AMA Journal of Ethics®
September 2024, Volume 26, Number 9: E679-683

CASE AND COMMENTARY

According to Which Criteria Should We Determine Whether and When IACUCs Are Sufficient for Protecting the Welfare of Nonhuman Animals Used in Research?

Peter John, MD, PhD

Abstract

Nonhuman animals used in biomedical research frequently suffer and are harmed as part of their use as experimental models. The Institutional Animal Care and Use Committee (IACUC) of a given institution is meant to ensure that research protocols follow federal guidelines, but research protocols such as those described in this case can generate unnecessary suffering; this problem suggests limitations of IACUCs' capacity to protect nonhuman animals' welfare. This commentary on the case considers how to more fully protect nonhuman animals used in scientific research and identifies barriers to more comprehensive protection of nonhuman animals' welfare.

Case

Cardiologist and scientist Dr J oversees a federally funded cardiac antiarrhythmic pharmacologic research lab in a well-known academic health center. Dr J teaches in many of the health sciences programs of the university and is often invited to lecture on topics ranging from research ethics to animal research protocol design to pharmacology and cardiac pathophysiology. Dr J is especially known among students for their lecture on how mid-21st-century animal rights campaigns informed passage of the Animal Welfare Act of 1966.

Dr J's team's protocols have always adhered to federal animal care and use guidelines, and Dr J served for many years on the university's Institutional Animal Care and Use Committee (IACUC). Dr J's team's research remains a controversial point of tension, however, between animal rights activists and patient advocacy groups, whose presence is always visible to students.

Dr J's team's research requires induction of cardiac arrhythmias in source-bred dogs. Antiarrhythmic pharmacologic agents are then administered to the dogs, and those agents' cardiac effects in the dogs are observed over time, sometimes until their deaths. Over the course of a typical study, many dogs experience cardiac arrest and painful gastrointestinal and pulmonary side effects of the pharmacologic agents.

Protesters, usually animal rights activists, and counter-protestors have long gathered with signs, pamphlets, and bullhorns outside the campus's known research facilities. Counter-protesters are usually patients and patient advocates, including children and parents of children with congenital heart conditions that predispose them to cardiac arrhythmias. Protesters' signs often show photographs of live mammals, presumably animals just like those used in research on campus, connected to invasively placed tubes and devices. Slogans like "Research is not 'care'! IACUCs are sham federal covers for animal cruelty!" are commonly seen on signs.

Students in Dr J's lectures sometimes ask Dr J about protesters' messages and question whether IACUC requirements are enough protection for research animals' welfare.

Dr J considers how to respond.

Commentary

Use of nonhuman animal models in biomedical research is, by its nature, utilitarian in its approach to reducing suffering. A goal of such research is to advance knowledge and thereby reduce human suffering and death from disease, but this goal is met at the cost of suffering to nonhuman animals used in experimental settings. If we acknowledge this sacrifice is necessary, we recognize that our next obligation is to reduce suffering in experimental animals. Although a given research institution's IACUC is critical in enforcing practice guidelines that minimize suffering in nonhuman animals, scenarios that lead to avoidable pain or distress reveal potential limitations in the capacity of IACUCs to protect animal welfare.

For the discussion here, I will focus entirely on vertebrate animals, particularly mammals such as the dogs used in Dr J's experiments, as these animals are most frequently used to model human diseases and have perceptions of pain and stress most like ours.

In the seminal 1959 publication that has become the landmark for modern laboratory practice, *The Principles of Humane Experimental Technique*, W. M. S. Russell and R. L. Burch describe the treatment of nonhuman animals with the terms *humanity* and *inhumanity*.[1] These terms are meant to be descriptive and not normative, to contrast actions that uphold the ethical goal of protecting animal welfare (ie, humane treatment) with actions that do not. *Inhumanity* is a term used by Russell and Burch to encompass several concepts, such as pain, fear, and distress.[1,2] It carries many of the same connotations as suffering, as will be described in this work. Suffering may be subdivided into a few discrete categories. First is pain, the inherently undesirable sensation transmitted by the nervous system of vertebrates as a result of physiological or physical trauma. Second, stress is a mental state that may be associated with fear or anxiety due to the perception of being in a hostile environment. Lastly, there are negative sensations that occur due to inadequate fulfillment of bodily needs, such as hunger in the absence of food.[3] Identifying specific modes of suffering is helpful for creating actionable targets for humane experimental design. Moreover, the successful protection of animal welfare necessarily indicates the absence of such suffering.

Minimizing Suffering

Laboratory animals are frequently exposed to painful or stressful stimuli, which may be inseparable from certain disease states or experimental interventions. However, not all suffering is necessary or justifiable. In their discussion of inhumanity, Russell and Burch contrast direct inhumanity—that which is an integral and inseparable aspect of the

experiment—with contingent inhumanity, which is "incidental and inadvertent" and not necessary for the success of a given experiment.[1] This distinction is critical to analyzing Dr J's experiments. In Dr J's experiments, cardiac disease and complications are likely unavoidable, as their purpose is specifically to study antiarrhythmic drugs. Unfortunately, these experiments are continued until the death of the animals. An essential aspect of humane experimental design is to define not only experimental endpoints but humane endpoints. *Experimental endpoints* refer to when the data required to fulfill the aims of the study have been obtained. In contrast, *humane endpoints* identify when an experimental animal experiences severe and irreversible suffering, requiring the affected animal to be removed and euthanized. In Dr J's experiments, it is necessary to induce arrhythmias in the experimental animals to initiate the experiment, but since it is not clear whether these arrhythmias need to be sustained until the death of the animal to obtain the relevant data, inducing persistent arrythmia should be discouraged. A compelling argument for this practice would be expected to justify why arrhythmias must be sustained until the death of the animal. Furthermore, the case states that "many dogs experience … painful gastrointestinal and pulmonary side effects of the pharmacological agents," which may lead to irreversible, life-threatening debility with associated severe pain and distress.[4] This debilitated condition is described as a moribund state, a commonly used humane endpoint in nonhuman animal experiments.[5] Since these adverse effects are seen in many experimental subjects, they should be anticipated, and the clinical findings should be clearly described and included as humane endpoints in Dr J's protocols. From a scientific perspective, if the tested pharmacologic agent is obviously toxic in nonhuman animals, then it would not be desirable for use in human trials either. Therefore, terminating experiments early due to the toxicity of the agents is not only humane but practical.

Identifying occurrences of contingent inhumanity (ie, avoidable suffering) is thus critical and a key criterion of whether an IACUC is adequately protecting animal welfare. A great deal of expertise is needed to determine the degree of pain and stress necessary and is the reason why IACUCs are mandated to have at least one member with experience in nonhuman animal research.[6] However, there is no guarantee that the IACUC members have adequate experience in a particular field of research. It is possible for protocols that unnecessarily expose nonhuman animals to harm to slip past IACUC review should the members lack the relevant experience. In Dr J's case, there may not be an IACUC member who is knowledgeable about experimental design for cardiac electrophysiology research using canine models, and, as a result, this IACUC would be limited in identifying unnecessary harms to the dogs used in the study. Therefore, the IACUC should seek out and recruit researchers who are subject matter experts to review the proposal. Taking this step may require looking for reviewers outside of an IACUC's home organization, particularly if the field of research is small or highly specialized.

Identifying Limitations in IACUC Review

Russell and Burch are best known for proposing 3 guidelines for preventing unnecessary pain and distress in animal research: replacement, refinement, and reduction.[1] *Replacement* refers to the replacement of animals with either inanimate models or with phylogenetically simpler nonhuman animals that may have less capacity for fear or pain. *Refinement* refers to the modification of animal protocols to reduce unnecessary suffering, as described in the above discussion on contingent inhumanity. *Reduction* is the practice of using as few nonhuman animals as needed for an experiment and maximizing the data gained from the animals used. However, the 3 *R*'s have been

criticized as being insufficiently comprehensive for the purpose of preventing unnecessary pain and distress in animals.[7,8] Curzer et al argue that the 3 *R*'s are framed to focus entirely on the improvement of existing research protocols on the presupposition that the proposed research will occur. Therefore, there must exist a fourth *R*, *reject*, to constrain research when anticipated harm to nonhuman animals clearly outweighs the knowledge that might be gained.[8] While this fourth *R* acts as a general ethical guide, it is also a practical mandate for all IACUCs. IACUCs may be reluctant to make such nuanced decisions if their members do not have sufficient expertise, as the criteria for excessive harm would vary greatly depending on the scientific field. As described previously, IACUCs should recruit subject matter experts with relevant experience to identify proposals for research in which the knowledge to be gained would not be enough to justify the harm posed to the animals in the study. Such proposals should be rejected at an early stage to prevent unnecessarily inhumane experiments from occurring.

We assume that IACUCs act as impartial and unbiased reviewers, but this assumption should not be taken for granted. Federal regulations expressly forbid members of an IACUC to have financial, personal, or professional conflicts of interest.[6] Nevertheless, bias may be subtle and difficult to eliminate entirely. Dr J is a highly successful and influential researcher who is likely well-known throughout the research institution, not to mention a former IACUC member. While these achievements in the field confer a great deal of credibility on Dr J's work, they do raise the concern that IACUC review may be less critical of Dr J than of a less influential investigator. This potential for partiality indicates another key criterion for IACUC reliability: members of the IACUC must perform impartial and unbiased review to ensure the protection of animal welfare. Instituting a standardized system of blinded proposal review, whereby the IACUC reviewers are not aware of the principal investigator for a given proposal, might help promote impartiality and reduce bias.

Conclusion

For IACUCs to perform their role as overseers of animal welfare in laboratory research, they must be able to identify and minimize occurrences of avoidable suffering, reject research in which suffering clearly outweighs the potential knowledge gained, and act impartially without undue influence. Yet while there will invariably be gaps in the ability of IACUCs to perform their duties, their role as impartial third-party reviewers is critical to prevent research protocols from breaching ethical guidelines. We must strive for analysis, refinement, and improvement of IACUC function, although thus far there is sparse literature on objective analyses of IACUC performance metrics.[9] By improving IACUC performance, we might better navigate the ethical terrain of using sentient nonhuman animals in laboratory research while ensuring their welfare.

References

1. Russell WMS, Burch RL. *The Principles of Humane Experimental Technique*. Methuen; 1959.
2. Tannenbaum J, Bennett BT. Russell and Burch's 3Rs then and now: the need for clarity in definition and purpose. *J Am Assoc Lab Anim Sci*. 2015;54(2):120-132.
3. Pietrzykowski T, Smilowska K. Kinds of harm: animal law language from a scientific perspective. *Animals (Basel)*. 2022;12(5):557.
4. Animal use in toxicity studies. In: Working Party on the Ethics of Research Involving Animals. *The Ethics of Research Involving Animals*. Nuffield Council on Bioethics; 2005:153-168. Accessed July 24, 2024.

https://www.nuffieldbioethics.org/assets/pdfs/The-ethics-of-research-involving-animals-full-report.pdf
5. Toth LA. Defining the moribund condition as an experimental endpoint for animal research. *ILAR J*. 2000;41(2):72-79.
6. Office of Laboratory Animal welfare. PHS policy on humane care and use of laboratory animals. National Institutes of Health. Revised 2015. Accessed February 15, 2024. https://olaw.nih.gov/policies-laws/phs-policy.htm
7. DeGrazia D, Beauchamp TL. Beyond the 3 Rs to a more comprehensive framework of principles for animal research ethics. *ILAR J*. 2021;60(3):308-317.
8. Curzer HJ, Perry G, Wallace MC, Perry D. The three Rs of animal research: what they mean for the institutional animal care and use committee and why. *Sci Eng Ethics*. 2016;22(2):549-565.
9. Budda ML, Pritt SL. Evaluating IACUCs: previous research and future directions. *J Am Assoc Lab Anim Sci*. 2020;59(6):656-664.

Peter John, MD, PhD is a second-year internal medicine resident at the University of Maryland Medical Center in Baltimore, Maryland. He obtained his MD and PhD at the Albert Einstein College of Medicine in New York and has career interests in clinical oncology, translational cancer research, and the medical ethics of end-of-life care.

Editor's Note

This essay is the winning essay of the 2023 John Conley Ethics Essay Contest. The case to which this commentary is a response was developed by the editorial staff.

Citation

AMA J Ethics. 2024;26(9):E679-683.

DOI

10.1001/amajethics.2024.679.

Conflict of Interest Disclosure

Author disclosed no conflicts of interest.

The people and events in this case are fictional. Resemblance to real events or to names of people, living or dead, is entirely coincidental. The viewpoints expressed in this article are those of the author(s) and do not necessarily reflect the views and policies of the AMA.

ISSN 2376-6980