Jerald Silverman, DVM, Column Coordinator

One animal, two protocols—an appropriate application of the 3Rs?

One of the IACUC's responsibilities is to help ensure that researchers use the least possible number of animals compatible with research requirements. Therefore, it seemed like a good idea to Patty Bergman to use the same animals for her own research that her colleague Yancy Wycroft was using for his research. His work involved behavioral testing of rabbits after exposure to different chemical scents, and hers required a weekly blood sample of 0.5 ml per rabbit. On the surface, this sounded like a fine idea to Craig Miller, the IACUC Chairman. Then Bergman clarified things. She wanted to have her own IACUC protocol, but do her experiments concurrently with those of her colleague, using the same animals he was using. This was a new twist for Miller. He had thought that Bergman planned on using the animals after Yancy was done with them.

"You know, Patty," Miller said, "since all you're planning on doing is taking a little blood once a week from each of the rabbits, wouldn't it just be easier to amend Yancy's protocol by adding you as one of the research personnel and indicating you will just be taking the blood?"

"I thought of that," said Bergman, "but Yancy said he wasn't comfortable with that arrangement. He's very confident that my taking a little blood won't affect his own research in any way, but his NIH [National Institutes of Health] grant doesn't say anything about the kind of work I'm doing or about taking any blood. He's afraid that if I add my work onto his protocol, there might be questions at NIH about a change in the direction of the work."

"I understand what you mean," Miller said, "but he's not changing the direction or scope of the work under his grant; he's just letting you use his rabbits for an unrelated purpose that doesn't affect his own research."

"Thanks," said Bergman, "but I already tried that argument and it didn't get me anywhere. As a practical matter, I'd rather have my own protocol anyway and not have to worry if Yancy put in his protocol renewal on time or did anything else that might affect my research. My work is NIH-funded so if it's a real problem for the IACUC, I'll just purchase rabbits for bleeding rather than use Yancy's animals. I'm only making this request because I'm trying to save animals and save money. It seems like a win-win deal all around."

"It is a good idea," said Miller, "but I really have to think about the consequences and legality of doing this. Let me get back to you."

Can Patty Bergman have her own IACUC protocol but use Yancy Wycroft's rabbits for blood draws at the same time he is using them for an unrelated research purpose? What IACUC problems, if any, can you foresee?

RESPONSE

Key may be AV

Mary Ellen Goldberg, BS, VMT, LVT

When I first read this question, I thought, "This is an excellent idea. What is the big deal?" However, the matter should be examined more closely. Using the same rabbits for a weekly blood draw is relatively minor and I see no reason why Bergman couldn't write her own protocol and indicate that Wycroft's rabbits would be used concurrently in her research; this is an excellent way to reduce animal use. However, I can see the concern that Wycroft has about his NIH-funded work. It seems, however, that if Wycroft called his Grant Administrator at NIH and discussed this matter, NIH would be more than willing to allow Bergman to draw blood from these rabbits, providing that it was done under the direction of the veterinary department. I might add that qualified technical personnel should be the ones to draw the blood from the rabbits so that they experience the least amount of pain and distress.

In *The IACUC Handbook*, Gracely writes the following regarding animal reuse: "The real question concerns reuse of an animal in a painful or distressing way after it has already been used in this way once." As noted in the proposed scenario, neither procedure is painful or distressing if performed by qualified, appropriate personnel[1].

However, the ARENA/OLAW *Institutional Animal Care and Use Committee Guidebook* states, "While there is no explicit requirement for the IACUC to do a side-by-side comparison of the information contained in the IACUC protocol review form and the information submitted to the Public Health Service (PHS), it is imperative that the protocol that the IACUC approves is consistent with the information submitted to the PHS. Institutions should devise a mechanism to verify that consistency. If the IACUC requires changes to the protocol that are not reflected in the grant application, then the PHS funding component must be notified in the follow-up certification of IACUC approval[2]."

In light of the above regulations, I believe that one way to accomplish the joint animal use for research involving two Principal Investigators (PIs) with separate studies would be for the

Attending Veterinarian (AV) to submit a letter to each granting agency indicating that the rabbits in question would be held in the laboratory animal facility under the supervision of Animal Resources and the Veterinary Department. The cost of the animals and per diems could be split by each PI. The letter could state the reason for this unique situation is to reduce animal numbers and save money, as clearly stated by Bergman. This would show each granting agency that IACUC approval would proceed only if the funding agency agreed to allow this animal usage. I think everything must be reported to the funding agency and be 'out in the open' to avoid any misunderstandings in case the situation is ever brought into question.

Alternatively, Bergman could wait until Wycroft's study is completed and have the rabbits transferred to her protocol. This would indicate that the responsibility for these rabbits had been transferred entirely to Bergman. However, this defeats Bergman's purpose as indicated early in the case report since she wanted to perform her experiments concurrently.

1. Gracely, E.J. in *The IACUC Handbook* (eds. Silverman, J., Suckow, M.A. & Murthy, S.) 13:12 (CRC Press, Boca Raton, FL, 2000).
2. ARENA/OLAW. *Institutional Animal Care and Use Committee Guidebook* 2nd edn. (National Institutes of Health, Bethesda, MD, 2002).

Goldberg is Policy and Procedures Manager II at Virginia Commonwealth University, Richmond, VA.

A word from OLAW

In response to the issues raised in this scenario, the Office of Laboratory Animal Welfare (OLAW) offers the following clarification and guidance:

This complex scenario raises multiple questions. To sort out the tangle, the IACUC is faced with establishing priority among overlapping directives. Is it more important to reduce the number of animals used or limit the number of procedures performed on individual animals? These issues must be reconciled with the IACUC's practical need to monitor the activities of individual investigators and specific animals. In a further complication, all of these issues must be handled in accordance with the terms and conditions of the funding.

The PHS *Policy* does not specifically address the use of animals in an approved study being reconsidered for additional use in unrelated research when the simultaneous use involves noninvasive procedures. Dual use of animals may be an appropriate way to reduce the number of animals used if it can be accomplished without a negative affect on the animals or the scientific integrity of either project. However, in the scenario described here, the proposed blood collections involve changes in the nature, frequency, and number of procedures to be performed and could result in greater discomfort to the rabbits than the previously approved behavioral protocol[1,2].

Since both PIs support the dual use, the IACUC should review the proposal, as it would any proposal, according to section IV.C.1.a–g of the PHS *Policy*[3]. If the IACUC approves the proposed changes, they may then decide whether to require that (1) the previously approved protocol be amended to include the approved changes, or (2) a separate protocol be developed to cover the use of the animals as blood donors. In either case the potential impact of the dual use on each research project must be described.

From a grants management perspective, the responsibilities to NIH funding components will vary depending upon the timing of grant approval and IACUC consideration:

- **If dual use of animals is planned before applying for the grant.** The description of animal use in a competing grant application should mention proposed simultaneous noninvasive dual use and describe any anticipated affect on the science.
- **If the decision in favor of dual use of the animals occurs after grant submission, but before grant award.** If simultaneous dual use is not described in the grant application and the IACUC approval is obtained after the application is submitted to NIH, then the IACUC approval date will be submitted to NIH after approval. This submission should include a description of the dual use.
- **If the decision in favor of dual use of the animals occurs after grant award.** After a grant award is made, the PI is responsible for the scientific or technical aspects of the grant, and would not need prior approval from the NIH Grants Management Official to implement dual use unless it constitutes a change in scope from the approved award. Change in scope is defined as a "change in the direction, type of research, or other areas that constitute a significant change from the aims, objectives or purposes of the approved project[4]." In this case, the addition of blood collection to the behavioral protocol does constitute a change in scope and would require prior approval. However, if a dual use is approved by an IACUC and implemented post-award, the dual use of the animals must be described in any subsequent progress reports to NIH.

There may be a simple solution for this particular scenario: because rabbit blood is readily available from commercial supply houses, perhaps the best solution would be for the investigator to purchase the needed reagent.

1. Public Health Service. *Policy on Humane Care and Use of Laboratory Animals* (US Department of Health and Human Services, Washington, DC, 1986; reprinted 2002).
2. NIH Grants Policy Statement, Part II: Terms and Conditions of NIH Grant Awards, Subpart A: General—Part 5 of 7, Administrative Requirements, Changes in Project and Budget. http://grants2.nih.gov/grants/policy/nihgps_2001/part_iia_5.htm.
3. OLAW website. Frequently Asked Questions, Protocol Review, Question 6. http://grants.nih.gov/grants/olaw/faqs.htm#proto_6.
4. US Government Principle IV. http://grants.nih.gov/grants/olaw/references/phspol.htm#USGovPrinciples.

Patricia Brown, VMD, MS, DACLAM
Acting Director
OLAW, OER, OD, NIH, HHS

RESPONSE

Let Bergman wait

Lu Forrest, DVM

Bergman's primary consideration is keeping with the dictums of the 3Rs. Although ethical in spirit, the logistics of having two protocols attached to one animal creates an untenable management situation. According to an OLAW brochure for NIH grantees, "the use of animals must be congruent with the description in a competing grant application[1]." With two separate protocols, the proverbial left hand may be oblivious to the deeds of the right. It is possible that either protocol might add procedures that would be unacceptable from an animal welfare standpoint, such as survival surgery, without the knowledge of the other party. Alterations in one research project could also negate the data collection of the other party—if new chemicals were added for example. In principle, one would hope that collaborators would communicate, but there is no way under this paradigm to ensure that communication.

It could also be quite difficult to fairly recharge each respective NIH grant depending on the nature of the study. If, for example, Bergman needed blood from one rabbit per week, but Wycroft had 50 in-house rabbits, what would be the recharge rate for NIH?

Thus it would seem that there are really two reasonable ways for these researchers to use the same animals. One way is to create a singular protocol together after having received approval from NIH for the procedural changes. The reluctance of both researchers to proceed in this fashion indicates that this option may not be workable. Another possibility that I believe to be better suited to this situation is for the animals that are remaining from Wycroft's project to be transferred to Bergman (presuming that the research constraints allow this to occur, which might not be the case if rabbits are sacrificed for tissue harvest in Wycroft's study, for example). This would also allow Bergman to transfer other rabbits from other researchers' studies should they become available, again fulfilling the dictums of the 3Rs.

1. OLAW. What Investigators Need to Know About the Use of Animals. http://grants.nih.gov/grants/olaw/InvestigatorsNeed2Know.pdf.

Forrest is Specialist, Department of Physiology and Biophysics, University of California, Irvine, Irvine CA.

RESPONSE

No accountability

Kirsten Love, DVM

The intent in submitting a proposal to the IACUC is to provide accountability for the animals being used for research. Accountability includes providing documentation and proof of what each animal is expected to endure during a particular study.

Concurrently running protocols on the same animals violates the requirement to declare all PIs and personnel working on the IACUC proposal because it undermines the accountability requirement. Everyone must be listed so that the IACUC can determine if the personnel are qualified[1–3]. Maintaining separate protocols for experiments on the same animals appears suspicious, as though the researchers are trying to hide something and somehow subvert full disclosure to the NIH or granting agency. Two protocols violates the spirit and wording of grant rules.

Creating a second protocol applying to the same animals undermines the ability to care for and singly account for the animals. If one of the rabbits became ill, there would be no clear recourse as to which PI can authorize treatment or euthanasia options. To carry Bergman's own argument through further, what if Wycroft's protocol is suspended for review? It would be easy to deny knowledge of the other studies taking place on his animals and difficult to localize the true source of the problem inciting the review.

While the researchers should be commended for their willingness to reduce the number of animals used, this particular proposition will not work. There remain several viable options. The first is to modify the existing Wycroft IACUC proposal to include Bergman's blood work as initially discussed. Routine blood work is often included in studies to confirm the health status of the participants. It would be unlikely the NIH would consider it a deviation from the original protocol. Depending on the time required to finish Bergman's study, Wycroft could wait and transfer the rabbits to her own protocol when available. The final option is to purchase new rabbits. Even though the final option requires new animals, it still provides the accountability to prove they receive appropriate care.

1. Public Health Service. *Policy on Humane Care and Use of Laboratory Animals* (US Department of Health and Human Services, Washington, DC, 1986; reprinted 2002).
2. ARENA/OLAW. *Institutional Animal Care and Use Committee Guidebook* 2nd edn. (National Institutes of Health, Bethesda, MD, 2002).
3. Animal Component of Research Protocol, Version 3, Main Body. http://www.researchtraining.org/referencedocuments/animalrefs/acorp/draftacorphome.html.

Love is Veterinarian, Animal Hospital of Polaris, Lewis Center, OH.