Post-publication problems: how to proceed when there's no record of IACUC approval?

Dr. Yoshihiro Katayama successfully completed his PhD research at Great Eastern University and returned home to Japan and his new job as an assistant professor of molecular biology. His mentor during his PhD studies, Dr. Henry Miller, was rightly proud of Katayama's work and looked forward to the publication of their final collaborative studies. When that research was finally published, it was well received and highlighted in a university news release. The chairman of the Great Eastern IACUC, Dr. Larry Covello, read the release and then read the published article. Covello could not remember any such study being approved by the IACUC, but the article clearly stated that the research had received IACUC approval. Covello asked the IACUC office to check Miller's IACUC files. No record of that research could be found. There was no record of Katayama being a principal investigator, so Covello asked Miller for an explanation. Miller said he was sure that Katayama had submitted an IACUC protocol, but after a search of IACUC and laboratory records, it became clear that Katayama had inadvertently used the IACUC approval number of one of Miller's other protocols for the research that led to the publication. There had never been an IACUC review of that work.

Neither Miller nor Katayama had ever caused a problem for the IACUC. However, the work was performed without IACUC approval or oversight; the findings were important; and they were published in a prestigious journal. What, if anything, do you think Miller and the IACUC should do? ❐

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Investigation, reporting, and program improvement

The Institutional Animal Care and Use Committee (IACUC) should rapidly conduct an investigation to gather complete information about what happened. Questions that need to be answered include: What species was involved and is that species regulated by the United States Department of Agriculture (USDA)? What was the funding source for the research and did it involve funding from the National Institutes of Health or the National Science Foundation? How many animals were involved? What procedures were performed on the animals and by whom? Were those same species, people, and procedures approved under another related protocol? Were the animals housed in a centralized animal facility or an investigator-managed, satellite facility and what prevented husbandry, veterinary, and post-approval monitoring (PAM) staff from noticing that unapproved procedures were taking place? Were the animals from an in-house production colony or purchased from an external vendor without first verifying that an IACUC-approved protocol was in place? Had all members of the research team been trained about requirements for prior IACUC approval? It is critical to learn where and how the system broke down to identify what could prevent similar occurrences in the future.

Once it becomes clear that Public Health Service-funded animal activities have taken place without IACUC approval, the Office for Laboratory Animal Welfare (OLAW) must be notified promptly. According to NOT-OD-13-044, "it is appropriate to submit a preliminary report prior to the completion of a full investigation and implementation of a corrective plan". Institutions must also provide a final report including a detailed explanation of the circumstances and actions taken. The final report must be signed by the Institutional Official (IO) and submitted either via email in PDF format or by fax. If the project involved a USDA-regulated species, the IACUC and IO should review USDA's December 2017 Technical Note titled "Incentives for Identifying, Reporting, Correcting, and Preventing Noncompliance with the Animal Welfare Act" for advice on reporting to USDA. Finally, most animal-related research articles include a statement about IACUC approval. Assuming that occurred in this scenario, Katayama should contact the journal to inform them that the project had not been IACUC-approved and let the journal determine whether a clarification needs to be published.

Based on the results of the investigation, the IACUC and IO should identify any programmatic changes appropriate to prevent problems like this from reoccurring. Does a PAM program need to be implemented or improved? Is the training program adequate to ensure all research team members know their responsibility to conduct animal procedures as described in IACUC-approved protocols? Do some individuals need refresher training? Do animal procurement and protocol transfer procedures involve a method of verifying IACUC approval? Do grant application processes include a method to verify grant congruency with IACUC-approved procedures? The IACUC and IO should implement changes as needed to prevent a repeat of the noncompliance while minimizing additional regulatory or training burden on the faculty and staff. ❐

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Difficult situation=difficult solution

Animal research is a privilege entrusted to scientists by the public. This situation is unfortunate, but the bottom line is that without an approved animal protocol, the publication, regardless of the findings, cannot stand as submitted. First, it is the responsibility of the PI to submit an animal protocol for the work that was already done and self-report the misstep in an official manner to the IACUC. It is a difficult situation, but not correcting this situation would make it worse. If the IACUC approves the protocol as the work was previously completed, then the PI should contact the journal to request an addendum to the article be placed explaining the mistake. Additionally, the IACUC could require that the investigator be present at a full committee meeting and explain in person to at least a quorum of the committee why there was a failure to ensure that the animal work was on an approved animal protocol before beginning the study.

If the IACUC cannot approve the experiment as performed, the PI must request the article be retracted. When the IACUC does approve the experiment with necessary modifications, the work should be repeated using the approved methodologies and then submitted to the same journal. If the science is good, reproducing the study should occur without incidence. The public would be more understanding of a mistake like this if the time and effort was taken to correct it.

The solutions proposed, while difficult for the new scientist, adhere to the spirit of the 3R's while also maintaining the highest standards for ethical publication. It is important that the situation is not minimized, regardless of how prestigious the journal is or how compliant a researcher may have been in the past. "Laboratory animals play a crucial role in biomedical research—indeed many advances now incorporated into human health care, would not have been possible without them. Informed and well-trained scientists have the privilege, but not the automatic right, to use animals as experimental subjects. This privilege must not be abused."[1]

Scientific research is based on the truthful and accurate data that the scientist discovers and ethically the PI must follow the rules of the institution when it pertains to using live animals in their experiments. The public and the institution depend on IACUC to make sure this right is not abused. ❐

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A WORD FROM OLAW

In response to this scenario, the Office of Laboratory Animal Welfare offers the following guidance:

In the scenario, a doctoral student and his advisor completed and published a study without IACUC approval of the animal activities. The problem was identified by the IACUC Chair after the student graduated and embarked upon a research career in his home country. The author poses the question, "How should the PI and IACUC handle this situation?"

All of the respondents correctly identified the serious noncompliance of conducting animal activities without IACUC approval. As identified by two of the respondents, the IACUC must investigate the incident, the investigation must be documented, and, if PHS funded, the noncompliance must be reported promptly to OLAW. A plan, schedule, and timeframe for correction, and prevention of recurrence of the noncompliance must be developed, reported to OLAW, and implemented, as described on the OLAW website, Reporting Noncompliance[1]. The PI should cooperate with the IACUC to develop and implement procedures to prevent recurrence.

In addition to the complete and well described procedures suggested by two of the respondents for investigation and correction of the noncompliance, the institution is required to 1) contact the NIH funding component to negotiate the potential refund of grant money used on an animal study without IACUC approval, and 2) notify the Program Officer about the publication of unapproved activities, as described in Guide Notices NOT-OD-07-044[2] and NOT-OD-10-081[3].

Additionally, The PHS Policy section V.B.[4] and the NIH Grants Policy Statement chapter 4.1.1.2[5] require the institution to verify, before award, that the IACUC has reviewed and approved those components of grant applications related to the care and use of animals. Institutions are responsible for ensuring that the information the IACUC reviews and approves is congruent with that provided in the grant application. Accordingly, the institution must assume responsibility for this serious noncompliance and negotiate a return of funds with NIH.

The journal in which the experiment was published must be notified that the animal activities were incorrectly identified as having been conducted with IACUC approval. The journal, not the IACUC or the authors, is responsible for determining their response.

The IACUC may not retroactively review and approve the animal activities. Such an action would not mitigate the noncompliance that has been committed and would extend the impact of the noncompliance. ❐

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Honesty is the best policy

The series of events as outlined portrays some major concerns about the Institution's IACUC quality control and their check and balance system(s). A deeper investigation of the type of study Katayama was conducting and the overlap that it had with Miller's other protocols is justified for the IACUC. The IACUC should understand how great a deviation this is and the Institutional Official should be informed of the findings, based on potential negative backlash for the institution. The bottom line is that unapproved animal work was done and published in a prestigious journal. An initial step is to notify the journal that the author of record did not have institutional approval or oversight of the study, as was stated in the paper. This could be classified as investigator misconduct, which might result in retraction of the article and potentially negative career implications for Katayama.

The IACUC also has regulatory responsibilities to report this to the appropriate oversight entities. If the work was PHS/NSF-funded, or depending on how the Institutional assurance on file for Great Eastern is written, the IACUC must promptly send a preliminary report to OLAW[1] in form of a fax, email or a telephone call. Once full action is determined, a final report should be submitted with actions taken for short and long term corrective plans and a schedule of implementation. If Great Eastern is an AAALAC-accredited institution, they should also notify AAALAC of a potential OLAW investigation[2]. If USDA-covered species were used in this study, there is not a requirement to report until the annual report. But in the spirit of good faith, they may want to make a verbal report to their VMO, to avoid a situation where the VMO hears about the issue in another communication stream (for example, via non-compliance sharing from an intra-agency memorandum of understanding)[3]. If this is the first incident of this type and it was discovered in a "timely" fashion (this could be very questionable here), and there is immediate correction of the issue and it is reported promptly to Animal Care (either orally or in writing) then the recent introduction of the Animal Care Tech Notes[4] may be used by Animal Care for this incident.

It is also apparent that Miller's lab was able to use animals from one protocol in another without raising any oversight concerns; this needs to be addressed, and Miller's other studies (as well as any other high-profile studies) should be immediately reviewed to assure there is alignment with approved protocols. It calls into question whether there is an appropriate and functioning Training and Post Approval Monitoring program at the institution, how animals are initially assigned to studies, and if there are mechanisms of assuring correct study assignments. Review and a QC program for assurance are needed.

Since Katayama is no longer at Great Western and the protocol never existed, suspension of this work or this investigator is meaningless. But because this was a collaborative study and Miller was Katayama's mentor, Miller has responsibility for what happened. The Miller lab should be on an elevated status of review and assurance through the IACUC for a defined period of time.

This scenario also begs the ethical question of animal use and how to avoid having to repeat studies, especially if this study is null and void administratively but had scientific merit, as indicated. If the IACUC discovers that Miller and Katayama are truly collaborators, that Miller is using a similar (if not the same) protocol, and that Miller had worked on the study and there had been oversight, then the IACUC has more opportunity to suggest not having to repeat the study, such as assignment of animals and reassignment of authority, given agreement by all. This could also change the nature of some of the notifications to the journal and oversight entities (with full explanations to them). If the work is very disparate and lacked oversight, unfortunately an IACUC-approved study should be repeated. ❐

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