

Is 'saving money' a valid justification?

One of the guiding principles of using animals for biomedical research is to use the smallest number of animals that may lead to statistically or biologically significant results. Supporting this concept, both the NIH and USDA state that “investigators may use fewer animals than approved. This does not require IACUC approval, notification, consultation, or administrative handling.”¹

Dr. Ed Stark was an established researcher with a propensity for doing things in a way that just skirted the line between right and wrong. This tendency often caused problems for the school's IACUC, as exemplified by an incident when Stark decided to reduce the number of animals in one of his IACUC approved experiments. He did this by euthanizing an entire group of negative (untreated) control mice without informing the IACUC. When the IACUC office finally found out what Stark had done, the committee chairman asked him for an

explanation because Stark had argued during the initial review of his protocol that the untreated controls were scientifically necessary. But now he said that the findings to date with his experimental groups were trending toward strong statistical significance and the vehicle control mice (those having corn oil mixed in their diet) were adequate controls to complete the study. He added that he wanted to avoid some of his per diem charges, so eliminating an unnecessary group of animals made good sense, and in any case the IACUC had no authority to even question him about how he conducted his experiment as long as there was no protocol noncompliance or animal welfare issues.

Stark's response did not sit well with the IACUC chairman who discussed the incident at the next full committee meeting. The chair's position was that there was nothing in the protocol that gave

Stark the authority to euthanize an entire experimental group of healthy animals that he originally stated were important to his study. On the other hand, he was aware of the NIH guidance about an investigator being allowed to use fewer animals without informing the IACUC¹ but he did not interpret that guidance as sanctioning the euthanasia of an entire experimental group just to save money.

How do you think the IACUC should resolve the issues raised by its chairman?

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1. Public Health Service. *Guidance on significant changes to animal activities*. Notice NOT-OD-14-126. (National Institutes of Health, Washington, D.C. 26 Aug. 2014.)

Unnecessary tension

In this scenario, there appears to be ongoing tension between Dr. Stark and the IACUC. However, it is unclear whether the tension exists with the IACUC as a whole or specifically with the IACUC chair. Regardless of the cause or nature of any underlying tension, both the IACUC and Dr. Stark have responded inappropriately in this scenario. With respect to Dr. Stark's actions, he was within his right to not use the control group as originally requested and justified during the initial protocol review. The justification was based on the knowledge and data he had at the time; results obtained during the course of his experiments showed that the untreated controls were no longer needed. Unless the IACUC or animal facility has a specific policy requiring notification of the IACUC of the euthanasia of experimental groups, no regulatory requirements exists for an investigator to notify the IACUC in this particular case. On the other hand, Dr. Stark could have investigated other options for the untreated controls prior to euthanasia.

For example, he could have reached out to the animal facility to determine if the mice could be used for training or transferred to another protocol where they could be used.

The quantity of mice euthanized is not indicated in the scenario, so it is difficult to determine if the response by the IACUC Chair is warranted. The IACUC has a responsibility to develop policies and procedures to assist researchers in making ethical decisions and to ensure researchers are aware of and understand those policies and procedures. This responsibility could include providing a process or resources for donating unused animals for training or to other researchers if animals are no longer needed for a particular study. Researchers should also be informed that decisions on use (or in this case, euthanasia) of animals should be based on balancing the research objectives with the health and welfare of the animals and should not be based on cost savings.

Researchers and the IACUC should work together to balance the health and

welfare of animals used in research and the scientific objectives of the studies where animals are needed. Recently, there has been a dramatic increase in regulatory burden for researchers and studies have shown that the burden is often self-imposed. As there are no specific policies dictating reporting of this kind of event to the IACUC, the response by the IACUC Chair is bordering on self-imposed regulatory burden. The IACUC has responsibility to oversee the responsible use of animals in research at the institution. As such, the committee should be working collaboratively with researchers to maintain the balance described above while affording the research an appropriate amount of flexibility to carry out their studies.

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The use of used

OLAW's "Guidance on Significant Changes to Animal Activities" (NOT-OD-14-126)¹ indicates investigators may use fewer animals than originally approved without IACUC or administrative notification or approval. This would include, for example, not performing a duplicate experiment that was intended only if statistical significance wasn't achieved with the initial group. However, in this particular scenario, Dr. Stark's actions were not consistent with intent of the OLAW notice. Although the number of animals being used for research may be reduced by eliminating experimental groups; that action may also negatively impact the IACUC's evaluation of the scientific validity of the experiment. Consequently, eliminating a test group within an experiment may compromise the IACUC's interpretation that the experiment will result in "either significant new knowledge or leads to

improvement of human and/or animal well-being" (Guide, p. 4)².

A fundamental IACUC charge is to "... evaluate scientific elements of the protocol as they relate to the welfare and use of the animals." (Guide, pg. 26)² In Dr. Stark's protocol, he described an experiment that required a negative and vehicle control group to be scientifically valid. Since the IACUC's approval of the experiment was based on an assessment that included two scientifically justified control groups (ensuring that the requested number of animals was the "fewest needed to obtain statistically significant data" (Guide, p. 201)²; it is the responsibility of the PI to conduct the experiment as described in the protocol. In this particular example, needed changes (i.e., eliminating an experimental group from an experiment) to the overall design of the experiment should be reviewed and approved by the IACUC before they are

initiated to ensure the committee agrees the scientific elements of the study remain valid.

While the PI's decision to eliminate a test group may have potentially decreased the number of animals needed for the study, in this particular case the experiment was started and included the negative control animals. The scenario indicates the animals were euthanized because the negative control group was no longer needed, but the scenario suggests they were euthanized to reduce per diem costs. Fundamentally, the PI made two poor decisions: 1) he conducted an experiment that was not consistent with that which was described in his IACUC approved protocol; and 2) he omitted a test group to reduce per diem costs.

The PI's interpretation of OLAW's Guidance on Significant Changes was incorrect. If, for example, Dr. Stark had explained to the IACUC that the experiment was redesigned, and the untreated control group was no longer needed for various reasons, then the use of fewer animals would have been appropriate. In this scenario, the PI misinterprets the definition "to use". Overseeing the use of animal activities in research, testing and instruction is a partnership between the institution, the IACUC, and the PI and, ultimately, this scenario represents an opportunity for education and team building between the IACUC and the PI. □

A WORD FROM OLAW

In response to the issues posed in this scenario, the Office of Laboratory Animal Welfare (OLAW) provides the following clarifications:

In this scenario, the PI has misinterpreted OLAW's significant changes guidance.¹ The euthanasia of otherwise usable animals without notifying the IACUC is not responsible animal use. Although OLAW's guidance states that "The use of fewer animals than approved may be handled without IACUC policy, approval, notification, consultation, or administrative handling", these actions can be required by the IACUC to not waste animals unnecessarily.¹ By eliminating an experimental group, the PI may confound the validity of the research. As the authorized entity to oversee animal welfare, the IACUC can question any aspect of animal use. This includes, as

stated in the Guide, "scientific elements of the protocol as they relate to the welfare and use of the animals."² The IACUC should consider educating investigators concerning institutional use of unneeded animals and create opportunities for PIs to transfer usable animals to holding or training protocols for future use. □

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Unfortunate but not noncompliant

The IACUC has no grounds to censure Dr. Stark. The chair was concerned that Dr. Stark euthanized a group of **healthy, naïve**, animals to save money. If instead Dr. Stark had euthanized any other experimental group of animals, I do not think anyone would have raised an issue.

Let's examine some alternative scenarios:

What if Dr. Stark had euthanized a group of **unhealthy** animals to eliminate unnecessary pain and distress? What if the study design was a painful disease model with a group of untreated control animals (e.g. mice with arthritis not receiving any anti-inflammatory or analgesic treatment)? If he determined mid-study that this control group was not scientifically necessary, he would have been lauded by the IACUC

for terminating the group early to save on unnecessary pain and distress.

What if Dr. Stark euthanized a group of healthy **non-naïve** animals to save on per diems, labor, expensive research reagents, and possible animal stress from handling and dosing? What if he started with four dosing groups, and discovered mid-study that the exposures in one oral group were too low to be biologically relevant? Terminating that group early would have been scientifically, ethically, and fiscally responsible.

Now we come to the actual scenario. Dr. Stark discovered, based on preliminary data, that the untreated control arm was not necessary. Keeping the group and analyzing terminal tissues anyway would have used up resources (labor, reagents, facility space, per diem payments). If these had been non-naïve

or unhealthy mice, it would have been clear that the ethical, scientifically justified, and fiscally responsible decision was early euthanasia. The fact that these were naïve healthy mice does not negate that. However, if the mice were indeed completely naïve, it would have been preferable to repurpose them by transferring them to another study or for training. If the IACUC wants to encourage this behavior, they could create a program to facilitate such transfers. □

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