

Is reproducibility an IACUC's concern?

Dr. Charlotta Jones studied the activation of rabbit spinal neurons by magnetic fields. Jones' latest IACUC protocol went through an uneventful pre-review by a laboratory animal veterinarian and now was undergoing designated member review by two scientists on the committee. One of the two had general familiarity with the technique used by Jones and knew that there were publications which questioned the reproducibility of that technique. As part of his written review he asked that Jones comment on the published critiques to assure the committee that animals were not being "inappropriately used." Jones took that request as an affront to her ability as a scientist and refused to comment on the critiques.

To avoid a personal argument with Jones, the reviewer called for full committee review and the IACUC invited Jones to the meeting. After the reviewer provided the background for his concerns and responded to a few questions, Jones entered the room, was introduced to the committee, and briefly described her

research goals and methods. When the chairman asked about the publications critiquing the reproducibility of her work, Jones replied that her previous publications had undergone peer review from respected journals, and that she was the recipient of peer reviewed federal funding for her research. She added that everybody in the room knew that in the past few years there have been many articles citing difficulties in reproducing the published findings of scientists in many fields of research and she did not see her studies as being immune from that problem. In her own case, she said, part of the problem may arise from some journals limiting the amount of technical details allowed in the Materials and Methods section of her publications, but the techniques she used were the same ones used by other researchers in her field. When a committee member suggested that Jones perform some pilot studies to help validate the reproducibility of her methods, Jones reminded the committee that three years earlier it had previously asked for, received, reviewed, and approved the findings from

her pilot studies and to repeat them again would be a waste of time and animals. The chairman thanked Jones for her participation and told her that she would be informed of the IACUC's decision.

During the subsequent discussion of the protocol, it became obvious that the scientists on the IACUC, who composed the majority of the committee's voting members, were in favor of approving Jones' protocol as submitted, largely because they felt that her federal funding provided strong evidence for the quality and importance of her research. The other members of the committee seemed likely to follow the lead of the scientists. Would you also follow the scientists? If not, what would be your concerns? □

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On the reproducibility of methods or findings

The vertebrate animal section of a grant proposal from federal agencies such as the NIH requires the PI to address four criteria: description of procedures; justifications; minimization of pain and distress; and method of euthanasia. In particular, a concise description of the proposed procedures to be used for live animals must be provided with enough details for evaluation by study section or review panel. Therefore, the funded research grant to Jones must have had enough details of the animal experiments to have been reviewed and approved by its funding agency.

Jones' findings using her technology have been published in respected journals, suggesting her methods have been peer-reviewed by referees with appropriate expertise in the field and accepted by the journals as well. Most journals require authors to include a statement in their manuscript that live vertebrate animal experiments have been reviewed and approved by the IACUC.

As all federal funded grants also require congruency with the IACUC, the studies proposed by Jones must have been approved

by the IACUC before the grant was officially funded. We suspect that the IACUC protocol application may be a *de novo* renewal of Jones' previously approved protocol. Therefore, Jones' technology was previously reviewed and approved by the IACUC. Furthermore, Jones' pilot studies had previously been asked for, reviewed, and approved three years ago, indicating that Jones and her team have appropriate expertise to conduct studies on the activation of rabbit spinal neurons by magnetic fields. We agree that another pilot experiment is not necessary.

While it is important to note that as new information becomes available, investigators may need to make changes to previously approved animal protocols, it is not very clear how the publications questioned the reproducibility of the technology used by Jones. If this is just a general discussion of her technology, it is generally not a concern from the IACUC's perspective. The IACUC may raise concern if these publications provide details of apparent flaws and experimental evidence in Jones' technology. It is understandable that a technology

may not be fully reproduced by another laboratory without appropriate training and detailed technical support, especially for vertebrate animal-related methods. The lack of detailed descriptions of the technology is often due to limited space for the Materials and Methods section in most journals. Certainly it would be of concern if no other labs could reproduce the technology and had detailed protocols from Jones. However, it seems that her technology is similarly done in other labs.

Taken together, we are more likely to approve this protocol considering that Jones has a reviewed and funded federal grant, prior peer-reviewed publications, and a previously approved IACUC protocol using this technology. □

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No need to duplicate prior pilots

We agree with Jones' contention that the federal funding agency (presumably the National Institutes of Health [NIH]) had already

evaluated the reproducibility of her research during the peer review process. The NIH has been aware of the concerns regarding the issue of reproducibility¹. Indeed, its

webpage states, "the NIH is committed to promoting rigorous and transparent research in all areas of science supported by a variety of grant programs. Grant application instructions and the criteria by which reviewers are asked to evaluate the scientific merit of the application include the expectation for full transparency in proposing and reporting experimental details so that grant reviewers may assess the proposed research and others may reproduce and extend the findings."² We can therefore conclude that this facet of the PI's research had been thoroughly vetted before the grant was awarded.

However, peer review does not preclude an IACUC member from raising the issue of reproducibility as a concern. As opined by the reviewer of Jones' protocol, an IACUC member's responsibilities may include assessment of the reproducibility of a study as a means to assure the committee that animals are not being inappropriately used. *The Guide for the Care and Use of Laboratory Animals* states: "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."³

Although the grant was awarded, it is possible that discrepancies exist between the methods described in the grant proposal and the animal use protocol. The IACUC is performing its due diligence by ensuring that the issues of reproducibility and grant congruency are effectively addressed at the protocol level before further studies are approved⁴. To this end, a pilot study can be very valuable in validating the reproducibility of a technique, and an IACUC is certainly authorized to require that one be performed. However, since pilot studies have already been performed by the PI and assessed by the committee in this circumstance, we agree with Jones' contention that duplicating those studies would neither be informative nor a responsible use of animals. We suggest that Jones include the results of the previous pilot studies in the animal use protocol to proactively address this concern.

While we cannot comment on the quality of peer review for the journals in which Jones has published, if those journals do in fact limit detail in the Materials and Methods section, it is possible that the manuscript might not provide sufficient

A WORD FROM USDA AND OLAW

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

In this scenario, the IACUC is deciding whether a pilot study is indicated to validate the reproducibility of a researcher's established methods because of concerns raised in publications about the techniques.

USDA-APHIS response

The Animal Welfare Act regulations require an IACUC to review an animal study proposal to ensure it meets the requirements that the work avoids or minimizes pain/distress, and contains a written assurance that the activity does not unnecessarily duplicate previous experiments^{1,2}. In addition, the regulations require a proposed activity to include a rationale for the numbers of animals to be used³. In this scenario, the IACUC is deciding whether a pilot study is indicated to validate reproducibility. The investigator however relayed that her work had been peer reviewed for Federal funding, and that pilot studies were already performed as requested by the IACUC three years ago, hence to do so again would be a waste of time and animals.

The Animal Welfare Act regulations do not give the IACUC the authority to prescribe methods or set standards of design, performance, or conduct of research⁴; however the IACUC has the authority to request additional information that supports the written assurance that the work is not unnecessarily duplicative, and the investigator's rationale for the appropriateness of the numbers of animals to be used. The IACUC also has the authority to invite consultants to assist in reviewing the protocol⁵ before deciding whether to approve, require modifications to approve, or withhold approval for the proposed activity⁶.

NIH-OLAW response

As noted by other reviewers, the PHS Policy and the Guide expect the IACUC

to consider whether the research design is sound^{7,8}. Besides further pilot studies, OLAW agrees with the other reviewers that the IACUC has better options to reconcile the reproducibility concerns. The IACUC may choose to 1) ask the researcher to include the outcome of the pilot studies in the renewal protocol, 2) increase post-approval monitoring of the study to confirm consistency in the application of the techniques in question, or 3) request that the researcher provide more details of how she internally validates her techniques. Regarding NIH grant applications proposing the use of animals, it is the institution's responsibility, not the IACUC's, to ensure congruency between the application and the IACUC protocols^{9,10}. Institutions have flexibility in which program carries out this responsibility. □

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information for others to reproduce a study. However, we do not think that a particular journal's editorial style is relevant to the IACUC's deliberations.

Based on the above references, and the fact that there were no veterinary or other scientific concerns, we are in agreement with both Jones and the scientific members of the IACUC. We would vote to approve the protocol (potentially with clarifications in

order to secure approval) without requiring duplicative pilot studies. □

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Consider both sides

In this scenario, both the IACUC scientist and the researcher, Dr. Jones, have valid points to consider. Reproducibility of data is a concern, especially with complicated animal models, and should be carefully considered so that animals are used thoughtfully. It can be necessary to include large numbers of animals in study groups in order to arrive at scientifically valid results if there is significant variability due to inherent lack of model reproducibility.

As an IACUC member I would not approve a protocol simply because it was federally funded. Federal funding status alone does not automatically make a research project scientifically valid, though it is helpful to know that an external review body of scientific peers did consider the work to be worthy of financial support.

It is the IACUC's task to determine whether the particular research protocol submitted to their review is scientifically valid and of sufficient importance to validate use of animals, that it conforms to the 3R's principles, and whether appropriate alternatives exist that should be considered.

As a reviewer I would have some additional questions for Jones. Are these Category E studies or studies otherwise anticipated to cause significant pain or distress to the animals for which analgesia is warranted? If so, the impact to the animals on study is greater and should be considered carefully against the anticipated benefits of the research. Does she anticipate using large groups of animals due to variability? Have her results been consistent across multiple

studies which would help support her own technique's internal reproducibility?

Since a previous pilot program was conducted, I agree that requesting Jones to repeat this work would be unnecessary and would not comply with the 3R's, unless she has significantly changed her technique or approach. If Jones can show that her current technique is yielding useful data, I would agree with the other scientists on the IACUC and approve the protocol. □

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