

Cardiac surgeon wanted: mouse experience required?

Harry Schwartz, M.D. was a skilled cardiac surgeon with many years of experience performing heart transplants, valve replacements, and other technically challenging procedures at the Great Eastern University hospital. Schwartz also had a long history of using dogs and swine for cardiac research and teaching. Therefore, the members of the Great Eastern IACUC raised no objections when Dr. Amos White listed Schwartz as the cardiac surgeon on his IACUC protocol. The protocol only required Schwartz to ligate the main cardiac arteries of adult mice. The animals were meant to recover from the procedure.

Unfortunately, all five of the mice operated on during the first day of surgery died before any of the school's veterinarians were advised of the problem. Later that day a veterinarian heard of the deaths and questioned Schwartz. Schwartz said that

it was reasonable for some mortality to occur at first because his surgical technique was being perfected. Nevertheless, the veterinarian told Schwartz to immediately stop his participation on the protocol until the IACUC could review the circumstances surrounding the animals' deaths.

When questioned by the IACUC, Schwartz said that he had truthfully answered all the questions on the IACUC application form. Specifically, he had responded that he was a board-certified surgeon with over 30 years of experience with cardiac surgery and he had operated on animal hearts on many previous occasions. However, the protocol application never specifically questioned if he had performed on mice the cardiac procedure he was to do for White, so he never addressed that subject. Although the IACUC could not understand how Schwartz could blatantly

misrepresent his expertise, Schwartz argued that there was no misrepresentation at all and that the fault was with the IACUC for not asking more specific questions on the application form. He told the committee that the deaths had occurred before the mice had emerged from anesthesia, and that now he was confident that he had perfected the skills needed to perform the technique and he was ready to proceed with the protocol.

What are the next steps to be taken by the IACUC? □

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Focus on the future: training is better than blaming

This is not an uncommon scenario and, as with any real-life situation involving multiple parties, the decision as to what to do next is a complicated one. Here we have a highly trained, highly experienced physician who has worked with many different species, including humans. To the lab, therefore, he was a logical choice to add to the research team when they needed a cardiac surgeon, and the IACUC of Great Eastern University (GEU) amenable approved this modification. After all, he was "only" needed to ligate a few cardiac arteries in some mice. However, it turned out that despite his vast training in other species, the surgeon did not have experience with the proposed survival procedure in the species in question, and the first five animals died soon after surgery.

The question posed in this scenario is, quite appropriately, "what should the IACUC do next," rather than "who is to blame." It does no good (especially for the animals) to squabble over who intentionally or unintentionally misled whom; instead, this can be used as an opportunity for collaboration between the IACUC, the veterinary staff, and the lab. The most immediate concern is the welfare of the animals, so the veterinarians did the right

thing in provisionally preventing the surgeon from performing surgeries on mice. It should now be made clear to both him and the PI (if it has not already) that surgeries cannot proceed until the IACUC and veterinarians are satisfied that, indeed, the "skills needed to perform" them have been "perfected."

Given their mandated role to consider the "adequacy of training and experience of personnel in the procedures used"¹⁻³, the IACUC then needs to clearly assess the surgeon's background with mouse cardiac surgery. This may require IACUC-specific training (e.g., mouse handling and aseptic technique modules in CITI or the AALAS Learning Library) but should also include a request for the surgeon's own reported background with this and similar work. Most importantly, perhaps, the IACUC should require that a veterinarian either oversee the next set of surgeries on a limited number of animals (preferred) or receive a report from the PI after these procedures are performed.

Once the IACUC is satisfied that these surgical procedures can be performed appropriately, some form of post-approval monitoring would be prudent, either as a formal follow-up a few weeks/months

later or as part of the next round of semiannual inspections. Either way, the IACUC should also consider how information regarding training/experience is initially acquired and assessed by the Committee and whether further clarification on animal use protocol applications is necessary. These steps should help to ensure the welfare of the animals while fostering meaningful collaboration between the IACUC and the research community in order to create a positive and safe working environment for all. □

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3. Public Health Service. Policy on Humane Care and Use of Laboratory Animals. IV.C.1. f (US Department of Health and Human Services, Washington, DC, 1986; amended 2002).

You know what happens when you assume...

A certain level of trust and understanding is required for an IACUC to support the use of animals in research while simultaneously

guarding animal welfare. Part of that trust includes when researchers are asked about their experience or the experience of their collaborators with a particular animal model.

In this instance, Schwartz may have answered the questions of the IACUC application truthfully but in a way that damaged the trust that the IACUC placed in him. His answers fulfilled the letter of the law but violated the spirit of the application questions.

With that in mind, the IACUC should not stand blameless, as they possessed prior knowledge of his lack of rodent cardiac experience. After all, *The Guide for the Care and Use of Laboratory Animals* states “The IACUC, together with the AV, is responsible for determining that personnel performing surgical procedures are appropriately qualified and trained in the procedures...”²¹. The committee’s knowledge of Schwartz’s apparent dearth of rodent surgical expertise should have prompted questions/concerns prior to the protocol ever being approved. In this case, the committee’s assumption may have inadvertently led to a waste of animal life.

While the outcome thus far in the scenario has been less than optimal, the potential for a teachable moment still exists for both the IACUC and Schwartz. First, Schwartz can be instructed by the IACUC that when unanticipated problems arise during a surgical procedure, he should stop and seek the opinion and guidance of other individuals with expertise. The death of 2-3 animals should’ve been enough to indicate he needed to consult with a veterinarian on the surgical technique. Reporting these types of problems (even once resolved) would build and strengthen trust among researchers, veterinarians, and the IACUC. It also serves to document and thus prevent similar problems from recurring in the future. Documentation of the problem and its resolution could be captured in a verbal report (for example, in the meeting minutes) to the IACUC or through an unanticipated problem report form provided to Schwartz. This report should include why Schwartz now feels that he can perform this procedure without any problems. It would be helpful to know from where Dr. Schwartz has gained this new found confidence when he has presumably not been performing this procedure since the time that the veterinarian asked him to halt his surgeries.

The IACUC should take steps to ensure that this type of mistake does not happen in the future. While the purpose of the question about experience in the IACUC application was designed to help determine Schwartz’s ability to successfully perform the cardiac procedure, it was not specific enough to do that. The IACUC might

A WORD FROM OLAW AND APHIS

In response to the issues posed in this scenario, the National Institutes of Health-Office of Laboratory Animal Welfare (NIH-OLAW) and the U.S. Department of Agriculture-Animal and Plant Health Inspection Service (USDA-APHIS) provides the following clarifications:

In this scenario, a surgeon skilled with cardiac procedures in humans, dogs, and swine is approved by the Institutional Animal Care and Use Committee (IACUC) to conduct similar procedures in mice. Without confirming his competency with the species, high mortality results. The IACUC must decide a course of action to remedy the issue and prevent further occurrences.

NIH-OLAW response

The first step to determine the cause of the mortalities is for the IACUC to thoroughly investigate how the surgeries were conducted. Complications resulting from the length of the surgeries and technique of the inexperienced surgeon may have contributed to the deaths, i.e., hypothermia, tissue dehydration, blood loss. Additionally, reviewing necropsy results and the anesthetic regimen may provide insight into the cause.

A further step toward correction is for the IACUC to modify the protocol form to ensure that a researcher’s experience with procedures are specific to the species proposed. The U.S. Government Principles¹, Health Research Extension Act of 1985² and the PHS Policy³ refer to appropriately trained personnel and required instruction and training by the institution⁴. The Guide requires institutions to ensure that research staff members performing experimental manipulation, including anesthesia and surgery, are qualified to accomplish such procedures humanely and in a scientifically acceptable fashion⁴.

The IACUC should require hands-on surgical training for the surgeon and monitor their competency. The IACUC should focus additional training for all researchers that emphasizes institutional expectations to minimize pain, distress, and (in this case) unnecessary mortality.

Training should also emphasize that when procedures do not go as expected the veterinary staff should be contacted promptly. Continuing IACUC oversight of animal activities through effective post approval monitoring is critical^{2,5}.

USDA-APHIS response

The Animal Welfare Act (AWA) excludes from the definition of animal, mice of the genus *Mus* that were bred for use in research⁶. As a result, the AWA regulations cannot be applied to the mice in this scenario. In light of this, the USDA defers to OLAW or any agency with the appropriate regulatory authority, in accordance with the requirement under the AWA to consult and cooperate with other Federal agencies concerned about the welfare of animals in research⁷. □

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- 7 U.S.C. Section 2132(g)
- 7 U.S.C. Section 2145(a)

consider a slight modification to their application so that it includes the species with which the researcher has had prior experience. The IACUC protocol in question should also be flagged for post approval monitoring (PAM) to determine what factors may have led to the death of the first 5 mice. The PAM process can not only help with the surgical procedure itself but can also shed some light on other perioperative elements (e.g. surgical preparation, anesthesia, recovery, analgesia, etc.)

These steps taken by both the IACUC and Schwartz will improve the quality of the research being conducted while also helping to refine the process of assessing the required training at the institution². These steps can also serve to enhance the trust between researchers and the IACUC which is in the best interest of the animals, the institution, and the research. □

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Human or mouse? Practice makes perfect

The IACUC must assure the personnel performing procedures in the IACUC submissions are trained and qualified. This can be attained by:

1. Proper training of personnel, allowing easy access to training modalities
2. Consultations by subject matter experts and more rigorous review of IACUC protocols by trained and engaged IACUC members
3. Additional questions added to IACUC submission form (which may include criteria for external consultants)
4. A PAM (post approval monitoring) program to encourage investigators to improve their data outcomes and avoid unrealized risks.

Following such considerations could have helped Great Eastern University avoid the current situation. A consultation, or pre-review, of the IACUC application by a veterinarian or expert designated by the Attending Veterinarian (AV) may have taken the lack of expertise with the species into consideration and prompted the IACUC to request more information regarding Schwartz' experience. As stated in ref. ¹ above, "The IACUC assumes responsibility on behalf of the institution and thereby has the function of overseeing the training program." At a minimum, there could have been additional assurance that proper methods of euthanasia were followed for compromised animals.

White, the principal investigator (PI) could have addressed the lack of expertise

of the surgeon by accounting for animals for training use by Schwartz within the IACUC application. This would have assured the IACUC that proper precautions would be taken for this novel procedure in the mice, including humane endpoints.

The IACUC could have requested to see curriculum vitae (CV) of the surgeon's credentials and experience when reviewing the IACUC application. This may have alerted the IACUC to the lack of experience with the intended species for use on this protocol. A requirement for CV submission when listing non-departmental personnel on protocols for surgical procedures would forewarn the IACUC for future submissions.

Additional questions in the IACUC application form template regarding experience (or training) would be helpful for the IACUC to assure if the "personnel conducting procedures on the species being maintained or studied will be appropriately qualified and trained in those procedures," as indicated in the Animal Welfare Act and Regulations². Additionally, the Guide for the Care and Use of Laboratory Animals states, "Researchers conducting surgical procedures must have appropriate training to ensure good surgical technique is practiced—that is, asepsis, gentle tissue handling, minimal dissection of tissue, appropriate use of instruments, effective hemostasis, and correct use of surgical materials and patterns."³

In response to the deaths of the animals, the AV (or one of the school's veterinarians) could observe the surgery to assure the IACUC that proper veterinary oversight is

conducted for the welfare of the animals. If the procedure is conducted according to the IACUC submission without incident, the AV (or school veterinarian) may communicate the assurance to the IACUC for the surgeries to be conducted by Schwartz. If the procedure is not conducted without incident, the AV (or school veterinarian) would halt the surgeries, taking proper precautions for clinical care and animal welfare. The AV (or school veterinarian) would communicate concerns to the IACUC to halt the IACUC application. Further explanation and follow-up between the IACUC and White should take place.

Further follow up on this IACUC application could be conducted as a PAM since there is a post approval monitoring program at Great Eastern University, if through further discussions it is deemed appropriate to continue with the IACUC submission. □

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