

## A word from OLAW

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

The key issues raised in the scenario are: 1) whether the experimental design is consistent with the strategic aims of the research; 2) concerns for animal welfare in considering two of the three “Rs”, reduction versus refinement; and 3) if the statistical power of the animal numbers in the control group is appropriate for the study.

Although an IACUC’s primary focus is on animal welfare, often it must include consideration of the soundness of the research design in its review of protocols. The *Guide* states that “While the responsibility for scientific merit review normally lies outside the IACUC, the committee members should evaluate scientific elements of the protocol as they relate to the welfare and use of the animals”<sup>1</sup>. If a rationale for the experimental design is unclear to the IACUC then the committee should request further clarification from the investigator.

Minimizing the number of animals is a worthwhile consideration, but it must allow for valid results and be balanced by the discomfort, distress and pain experienced by each individual animal<sup>2</sup>. The *Guide* states that “reduction involves strategies for obtaining comparable levels of information from the use of fewer animals or for maximizing the information obtained from a given number of animals (without increasing pain or distress) so that in the long run fewer animals are needed to acquire the same scientific information” and that the goals of refinement versus reduction “should be balanced on a case by case basis”<sup>1</sup>.

Whenever an IACUC is faced with complex issues, including the statistical justification for control and experimental groups, it should consider using consultants to provide expert counsel<sup>3</sup>.

1. Institute for Laboratory Animal Research. *Guide for the Care and Use of Laboratory Animals* 8th edn. (National Academies Press, Washington, DC, 2011).
2. Interagency Research Animal Committee. *U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research and Training*. (Office of Science and Technology Policy, Federal Register, Washington, DC, 1985).
3. Public Health Service. *Policy on Humane Care and Use of Laboratory Animals* (US Department of Health and Human Services, Washington, DC, 1986; revised 2015).

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the long run fewer animals are needed to acquire the same scientific information”<sup>1</sup>.

In this scenario, the reviewer’s suggestion to prioritize reduction before welfare would reduce the number of animals used in Foxworthy’s experiment, but it would also increase the pain and distress for each of those animals, probably beyond an acceptable threshold. The Office of Laboratory Animal Welfare endorses prioritizing the welfare of individual animals above the principle of reduction, prescribing that “procedures with animals will avoid or minimize discomfort, distress, and pain to the animals, consistent with sound research design”<sup>2</sup>. Foxworthy’s preference, using more animals so that each animal experiences less pain, is a better option than the alternative, using fewer animals with each animal experiencing more pain. Foxworthy’s design will maximize the welfare of each rat in his experiment and reduce the presence of unwanted variables in the resultant dataset.

Every IACUC is charged with evaluating the experimental models and design proposed in each protocol. They must consider what level of pain and distress is acceptable for each animal and what methods are most likely to generate reliable data. IACUC members should recognize that experimental groups are made up of individual animals, and it is the IACUC’s responsibility to help ensure the welfare of each and every animal used for research at the institution. Principal investigators must strive to generate high quality data while concurrently minimizing the pain and distress of their research animals. In this scenario, Foxworthy should be allowed to perform his research as described in his protocol with group sizes large enough to minimize pain and distress for each animal.

1. Institute for Laboratory Animal Research. *Guide for the Care and Use of Laboratory Animals* 8<sup>th</sup> edn. (National Academies Press, Washington, DC, 2011).
2. 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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is therefore not a suitable control because the limb is not separate from the whole animal and not immune to systemic pain. It would compromise both the welfare of each rat and the experiment’s data, which would introduce new unwanted variables and interactions, if Foxworthy were to follow the reviewer’s suggestion.

Amendments in adherence to the principle of reduction must be evaluated with the entire experiment in perspective, as rigid interpretation of this principle can demand that an IACUC compromise its other responsibilities. It is a clear mandate of biomedical research that investigators reduce the number of animals used in experiments, so researchers must clearly

justify their sample sizes. But they must also maintain concern for the welfare of each individual animal in their experiments. For Foxworthy’s proposal, the IACUC must consider what level of pain and distress is acceptable for each rat. The upper limit of distress for each rat must be defined and not exceeded, even if this requires compromising other principles, such as reduction. The *Guide for the Care and Use of Laboratory Animals* explicitly states that “reduction involves strategies for obtaining comparable levels of information from the use of fewer animals or for maximizing the information obtained from a given number of animals (without increasing pain or distress) so that in