

If a researcher disagrees with a veterinarian's recommendations, whose say goes?

Professor Archibald Boyd was a noted primate neurophysiologist and clinical neurologist at Great Eastern University. His research focused on single-cell brain recordings from macaques that had been surgically fitted with metal implants attached to their skull. As part of the school's every third-year protocol renewal requirement, Boyd's IACUC protocol was reviewed by one of the school's veterinarians. The veterinarian, with the agreement of the other veterinarians, recommended a three-drug multimodal surgical analgesia regimen consisting of buprenorphine (an opioid), a local nerve block with bupivacaine, and meloxicam, a nonsteroidal anti-inflammatory drug (NSAID). Boyd's original protocol used only buprenorphine for postoperative pain relief. The veterinarian noted that the procedures Boyd used required significant muscle dissection and periosteal disruption, and even placement of a monkey's head in the needed stereotactic apparatus could be painful.

The veterinarian added that the multimodal analgesia being recommended would bring Boyd's protocol in line with similar protocols now used with monkeys at Great Eastern and would be consistent with standard practice used at several primate centers and universities.

Boyd resubmitted his protocol without the recommended additional analgesics and without indicating if there was any scientific rationale for avoiding the NSAIDs or nerve block, such as interference with his data. However, he did write that he believed the additional drugs were unnecessary because his animals always looked good the morning after surgery, consistent with what would be expected after a long procedure. And, he added, the procedure itself was little more than a skin incision, some muscle dissection, and fixing the apparatus to the skull. He claimed that the *Guide for the Care and Use of Laboratory Animals*¹ and the Animal Welfare Act's regulations² did not require multimodal analgesia, and that the

veterinarian's role was limited to consultation and advisement. Although the IACUC had approved multimodal analgesic treatment in other primate protocols, it agreed that it should not force an investigator to follow a veterinarian's recommendations. After a full-committee discussion, the protocol was approved as resubmitted by Boyd.

What is your opinion of the IACUC's actions? □

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References

1. Institute for Laboratory Animal Research. *Guide for the Care and Use of Laboratory Animals*, 8th ed. (National Academies Press, Washington D.C., 2011).
2. Animal Welfare Act Regulations. 7 U.S.C. 2131-2159; 7 CFR 2.22, 2.80, and 371.7.

IACUC fails to remember veterinarian as SME

The IACUC cannot simply state they “agree that it should not force an investigator to follow a veterinarian's recommendations,” as it is the job of the attending veterinarian (AV) to ensure the appropriate use of analgesia^{1,2}. The AV is the Subject Matter Expert (SME) on appropriate analgesics in postsurgical animals. Although the veterinarian did not make a strong argument for changing the analgesic protocol, as stating “other protocols are doing this” is not a justification for changing this particular one, it is a reason to discuss the potential changes; Boyd should have acknowledged this. The veterinarians' proposal would have been stronger had they referenced historical assessment of Boyd's post-op animals as well as current methods—their approach is a refinement of analgesia and one that the IACUC should have considered more seriously.

Boyd's assessment of his post-op animals is based on observations collected on the following morning and says nothing about the immediate post-operative period—the period of time between recovery from anesthesia and the next morning, which could be anywhere from 12–18 hours after

the administration of analgesic—and his statement about previous pain control being sufficient has not been adequately proven. The veterinarians' suggestions for a local nerve block, which provides immediate pain control up to several hours post-op, and NSAID, which provides for reduction in inflammation as well as swelling associated with surgical trauma, would be a welcome adjunct to an opioid analgesic. In fact, our personal experience has been that NSAIDs reduce the need to use a controlled substance such as buprenorphine. In other words, the proposed changes in analgesia, as suggested by the AV, would benefit Boyd's post-operative care and potentially improve the well-being of his research animals. Had he done his due diligence in searching the literature, he might have discovered this. Boyd failed to justify the refusal upon scientific grounds, which should have been reason for the IACUC to deny his proposal.

The IACUC may require that Boyd do further research into appropriate pain control as this area has been evolving. What worked in the past isn't always appropriate. Without scientific data that supports his resistance to change, Boyd cannot justify his analgesic

regimen, particularly as other institutions develop further refinements that need to be assessed with respect to his own research.

In an ideal situation, both Boyd and the IACUC could have discussed the researcher's needs and historical assessment of the nonhuman primates, with a greater understanding of the timing around post-operative assessments and how they relate to the analgesics used. They could have also accepted the changes in current analgesic treatments, and even added the recommended analgesics as alternatives in situations where animals were noted to be potentially in pain or distress, so those analgesics could be used without having to wait for approval. □

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References

1. 9 CFR Part 2 §2.31 Institutional Animal Care and Use Committee (d) (iv) (A) and (B)
2. 9 CFR Part 2 § 2.33 Attending Veterinarian (b) (4)

A WORD FROM OLAW AND APHIS

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

In this scenario, the IACUC approved the renewal of a protocol involving survival surgery on a macaque without the analgesia regimen recommended by the veterinarian.

NIH-OLAW response

The IACUC's approval of the protocol is in direct conflict with the PHS Policy IV.C.1.b and the Guide. The Policy explicitly requires the IACUC to determine that painful procedures will be performed with appropriate analgesia unless "justified for scientific reasons in writing by the investigator"¹. The IACUC did not obtain such a justification. The IACUC must also confirm that the protocol will be conducted in accordance with the USDA Animal Welfare Regulations which have similar requirements to the Policy as noted in the USDA response.

The Guide, page 121, states that "the selection of appropriate analgesics and anesthetics should reflect professional veterinary judgment as to which best meets clinical and humane requirements as well as the needs of the research protocol"². The IACUC failed to rely on the veterinarian's professional judgement and instead opted for subjective observations from the principal investigator on the macaques' post-operative conditions.

Based on animal welfare concerns, the veterinarian's recourse is to request that the IACUC revisit review of the protocol. Obtaining outside consultation from others conducting similar procedures may improve the current dynamics. If the IACUC does not agree to amend the protocol, the veterinarian may file a minority view to document the concerns to the Institutional Official³. PHS Policy IV.F. requires institutions to include

minority views in the annual report to OLAW^{4,5}. OLAW in turn would counsel the IACUC on their responsibility to ensure that animals receive adequate analgesia.

USDA-APHIS response

The Animal Welfare Act (AWA) regulations specify that the IACUC is to ensure procedures involving animals will avoid or minimize discomfort, distress, and pain to the animals⁴ and that the procedures that may cause more than momentary or slight pain or distress will be performed with appropriate sedatives, analgesics, or anesthetics, unless withholding such agents is justified for scientific reasons, in writing, by the principal investigator (PI) and will continue for only the necessary period of time⁵. The IACUC is also to ensure activities that involve surgery include the appropriate provision of pre-operative and post-operative care in accordance with established veterinary medical and nursing practices⁶. The regulations require the PI to involve the Attending Veterinarian (AV) in the planning of an activity⁷ that will cause more than momentary and slight pain/distress. The AV is to provide the PI with guidance on handling, immobilization, anesthesia, analgesia, tranquilization, euthanasia, and adequate pre- and post-procedural care in accordance with current established veterinary medical and nursing procedures⁸. The research facility shall ensure that the AV has appropriate authority to ensure the provision of adequate veterinary care⁹.

In this scenario, Boyd involved an AV (or designee) in the planning of the study. The veterinarian recommended Boyd include bupivacaine and meloxicam in the analgesic regimen to minimize pain and distress based on current veterinary practices and the fact this regimen was already in practice at the facility. Boyd however did not accept the veterinarian's recommendation because he believed buprenorphine post-operatively to be sufficient based on personal opinion. The study was approved after full Committee review.

The IACUC does not have the authority to prescribe methods or set standards of design, performance, or conduct of research¹⁰, but they have the authority, and the responsibility, to require modifications to secure approval or withhold approval¹¹ of a proposal when procedures are not performed with adequate analgesics or anesthetic, or when no scientific justification for withholding analgesics is provided⁵. In this case Boyd did not provide a scientific justification for withholding the recommended analgesics. Noncompliances could result when approval of a protocol does not avoid or minimize pain or discomfort to the animals⁴ or when the veterinarian does not have the appropriate authority to ensure the provision of adequate veterinary care⁹, which includes adequate pre- and post-procedural care in accordance with current established veterinary medical and nursing procedures⁸. □

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References

- Office of Laboratory Animal Welfare, National Institutes of Health. *Public Health Service Policy on Humane Care and Use of Laboratory Animals*. (US Department of Health and Human Services, Bethesda, Maryland, USA, 2015).
- Institute for Laboratory Animal Research. *Guide for the Care and Use of Laboratory Animals*. 8th ed. (National Academies Press, Washington D.C., 2011).
- National Institutes of Health. Public Health Service Policy on Humane Care and Use of Laboratory Animals - Frequently Asked Questions. *Institutional Reporting to OLAW, Question C.6*. (US Department of Health and Human Services, Bethesda, MD, USA, revised 2017).
- 9 C.F.R. § 2.31(d)(1)(i)
- 9 C.F.R. § 2.31(d)(1)(iv)(A)
- 9 C.F.R. § 2.31(d)(1)(ix)
- 9 C.F.R. § 2.31(d)(1)(iv)(B)
- 9 C.F.R. § 2.33(b)(4)
- 9 C.F.R. § 2.33 (a)(2)
- 9 C.F.R. § 2.31(a)
- 9 C.F.R. § 2.31(c)(6)

Embracing change

We've all had to deal with change at some point in our lives and it takes time to acclimate to the way new things unfold. I'm sure that is the case for Boyd. He is comfortable, accustomed with the way his research has been running. When we talk about life forms, however, it is wise to embrace change.

Boyd is correct when he says that the veterinarian's role is to advise and consult, but the veterinarian is not limited to that. The veterinarian is responsible for the welfare of the

animal and should exercise his/her professional judgement in that regard. In general animal practice, veterinarians' use only the most current medical and nursing procedures— why not use these standards for our research animals? Analyzing pain is subjective, and as such a multi-modal approach to subside or even eliminate the pain is imperative.

I would have to say I am disappointed in the IACUC's decision. I agree, it is not by force that we change someone's opinion, but

if we are not the animals' advocate, why are we even here? □

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Less than full analgesia can leave significant pain under-treated

The IACUC made a poor decision in this scenario. The decision may not be compliant with regulations and needlessly puts the monkeys at risk of pain and suffering beyond that necessary to obtain quality data.

Given the challenges of accurately diagnosing minute-by-minute pain in monkeys, and the reality that the monkeys cannot self-medicate, all should err on the side of presuming pain and maximizing safe use of analgesics. All available guidance presumes leadership and judgment of veterinarians, who should be current in their field and actively involved with the animals. This standard of care to treat preemptively with multimodal analgesia is not isolated to GEU's veterinarians—it is included in the *Guide* and in guidance from professional veterinary groups¹⁻⁴. IACUCs follow a principle by which we assume what is painful to humans may be painful to animals; a corollary is that effective pain management for humans may be a helpful guide for animal pain management. The standard of care for comparable major survival surgeries in humans includes multimodal pain management strategies, not just intermittent boluses of mid-potency opioids⁵.

True, the Animal Welfare Act does not specify that investigators must follow the veterinarian's consultation⁶. But the committee has approved a lower level of pain management than current veterinary standards promote. This puts the monkeys at risk of more than minor pain, with no scientific justification for compromising their welfare. It may violate the “adequate post-procedural care” provision of mandated

adequate veterinary care, and raises questions about the investigator's training to provide proper post-procedure care and proper use of analgesics. If meeting minutes accurately reflect the consultation and deliberations, the USDA inspector should scrutinize this issue closely. The approved practice would not put the animals into Column E of the annual report, as that is only appropriate when the analgesics are suspected to interfere with data—not when IACUC and investigators allow what looks like under-treatment of pain for other reasons.

Faced with the investigator's vague assertions about how the animals look and without veterinary evaluation of the animals (at least, not in this scenario), the committee could mitigate its bad decision by requiring that the veterinarians and investigator develop a proper pain scoring system and compare multimodal analgesia to buprenorphine-only analgesia. Published clinical pain management data on monkeys are scarce. The GEU people could quantify measures such as time to reach for treats where monkeys must work for them, food and water consumption, postures and facial expressions. Human presence can affect these outcomes, so plans for video-monitoring would be necessary. The IACUC needs to hear more than that the animals “looked good.”

I am also concerned about the IACUC's relationship with the veterinary team as described here, and why the committee would side with an investigator's veterinary judgment over standard veterinary practice and the on-site veterinarians' recommendations. Have the vets failed to properly educate the IACUC and researchers

on the complexities of animal pain recognition, prevention and treatment? Are the veterinarians not forcefully advocating for best possible animal welfare? Does the IACUC have other reasons to dismiss GEU's veterinarians' judgment, and if so, should they ask the institutional officer to engage in some sort of review of the vet team's qualifications and practice? This is the biggest concern in this scenario, as it may indicate inadequate veterinary care and pain management for more GEU animals than just Boyd's monkeys. The IACUC has an opportunity to use this situation to improve pain management and veterinary care for all of the university's animals. □

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References

1. Institute for Laboratory Animal Research. *Guide for the Care and Use of Laboratory Animals*, 8th ed. (National Academies Press, Washington D.C., 2011).
2. American College of Veterinary Anesthesia and Analgesia. *American College of Veterinary Anesthesiologists' position paper on the treatment of pain in animals*. 2006. http://acvaa.org/docs/Pain_Treatment Accessed September 15, 2019.
3. Kohn, D., Martin, T. E., Foley, P. E., Morris, T. H., Swindle, M. M., Vogler, G. A. & Wixson, S. K. *JAALAS* 46(2), 97–108(12) (2007).
4. Carbone, L. Pain Management Standards in the Eighth Edition of the *Guide for the Care and Use of Laboratory Animals*. *JAALAS* 51(3), 322–328 (2012).
5. Beverly, A., Kaye, A. D., Ljungqvist, O. & Urman, O. *Anesthesiology Clinics* 35(2), e115–e143 (2017).
6. Animal Welfare Act Regulations. 7 U.S.C. 2131–2159; 7 CFR 2.22, 2.80, and 371.7

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