How should the IACUC balance an efficient approval process with minimizing risk?

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As if it wasn't hard enough to get a protocol approved by the Great Eastern University IACUC, it became even harder, or at least more frustrating, for Dr. Joyce Neiman when her protocol's "final" approval was delayed while waiting for an approval from the school's Department of Occupational Health and Safety (OHS). This was a standard practice for any study that used a controlled substance as a test material rather than for veterinary clinical use, and Neiman's lab would be studying opioid metabolism in various animal species.

The OHS approval for Neiman's study arrived at the IACUC office about a week after the IACUC's approval and it included detailed instructions on drug safety, security, record keeping and disposal. It also required that Neiman and her research staff sign a copy of the instructions to indicate their agreement with the OHS requirements. Neiman gathered the needed staff signatures and returned the signed instruction form to the IACUC office. However, the office staff told her that the protocol still required a "final approval" by the IACUC and the next full committee meeting would be in three weeks. Neiman thought that was ridiculous because the IACUC had already approved the protocol and she didn't see why it now had to approve the signed OHS instruction form. Nevertheless, rather than getting into an argument with the IACUC office staff, she volunteered to personally get the final approval signatures from the IACUC members and bring them to the office. However, the office told her that would be considered polling and federal regulations did not allow for a vote by polling. She then asked to have the final approval processed by the designated member review process, but she was informed that at Great Eastern, designated member review typically took at least two weeks, and in terms of time, it was probably safer for her to just have the protocol approved at the full committee meeting.

Is the Great Eastern IACUC unreasonably delaying the start of Neiman's research or is the IACUC office just playing by the rules?

RESPONSE

Playing by the rules, but processes could be more PI friendly

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This scenario brings up several questions: can/should an IACUC protocol be delayed until all ancillary institutional committee applications are reviewed and approved? Once they are approved, should the IACUC protocol go through another round of review by Designated Member Review or Full Committee, as the case may be? Can a PI get approval signatures from individual IACUC member, otherwise known as 'polling'?

According to the Public Health Service Policy[1], organizations must base their animal care and use programs on the *Guide for the Care and Use of Laboratory Animals*[2]. *The Guide* requires that an Occupational Health and Safety Program (OHSP) be part of the animal care and use program[3] and it references the Occupational Health and Safety in the Care and Use of Research Animals[4] as guidance on establishment and performance of an OHSP. Examples of oversight of OHSP Program include, but are not limited to, verification of enrollment, training of individuals on Animal Use Protocols[5]; compliance with ancillary institutional committees such as the Institutional Biosafety, Radiation Safety, Institutional Review Board and Chemical Safety[6]. The IACUC is also required to review the OHSP during its semi-annual program evaluation[6], which considers "some of the most important personnel issues, [..]the occupational health and safety of animal care, use, and support personnel"[7] and including the "use of hazardous materials and provision of a safe working environment"[2]. The IACUC must report deficiencies in the OHSP to OLAW/NIH[7].

These expectations are not surprising as the Program has unique insights about the presence of biological, chemical, or radiation hazards in feed, animal secretions, and animal waste and about the extent of potential human exposure during animal experimentation and husbandry. Although the institution carries the ultimate responsibilities for establishing and administering a functional OHSP, the IACUC is responsible for day to day oversight for all parts of the Program, including the OHSP[7]. Therefore, the IACUC is the best position for approval of animal use activities involving hazards[6]. Indeed, the IACUC Handbook[7] states that the IACUC must have members with sufficient technical expertise to evaluate health risks associated with Animal Use Protocols, so the implication is that safety committees inform the IACUC review process, rather than review in parallel with the IACUC, although two-way communication is critical to ensure personnel safety. In fact, one

A Word from OLAW

The Office of Laboratory Animal Welfare (OLAW) provides the following recommendations on ways the IACUC could streamline the protocol review process when additional approval(s) is required in a way that reduces burden on the investigator while maintaining compliance with PHS Policy requirements.

In research using animals, occupational health and safety considerations require coordination between the investigator, the IACUC, and the safety office[1]. It is incumbent on all involved to obtain the necessary review and approvals before the work can begin. The IACUC at Great Eastern has chosen to employ a burdensome process that delays the investigator's work. Numerous approaches could mitigate this burden. One option is for the IACUC to delay notification of approval to the investigator until after the safety review is complete[2]. The approval date of the protocol should be on or after the date of the safety approval as determined by the individual IACUC's operating procedures[3]. An equally effective option is to submit the work that requires safety approval as an amendment to the protocol after the safety office has cleared the activities and provided any instruction or training[2]. Many IACUCs conduct protocol review in parallel with the safety review. This practice expedites the process as long as the outcome of both reviews are effectively communicated. If the safety office approves the work without modifications, the IACUC may document this approval administratively without further IACUC review by, for example, a check box, an approval number or a safety representative's signature[2]. Any of these methods are acceptable for documentation of the safety approval.

Another consideration in avoiding misconceptions by investigators about the status of a submitted animal use protocol is to avoid the phrase "conditional approval". As stated in OLAW guidance, the PHS Policy does not allow IACUCs to grant conditional approval for animal use protocols[2]. Committees may only approve, require modification (to secure approval) or withhold approval of a protocol[4].

1. Institute for Laboratory Animal Research. *Guide for the Care and Use of Laboratory Animals* 8th edn. p. 17 (National Academies Press, Washington, DC, 2011).
2. Brown, P. & Gipson, C. A word from OLAW and USDA. *Lab Anim. (NY)* **40**, 297 (2011).
3. Office of Laboratory Animal Welfare. *Guidance to Reduce Regulatory Burden for IACUC Administration Regarding Alternate Members and Approval Dates.* Notice NOT-OD-11-053. (National Institutes of Health, Washington, DC, 18 March 2011). http://grants.nih.gov/grants/guide/notice-files/Not-oD-11-053.html
4. Public Health Service. *Policy on Humane Care and Use of Laboratory Animals*, IV.B.6. (US Department of Health and Human Services, Washington, DC, 1986, revised 2015).

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of the common tasks of IACUC administrators is to confirm approval(s) by other institutional committees[8].

Given the responsibility of the IACUC to provide oversight of the OHSP in conjunction with animal use, and given the IACUC's mandate to either approve, require modification, disapprove Animal Use Protocols, or table or defer review, common and best practice is to wait for all relevant approvals from other institutional committees to approve an Animal Use Protocol[3]. This is why it is surprising that Great Eastern University had "approved" the Animal Use Protocol before receiving word from the ancillary committees, which may have given Neiman unfounded hopes that her animal work could start.

The Great Eastern University IACUC office is correct that PHS policy[1] and AWIG[5] do not allow polling as a means to secure votes from IACUC members. Votes must take place simultaneously at convened meetings. These meetings can be virtual in certain circumstances, but require synchronous voting in real-time.

Aside from the confusion caused by calling the Animal Use Protocol "approved" before it was truly so, Great Eastern University is playing by the rules. However, we can think of two potential ways to improve its processes: they could defer review of Animal Use Protocols until all the ancillary approvals are in place, which would help manage PIs' expectations; or they could consider letting the IACUC administrator confirm receipt of delayed ancillary approvals, which would trigger an expedited approval by Designated Member Review, as long as said approvals did not affect conclusions previously reached by the IACUC.

1. U.S. Department of Health and Human Services. Public Health Service Policy on Humane Care and Use of Laboratory Animals (2015).
2. Institute for Laboratory Animal Research. *Guide for the Care and Use of Laboratory Animals* 8th edn. (National Academies Press, Washington, DC, 2011).
3. Greer, William G., & Ron E. Banks. The IACUC Administrator's Guide to Animal Program Management: Setting Up and Directing an IACUC Office (CRC Press, Boca Rotan, FL, 2016).
4. National Research Council, Commission on Life Sciences *et al. Occupational Health and Safety in the Care and Use of Research Animals* (National Academies Press, Washington, DC, 1997).
5. United States Department of Agriculture. *Animal Welfare Inspection Guide* (2013)
6. National Institutes of Health, Office of Laboratory Animal Welfare. *Institutional Animal Care and Use Committee Guidebook* (2002).
7. *The IACUC Handbook* 3rd edn. (ed. Silverman, J., Suckow, M. & Murthy, S.) (CRC Press, Boca Raton, 2014).
8 Petrie, W.K., Podolsky, M.L, Wallace, S.L., & Lukas, V. The Care and Feeding of an IACUC: The Organization and Management of an Institutional Animal Care and Use Committee (CRC Press, Boca Raton, FL, 1999).

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RESPONSE

Did the IACUC jump the gun?

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Before directly addressing the question posed, someone considering this situation would have to make a number of assumptions. The first assumption is that Neiman and her lab have already obtained the required DEA registration and state licenses necessary for using controlled substances in research. A second assumption is that Neiman is not using opioids from

schedule 1, because if she were, according to the Controlled Substances Act of 1970 (ref. 1; §1301.18), she would have to submit some form of institutional approval in her application. Since her study is with animals, the third assumption is that the IACUC's final approval would have been the document to submit along with her DEA 225a form to attain her registration. If this were true, then the issues revealed in the situation would not have occurred.

According to the PHS Policy[2] and the AWAR[3], the IACUC can only approve, require modifications, or withhold approvals. In this situation the IACUC's approval occurred one week before the OHS' approval. So what was the "final approval" that was delayed? There currently is no regulation concerning provisional or conditional approvals. Furthermore according to the NIH website, if a protocol lacks substantive information necessary for the IACUC to make a judgment, then it should be considered incomplete and review deferred until the requisite information is provided by the investigator. Would the OHS approval be considered substantive enough? I propose that the IACUC should have waited until all documents were submitted before reviewing.

Was the OHS approval substantive or necessary for the IACUC to give their final approval? It may have been for this particular university, but is there regulatory support for this practice? According to the IACUC Handbook[4], the IACUC's role is to ensure that the controlled drugs to be used are available and used in accordance with the research protocols and that they are within established expiration dates. The OHS has a responsibility to assist researchers in negotiating the legal requirements necessary for using controlled substances. There is no regulatory requirement for either the IACUC or the OHS to serve as the regulatory body for DEA-regulated drugs in animals. Although it may be mandatory at this university, there is no regulatory support specified for this practice. All the relevant requirements for the use of controlled substances could be reviewed more intensely via post-approval monitoring process.

If the IACUC staff were uncomfortable with this approach, could they have used the polling method to ask of the IACUC members their agreement or disagreement? To help ease the frustration for Neiman, could they have contacted the IACUC members to simply indicate if the OHS approval now warranted a review of the entire protocol, or if the protocol could attain its final approval by the administrative route?

In conclusion, I believe that the best approach would have been for the IACUC to receive and review the entire package before letting the researcher know of their decision, thereby reducing the confusion experienced.

1. U.S Department of Justice. *Code of Federal Regulations* (2010). (§1301.18)
2. U.S. Department of Health and Human Services. Public Health Service Policy on Humane Care and Use of Laboratory Animals (2015).
3. United States Department of Agriculture. *Animal Welfare Act and Animal Welfare Regulations* (2013).
4. *The IACUC Handbook* 3rd edn. (ed. Silverman, J., Suckow, M. & Murthy, S.) (CRC Press, Boca Raton, 2014).

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RESPONSE

Let's talk about self-imposed regulatory burden

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Neiman is justifiably frustrated. This is an instance where someone in the IACUC office needs a deep understanding of, and experience with, the regulations to guide the institution with regard to federal requirements involving research animals. This is also an opportunity for Great Eastern University to look at their policies and procedures pertaining to the use of research animals to decrease self-imposed regulatory burden. Hopefully, this can result in increased PI satisfaction and compliance.

In its June 8, 2017 report "Reducing Regulatory and Institutional Burden Associated with Animal Research," the Council on Governmental Relations questioned the increasing incidents of self-imposed regulatory burden and challenged institutions to decrease what is perceived to be significant roadblocks to research that do not improve laboratory animal welfare. This is an important activity for all institutions, including Great Eastern University, to do.

Great Eastern University may have legitimate reasons to have the Department of Occupational Health and Safety (OHS) involved with controlled substance use in laboratory animals; however, it is unclear how and why this would entangle IACUC approval. The OHS approval only concerned information on drug safety, security, record keeping, and disposal of the controlled substances—nothing that had to do with the actual use in research animals; this information is in the IACUC protocol.

Let's assume that Great Eastern University's management team had performed a risk assessment for this process and felt that, in order to mitigate risks, the IACUC had to have oversight of the OHS approval. The process could have been simplified by having the required IACUC re-approval be administrative; the IACUC office could have confirmed that there was OHS approval and then given the final approval of the protocol. This action conforms to OLAW FAQ D.4 (https://grants.nih.gov/grants/olaw/faqs.htm).

In this case, the re-review requirements of the Great Eastern University IACUC also requires refinements. If, for some mysterious reason, it was necessary to have the IACUC re-approve the protocol, it could have been performed by the Designated Member Review system (DMR). The IACUC should tailor the time it takes for DMR reviews with what is being reviewed. A simple review to verify OHS approval should not take two weeks to perform; this is unnecessarily delaying research. The IACUC should develop guidelines for timeframes when using the DMR review process.

Given all the regulatory and financial burdens faced by PIs today, it is imperative that the IACUC do what it can to facilitate research. The IACUC should always be looking to streamline its review processes and this can involve critical self-examination. We propose that self-imposed regulatory burden is driven by the institution's need for the lowest possible risk when working with research animals. Institutions need to balance this need with the need for PIs to perform their animal work without undue hindrance. It is a difficult challenge for all of us working with research animals, but one that must be met.

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