS *Policy*² do not require that all members must respond, only that all members are given the opportunity to do so. Again, the designated reviewers were satisfied with Ross's justification, and no other members objected to her proposal.

IACUC members do not vote on proposals reviewed by designated member(s) but have the opportunity to request full committee review. In keeping with the objectives of the DMR process, which include decreasing the load of protocols that must be reviewed by the full committee, deadlines for member response must be set to maintain order. The deadline should be set for a time when all members will reasonably be able to review the proposal and voice their opinion on its designation (5–7 days). The burden of answering committee-related correspondence lies with the individual members.

The PHS *Policy*² states that "applications and proposals that have been approved by the IACUC may be subjected to further appropriate review and approval by officials of the institution." Neither Covelli, as chairman of the IACUC, nor the Institutional Official is required by the regulations to revisit an approved protocol in response to the complaints of an IACUC member. I believe that to do so, especially with the conflict of interest concerns between Wilson and Ross, would be inappropriate; hence, Covelli handled the situation within the expectations and allowance of governing regulations.

1. Russell, W.M.S. & Burch, R.L. *The Principles of Humane Experimental Technique* (Methuen, London, 1959).
2. Public Health Service. *Policy on Humane Care and Use of Laboratory Animals* IV, C, 2 and IV, C, 8 (US Department of Health and Human Services, Washington, DC, 1986; amended 2002).
3. Animal Welfare Regulations. Sections 2.31, e, 1; 2.31, e, 2; and 2.31, d, 2 (2005).
4. Institute for Laboratory Animal Research. *Guide for the Care and Use of Laboratory Animals* 10 (National Academies Press, Washington, DC, 1996).
5. Public Health Service. *Principle II. US Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training* (US Department of Health and Human Services, Washington, DC, 2002).

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RESPONSE

Re-review not required

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This scenario invites deliberation of core issues brought forth by Wilson in the three assertions that comprised his formal request to the IACUC: (i) the justification of animal numbers, (ii) the function of Designated Member Review (DMR) and (iii) the right of an IACUC member to demand the re-review of an approved protocol.

Wilson disputed the number of animals requested by Ross because she had a previous protocol that utilized a similar assay but required only half as many animals. Institutions using animals regulated by the Animal Welfare Act and Animal Welfare Regulations¹ and submitting applications to the Public Health Service (PHS) are obligated to assure that proposals contain a rationale for the number of animals to be used². The direct application of animal numbers or group sizes from one protocol to another is inappropriate without giving consideration to the specifics of study design and statistics. Perhaps Ross' earlier protocol was a pilot study designed to arrive at a variance for application to future projects. Armed with that information, Ross might have requested additional animals in the current protocol to achieve statistical significance using that assay. Regardless, the reviewers were satisfied that the justification for the number of animals was scientifically sound, and their approval should be upheld.

Regarding Wilson's challenge of DMR approval, we presume that the IACUC acted within the procedures outlined in Great Eastern University's Assurance and that all IACUC members were given sufficient time to receive materials and request a full committee review². The fact that Wilson's travel prevented him from responding in a timely manner is unfortunate, but his failure to respond within the consideration period given may be interpreted as approval to use DMR for review.

Wilson also requested a re-review of Ross' protocol, claiming that this was within his rights as an IACUC member. Indeed, the IACUC's involvement with a project does not end with protocol approval. Both the Animal Welfare Act and Animal Welfare

Regulations¹ and the PHS *Policy on Humane Care and Use of Laboratory Animals*³ require the IACUC to carry out continuing review of a protocol no less than annually¹. Under certain circumstances, such as in situations of protocol non-compliance, the IACUC is also obliged to conduct an investigation. If warranted, the IACUC may convene to re-review the protocol and take appropriate action¹. In this case, however, there is no such basis for Wilson's request for re-review of the protocol. Furthermore, granting his request would supplant the authority of the IACUC and DMR process. At the time of annual renewal, Wilson would be free to review Ross' progress report and express any reservations at that time.

In conclusion, we believe that Covelli acted within the word and spirit of existing federal regulations.

1. Animal Welfare Act and Animal Welfare Regulations.
2. Silverman, J., Suckow, M.A. & Murthy, S. *The IACUC Handbook* (CRC Press, New York, 2000).
3. Public Health Service. *Policy on Humane Care and Use of Laboratory Animals* (US Department of Health and Human Services, Washington, DC, 1986; amended 2002).

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RESPONSE

IACUC should discuss

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It is our opinion that Covelli did not act within the word or spirit of existing federal regulations. Once a concern regarding an approved protocol was reported, Covelli should have called for a convened meeting of the IACUC to review the complaint. The committee should then follow established procedures for initial evaluation and actions. It was stated that Great Eastern University's policy granted the authority to determine whether any complaint warranted further investigation to the IACUC chair. This policy may be in error. If decisions regarding animal use and welfare are mandated to be considered by a committee, then allowing a

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 scenario raises questions regarding the IACUC chair's authority to decide whether to re-review an approved protocol, the use of designated member review (DMR) to review protocols in accordance with the Public Health Service (PHS) *Policy on Humane Care and Use of Laboratory Animals (Policy)*¹ and the Animal Welfare Act and Regulations (AWARs)², and conflict of interest in IACUC review.

One of the functions of the IACUC as required by the PHS *Policy* and the AWARs is to review concerns involving the care and use of animals at the institution^{1,2}. Review of concerns is not a matter of choice; concerns must be brought to the IACUC's attention. It is not within the IACUC chair's authority to resolve concerns in accordance with his or her personal opinions. Concerns about animal activities at an institution must be reviewed at a convened meeting of the IACUC. In the situation described above, the IACUC should determine whether to re-review the protocol. The PHS *Policy* and the AWARs do not empower individual IACUC members to require the IACUC to re-review protocols. The IACUC should also verify whether institutional procedures concerning DMR were consistent with provisions of the PHS *Policy* and the AWARs.

Regarding DMR, if an IACUC member fails to respond to a request for DMR of a protocol on or before a predetermined deadline, OLAW and USDA allow this lack of response to indicate agreement with DMR. The PHS *Policy* and the AWARs require that, as a minimum, all IACUC members be given a list of proposed activities and that written descriptions be available to them^{1,2}. Any member of the IACUC may then request review of any activity by the full committee. In the absence of such a request, the chair may appropriately designate at least one qualified person to review, approve, require modifications or request full committee review.

The PHS *Policy* and the AWARs clearly state that no IACUC member "may participate in the IACUC review or approval of an activity in which that member has a conflicting interest (e.g., is personally involved in the activity) except to provide information requested by the IACUC"^{1,2}. Conflict of interest may arise under a number of circumstances, including where "a member's personal biases may interfere with his or her impartial judgment, a member is involved in a competing research program, or access to funding or intellectual information may provide an unfair competitive advantage"³. Any member with a conflict of interest should inform the IACUC chair and should not participate in the IACUC review. If an investigator who has submitted a protocol or an amendment believes that an IACUC member has a potential conflict, the investigator may request that the member be excluded³. Neither recused nor excluded members may contribute to the quorum necessary to conduct IACUC business.

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, Chapter 1, Subchapter A — Animal Welfare: Part 2 Regulations. §2.31.
3. Office of Laboratory Animal Welfare. *Institutional Animal Care and Use Committee Guidebook* 2nd edn. 15 (US Department of Health and Human Services, Bethesda, MD, 2002).

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single individual to determine the merit of complaints regarding animal use and welfare seems to be in opposition to the word and spirit of the regulations.

Wilson made errors as well. He asserted that an IACUC member has a right to request a re-review of an approved protocol

if he or she believes it is necessary. The term re-review implies that a protocol may need to be approved twice. The *Institutional Animal Care and Use Committee Guidebook*¹ clearly indicates that previously approved protocols can be discussed at convened meetings. Therefore, Wilson would have been within his

rights to call for a discussion on this protocol at the next convened meeting. In our opinion, a discussion is not the same as a review.

We also noted two potential procedural errors. First, the Designated Member Review (DMR) process may need to be reviewed and changed to prevent this type of complaint. One weakness in the DMR process at many institutions is that the committee accepts a lack of reply to a request for DMR as an approval to go ahead with the DMR. This could be avoided by requiring each IACUC member to respond to each DMR request before proceeding with the DMR. At a minimum, each member should acknowledge receipt of the request. The Public Health Service provides guidance for DMR in its Notice NOT-OD-09-035 (ref. 2). Although this Notice does not require that each IACUC member respond to DMR requests, requiring members to reply to each DMR request indicating whether or not they request full committee review for the protocol will confirm that each member had the opportunity to request full committee review.

The second procedural error involves a conflict of interest (COI). The *Institutional Animal Care and Use Committee Guidebook*¹ provides examples of COI, one of which states that an IACUC member's personal biases may interfere with his or her impartial judgment. If this is the case, then the investigator submitting the protocol (in this scenario, Ross) can request that the biased member (in this scenario, Wilson) be excluded from the review of his or her protocol. It seems reasonable that if the IACUC chairman has knowledge of a conflict between an IACUC member and investigator, he could excuse that IACUC member from review of that investigator's protocol on the basis of the COI without a request from the investigator.

1. Office of Laboratory Animal Welfare. *Institutional Animal Care and Use Committee Guidebook* (US Department of Health and Human Services, Washington, DC, 2002; reprinted 2008).
2. Office of Laboratory Animal Welfare. *Guidance to IACUCs Regarding Use of Designated Member Review (DMR) for Animal Study Proposal Review (FCR) Subsequent to Full Committee Review (FCR)*. Notice NOT-OD-09-035. (National Institutes of Health, Washington, DC, 8 January 2009).

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