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Key Design Elements Can Ensure Ethical, Successful Research Involving Animals

By Jane Anderson

An appropriate statistically based study design is the fundamental tool in animal research, not only for translation but also for replacement, reduction and refinement, known as the three Rs. Institutional animal care and use committees (IACUCs) also need to more carefully review experimental design to make sure studies will improve science while minimizing harms, an expert said.

Penny Reynolds, assistant professor of anesthesiology at the University of Florida College of Medicine, explained at a webinar sponsored by the NIH Office of Laboratory Animal Welfare that incorporating three study design elements—bias minimization, the design skeleton and screening for sample size—can help more research be successful while honoring the three Rs.[1]

This matters, Reynolds said, because of "the really dire rates of translational success for most of preclinical research. The industry rule of thumb is less than 50% of preclinical, animal-based results even make it to industry, and about less than 5% ever make it to clinical trials. And for some areas of research, like Alzheimer's research, it's more like zero."

There have also been well-documented problems and replication translatability of animal-based research in primary literature "and in major publications like *Nature* and *Science* for the past 15 years," she said. "And also, just as scientific practice generally is evolving, best practice certainly is, and we need to adjust to that and inform researchers of what the new expectations are."

In June 2021, the Advisory Committee to the Director's Working Group on Enhancing Rigor, Transparency, and Translatability in Animal Research released its final report on how researchers can improve the rigor, transparency and reproducibility of NIH research involving animals, paying close attention to the late stages of the translational pipeline.[2]

In that report, Reynolds said, there were two common themes: "The first one is that animal-based research is poor overall. And the second one is that the degree of understanding and training in statistics and statistical concepts on the part of investigators and researchers is very, very poor." The number one priority identified both by the report and by the investigators themselves is that researchers need better training in statistics and study design, she said.

"But the big thing that comes out from this is that it doesn't matter how good the science is or how good the animal models are," Reynolds said. "Unless studies are properly designed, properly analyzed and completely, appropriately and thoroughly reported, nothing of that will even matter—their models are useless." Still, that report is "another in a long series of reports which say that study design really needs to be considered more rigorously than it is," she said.

Beginning around 2015, NIH started to recommend that IACUCs "could be a bit more proactive in facilitating good quality research," Reynolds said. Despite considerable pushback, some of which is due to a lack of

knowledge on good study design, she said, "This is also part of our duty of care to minimize those indirect harms caused by wasting animals in research which will ultimately be non-informative."

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