Jerald Silverman, DVM, Column Coordinator

Referencing an approved protocol in an amendment

Dr. Erica Waite had two IACUC-approved protocols. Her first protocol, identified by the IACUC as M22-16, included the use of mice in type 2 diabetes studies. That protocol and the NIH grant that supported her research specifically included the use of glucose tolerance tests (GTTs) and insulin tolerance tests (ITTs) on the mice. Waite also had a second NIH grant and a second IACUC protocol (M33-16). M33-16 also included the use of mice in type 2 diabetes studies, but the needs of this research only required performing GTTs on the animals. Both her grants and IACUC protocols adequately described the methodologies for performing the required tolerance tests.

About six months into study M33-16, Waite's research revealed insulin-related findings that were totally unexpected but quite interesting. She submitted an amendment to her IACUC protocol in which she requested to perform ITTs on a cohort of the mice. Waite wrote in the amendment that she would be using the exact same methodology and equipment that was already approved for the animals in M22-16. However, the IACUC office staff informed her that she could not simply reference the methodology used in M22-16; rather, she would have to rewrite the entire methodology into the amendment request for M33-16. That made no sense to Waite. She asked the IACUC office why in the past she was able to indicate on a protocol form that the school's transgenic mouse core would construct genetically modified mice for her, yet she did not have to include all the details of the surgery that occurred in the transgenic core? She wanted to know why she was allowed to reference the transgenic core, which had an IACUC-approved protocol, but not her own M22-16 protocol.

Did the IACUC office give Waite the correct regulatory information? What is the reasoning behind your opinion and how would you approach this question?

RESPONSE

Methods are too important to gloss over

Jessica K. Lang, BSc, BUS, rLATG, CM & Laike Stewart, DVM, DACLAM

We believe that the IACUC gave Waite accurate information. The experimental design of a project is often the most important part of a protocol for how a PI plans to answer the questions for which the described research is being undertaken[1,2]. Each IACUC-approved protocol and its associated amendments should be stand-alone documents. Simply referring to her other approved protocol does not satisfy that requirement.

The word 'core' implies that the pertinent research is run by the animal facility and therefore might have more regulatory oversight or overlap with the IACUC. Additionally, the IACUC is probably much more familiar with that protocol since there are multiple users using the core facility. Furthermore, the creation of transgenic mice is likely a procedure that most IACUC members have familiarity with, unlike the ITTs. Therefore, it would be redundant to require that each PI using the core recopy the entire construct process into their individual protocols. We would approach Waite's question by explaining to her that it is easier to have access to a complete centralized protocol than to need to refer to another document.

1. Petrie, W.K. & Wallace, S.L. *The Care and Feeding of an IACUC: The Organization and Management of an Institutional Animal Care and Use Committee* 2nd edn. (CRC Press, Boca Rotan, FL, 2015).
2. Institute for Laboratory Animal Research. *Guide for the Care and Use of Laboratory Animals* 8th edn. (National Academies Press, Washington, DC, 2011).

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RESPONSE

All references are not created equal

Jamie Lewis, BA, CPIA, RLATG & Judy Barnett, BS, CMAR, RLATG

We assume that Waite's research is PHS-funded; as such, statements in the PHS *Policy on Humane Care and Use of Laboratory Animals* regarding protocol content are crucial to answering whether the IACUC staff gave her correct information. The policy states that "the IACUC shall confirm that the research project … is consistent with the *Guide*"[1].

The *Guide for the Care and Use of Laboratory Animals* describes protocol content as "a detailed description of the proposed use of laboratory animals. The following topics should be considered in the preparation of the protocol by the researcher and its review by the IACUC: a clear and concise sequential description of the procedures involving the use of animals that is easily understood by all members of the committee…impact of the proposed procedures on the animal's well-being…appropriate sedation, analgesia and anesthesia"[2].

Clearly the intent is for the protocol to describe what is being done to the animals and understand how pain and distress from the procedures will be mitigated. Does it need to be a stand-alone document to do this? The regulations do not cover whether methodology descriptions in protocols can reference other documents, but there is guidance on standard operating procedures (SOPs) from OLAW. PHS specifically allows IACUC-approved SOPs to be used for "routine

A word from OLAW

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

The Office of Laboratory Animal Welfare (OLAW) recognizes the accurate, well-considered advice of the commenters and offers the following guidance, directed at the overarching context of the scenario.

IACUCs at PHS Assured institutions have the responsibility and authority to ensure that animal activities are conducted in compliance with the standards of the Public Health Service (PHS) *Policy on Humane Care and Use of Laboratory Animals* (Policy). The Policy (IV.C.1.) states, "…the IACUC shall conduct a review of those components related to the care and use of animals and determine that the proposed research projects are in accordance with this Policy"[1].

IACUCs must ensure the appropriate care and use of animals while supporting high quality science. They must institute appropriate measures to prevent, reduce, mitigate, and correct noncompliance (PHS Policy IV.F.3.a) while minimizing regulatory burden on the research team, veterinary staff, and the IACUC[1]. IACUCs make these decisions by weighing the balance of risk and burden based on federal standards, institutional animal care and use policies, and requirements of the research.

IACUCs meet these competing demands in various ways. Examples include allowing PIs to reference SOPs in protocols, encouraging PIs to include flexibility in the initial protocol—such as with dose ranges, drug formularies and procedure frequency—and developing policies to permit use of veterinary verification and consultation (VVC) for significant changes to previously approved animal activities[2].

The *Guide for the Care and Use of Laboratory Animals* presents the following standard of what is necessary for the IACUC to assess proposed research: "a clear and concise sequential description of the procedures involving the use of animals"[3]. The IACUC is within its authority to require Waite to submit an amendment to protocol M33-16 that describes the proposed procedure, rather than referencing protocol M22-16. Description of the procedure will mitigate potential noncompliance, including inadequate IACUC review, deviation from the protocol due to subsequent significant amendment to M22-16, or differing expiration dates of the two protocols. In this scenario, the IACUC has wisely decided that the burden of cutting and pasting a procedure into a request for significant changes offsets the greater risk of potential noncompliance.

1. Public Health Service. *Policy on Humane Care and Use of Laboratory Animals* (US Department of Health and Human Services, Washington, DC, 1986, revised 2015).
2. National Institutes of Health. Guidance on significant changes to animal activities. Notice NOT-OD-14-126. (National Institutes of Health, Washington, DC, 26 August 2014).
3. Institute for Laboratory Animal Research. *Guide for the Care and Use of Laboratory Animals* 8th edn. (National Academies Press, Washington, DC, 2011).

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aspects of research… IACUCs may approve SOPs that can be cited by investigators in their protocols"[3]. In addition, OLAW Notice NOT-OD-14-126 states that "IACUCs may approve policies (e.g., guidance documents, standard operating procedures, drug formularies) for the conduct of animal activities"[4].

We assume that the IACUC has approved SOPs for procedures in the transgenic mouse core. This would explain why Dr. Waite had been able to omit transgenic mouse core surgery details from her protocol. However, Waite is now asking that an individual protocol with IACUC-approved procedures be referenced in the same manner as an SOP.

There are fundamental differences between SOPs and animal use protocols that make these two documents not interchangeable for this purpose. SOPs are highly structured and are generally focused on one specific task; making information easy to locate and review. This is not always the case with animal use protocols, which could contain many procedures that reviewers, inspectors and researchers might need to sift through. Additionally, gaining access to referenced protocols might be difficult or prohibited, as access might be restricted to only staff members that are specifically needed for that protocol.

In conclusion, regulations could be interpreted such that a protocol should be a stand-alone document with respect to animal manipulations and mitigation of pain and distress. Regulatory guidance specifically allows IACUCs to approve guidance documents and SOPs for routine manipulations, which encourages accuracy in descriptions and efficiency from reviewers. However, the referenced manipulation must still be accurately considered in the context of the protocol from which it is derived, to ensure the welfare of the animals.

We think that the IACUC staff gave Waite accurate regulatory information but did not explain that references must be approved ahead of time by the IACUC in the form of guidance documents or SOPs, and that a previously approved animal use protocol does not meet these criteria.

1. Public Health Service. *Policy on Humane Care and Use of Laboratory Animals*. (US Department of Health and Human Services, Washington, DC, 1986; amended 2002).
2. Institute for Laboratory Animal Research. *Guide for the Care and Use of Laboratory Animals* 8th edn. (National Academies Press, Washington, DC, 2011).
3. Office of Laboratory Animal Welfare. Frequently asked questions PHS policy on humane care and use of laboratory animals. *National Institutes of Health Office of Extramural Research*. http://grants.nih.gov/grants/olaw/faqs.htm#630 (2016).
4. National Institutes of Health. NOT-OD-14-126: Guidance on significant changes to animal activities. *National Institutes of Health Office of Extramural Research*. http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-126.html (2014).

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RESPONSE

More or less administrative burden

Joanne Tetens-Woodring, DVM, MS, PhD, DACVS, DACLAM, George Babcock, PhD & Mahesh Jonnalagadda, DVM, MS, PhD, DACLAM

The laboratory animal and research communities all understand and struggle with the increasing administrative burden that has been thrust upon us with new regulations and revised interpretations of existing regulations. Nonetheless, in the scenario presented here, the IACUC office gave Waite the correct information. As described in the *Guide for the Care and Use of Laboratory Animals*, a clear and concise sequential description of the procedures involving the use of animals that can be easily understood by all members of the committee should be described in the IACUC protocol[1]. The PHS *Policy on Humane Care and Use of Laboratory Animals* requires an IACUC to review and approve activities on a project-specific basis, taking into account such factors as the aims of the study, consideration of alternatives and minimization of pain and distress[2]. Applications and proposals for awards submitted to the PHS require a complete description of the proposed use of animals and procedures to assure that discomfort and injury to animals will be limited to that which is unavoidable in the conduct of scientifically valuable research. Prior to protocol review, each IACUC member should be provided with written descriptions of each research project that involves the care and use of animals. It is essential that IACUC members be able to review a protocol in its entirety without needing to pull information from other protocols in order to ascertain the full effect that proposed procedures will have on an individual animal.

Since each IACUC protocol requires a complete, *de novo* review at least once every three years, failing to describe procedures fully in each protocol could result in additional challenges for Waite and the institution. If IACUC approval of Waite's protocol M22-16 should expire, that protocol would then lack valid approval. If Waite references protocol M22-16 methodologies and equipment in protocol M33-16, then, in theory, those referenced procedures in M33-16 would also be invalid when M22-16 expires.

In order to minimize administrative burden for Waite and other PIs, the IACUC could consider having on hand policies that have already been reviewed and approved—guidance documents and standard operating procedures (SOPs)—available for citation by PIs in their IACUC protocols[3]. These policies should be reviewed by the IACUC at least once every three years to ensure they are up-to-date and accurate. In the case presented here, Waite's IACUC could review and approve an SOP for insulin tolerance tests, at which time Waite could reference the SOP in her protocols. We presume that the IACUC protocol for the transgenic core has associated SOPs and that is why Waite can reference the core's protocol but not her own IACUC protocol M22-16.

1. Institute for Laboratory Animal Research. *Guide for the Care and Use of Laboratory Animals* 8th 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).
3. National Institutes of Health. NOT-OD-14-126: Guidance on significant changes to animal activities. *National Institutes of Health Office of Extramural Research.* http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-126.html (2014).

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