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Reporting of Studies Using Animal and Human Subjects in APS Journals: How the Society Protects Authors from Ethical Minefields

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Why does APS care about ethical standards?

As a scholarly publisher, APS has a responsibility to ensure not only the novelty, but also the integrity of the research that is published in the pages of our journals. Integrity of the scientific literature is vital for a number of reasons. First, science is an iterative process, and physiology is no exception to this rule. Thus, advances must rest on the research that came before. If the latter is untrustworthy for any reason, it may hamper our ability to move the field forward and to uncover insights into the mechanisms of health and disease. Second, many, if not most, physiologists are dependent on funding from federal and other sources to pursue their research goal. Often very substantial sums are expended, and the taxpayers that finance a considerable portion of biomedical research are entitled to expect application of the highest ethical standards to the work that is so supported. As the tangible end product of such funded research, papers published in APS and other journals should be beyond reproach. Third, in many countries, federal, as well as local, regulations govern the conduct of research, and especially the use of animal and human subjects therein.

Animal subjects research is a particular concern for the APS. Not only does the subject matter of physiology often mandate testing of our hypotheses in integrative, such as animal, models, but this imperative also makes the Society, and its publications, subject to special scrutiny. Indeed, activist groups that are vocal in their opposition to animal experimentation routinely scan our journals to detect any studies that they consider may have been conducted using inappropriate approaches. These issues have led the APS to be especially vigilant in ensuring that animal studies are consistent with all appropriate policies and standards.

Physiologists also often conduct studies using human subjects, be they patients with a specific condition or healthy volunteers. Even if studies are performed in the context of routine clinical care and/or can be considered to represent a minimal, if any, risk to the subjects, it is still important that readers can appreciate that all appropriate measures were taken to protect the subjects involved from risks both to their safety and their privacy. However, for both human and animal experimentation, the APS is usually not in a position to judge directly whether the work reported is in accordance with appropriate standards and regulations. We rely heavily on the opinion of institutional bodies, particularly to explain the acceptability of the study in question in the local context.

APS' ethical standards for experiments conducted on animal and human subjects

APS' ethical standards for experiments performed on animals are articulated in the "APS Guiding Principles for the Care and Use of Vertebrate Animals in Research and Training" (http://www.the-aps.org/pa/resources/policyStmnts/paPolicyStmnts_Guide.htm). These principles require that procedures conducted on animal subjects must be prospectively approved by an oversight body such as an institutional animal care and use committee (IACUC), unless the laws in place in the country where the research is performed specifically exclude the species utilized in the study. For example, in the United States, it is expected that research conducted on vertebrate animals will be approved by an IACUC prior to the work being initiated. APS requires that authors include a statement in their manuscript stipulating that the relevant oversight body approved the research conducted on animals. Furthermore, APS requires that appropriate anesthetics be used during animal surgeries, and that analgesics and/or other techniques be used to minimize discomfort and pain (including postsurgical pain) except when the intervention would compromise experimental goals. In such cases, the oversight body must specifically approve the exclusion of measures to alleviate pain. Furthermore, it is expected that appropriate endpoints will be selected for the study, and that animals will be humanely euthanized in accordance with the American Veterinary Medical Association's Guidelines on Euthanasia prior to death related to experimental manipulations. APS will only publish experiments with death as an endpoint if euthanasia would compromise the experimental goals and the oversight body has specifically approved this exception.

Research on human subjects published in APS journals must conform to the most recent revision of the World Medical Association's "Declaration of Helsinki—Ethical Principles for Medical Research Involving Human Subjects" (http://www.wma.net/en/30publications/10policies/b3/). The most fundamental principle is respect for the individual (Article 8), their right to self-determination and the right to make informed decisions (Articles 20, 21 and 22) regarding participation in research, both initially and during the course of the research. Furthermore, the relevant ethics committee in the country where the work is conducted must approve research performed on human subjects. In the United States, this ethics committee is called an "institutional review board" or IRB. APS expects authors to include a statement in their manuscript stating that approval of the ethics committee was obtained before the work commenced.

Identification and review of ethical issues related to research conducted on animal and human subjects

A reviewer, editor, or staff member in the Publications Office can identify potential ethical concerns related to animal or human subjects research in a manuscript submitted to an APS journal (or indeed, one that has already appeared in print). These concerns are then brought to the attention of the Editor-in Chief of the journal, who is required to inform the Chair or Vice-Chair of the APS Publications Committee as well as the APS Ethics Officer. The latter two individuals manage any needed investigation arising from the initial concern. At this point, review of a submitted manuscript is suspended until the ethical concern is resolved. Typically the Ethics Officer consults confidentially with experts to determine the validity of the concern;

the Chair of the APS Animal Care and Experimentation Committee is involved when concerns relate to the use of animals in a study. The most common issue that triggers an ethical review is omission of a statement that the work was reviewed and approved by the relevant oversight committee. Concerns have also been raised about animal studies that failed to adequately describe anesthetics used during surgery or analgesics administered to relieve postsurgical pain, as well as studies that used death as an endpoint. Other possible issues that may trigger an ethical review of studies on animals are the use of prolonged restraint or atypical housing or husbandry conditions.

In some cases, the concern is rapidly dismissed because it is determined to be erroneous. For example, if concerns were raised by a reviewer about the lack of IACUC approval for a study conducted on Drosophila in the United States, the concern would be dismissed because the use of this invertebrate species is not regulated. In other cases, the concern is relayed to the authors, who are asked to address the issue. For instance, if the use of postsurgical analgesia was not described in the manuscript, the authors may be queried about this omission. If it is determined that the concern was related to an insufficient level of detail in describing procedures that were conducted, such as the omission of a description of the postsurgical care of animals, the authors are asked to revise the paper to clarify precisely how the study was conducted. In some circumstances, authors may be asked to submit a copy of their protocol approved by the oversight body or a letter from the director of the oversight body (e.g., the Chair of an IACUC) to verify their assertions that the procedures had been prospectively approved. It is common for APS to request such verification for studies employing death as an endpoint, studies that excluded postsurgical analgesia, or those that incorporated nonstandard procedures such as prolonged restraint. Documentation provided by an author is handled confidentially, and is never released to a third party. Once APS is satisfied that the study was conducted ethically and in accordance with procedures approved by the oversight body, the scientific peer review of the manuscript will continue.

Minimizing the risk of an ethical concern being identified regarding procedures conducted on animal and human subjects

It is understandably distressing for an author to be questioned about the procedures that he/she has employed in working with animal or human subjects. However, in the vast majority of cases, ethical concerns raised during the review of a manuscript submitted to an APS journal are dismissed because it is determined that the problem was related to an inadequate or incomplete description of the relevant procedures. As noted above, an ethical review is automatically triggered if relevant manuscripts fail to include a statement indicating that the appropriate oversight body approved the work. Thus, most ethical concerns can be avoided by disclosing salient information. For example, when reporting a study conducted on animals, all pharmaceutical agents that were administered, including pre- and post-operative treatments, should be indicated, and the time course of treatment should be described. Any nonpharmaceutical methods used to alleviate pain and distress, such as gradual acclimation for studies involving restraint, should also be discussed. A complete description of the methodology used during a study, including techniques included to assure animal welfare, will allay most potential ethical concerns of reviewers, editors, and readers. Of course, this will also permit others to repeat the work or build upon it. If a study includes non-standard procedures conducted on animal or human subjects, it is prudent to consult with the journal editor prior to submission of the manuscript for advice on how to describe the work, as well as assurances that can be prospectively provided to avoid ethical concerns that could be raised during the review process.

Possible sanctions when ethical problems are identified

In rare cases, concerns are not alleviated following consultation with the authors of a submitted or published manuscript, despite the receipt of animal or human protocols and supporting information. In these cases, the APS has reason to believe that the studies reported were not in compliance with APS guiding principles and/or the legal framework that regulates such studies in the country or countries where the work was completed. Under these circumstances, the APS usually has a legal, as well as a moral, obligation to pursue the investigation further, including by directly communicating with the relevant authorities at the institution(s) where the work was completed. An example of such a situation would be when the manuscript specifies that a particular technique or treatment was employed,but a review of the protocol reveals that the use of the technique was not approved by the IACUC, IRB or equivalent. Discovery

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of such an infraction may prompt rejection of the manuscript in question if still under review, or retraction if the paper has been published. In severe cases, the APS may choose to sanction the authors involved by imposing a ban on submissions from the authors, as well as the ability to serve as a reviewer, for any APS journal for a specified period (typically one to two years). While punitive, these measures protect both the society, as well as the integrity of the literature we publish, and can be an important proactive measure in deflecting the attentions of animal rights activists.

Why APS' strict adherence to ethical guidelines benefits authors

Authors react to questions about their animal and human subjects protocols with a range of emotions ranging from mild dismay to considerable anger and indignation. However, it is important to remember that our procedures protect not only the APS and its publications, but also the authors themselves. Particularly in the case of simple errors and omissions, an ounce of prevention in terms of clarifying the work actually performed can easily avoid many pounds of grief when readers or, worse, activists and/or the media raise concerns about the work once it is in the public arena. In our view, authors should be reassured by the fact that APS so carefully scrutinizes manuscripts for their compliance with our policies before the work has appeared in print. While we cannot catch everything, the combined review by editors, peer reviewers, editorial staff and copy-editors, and members of the Publications and/or Animal Care and Experimentation Committees represents a powerful approach to avoiding at best embarrassment, and at worst legal challenges. Inquiries can likewise represent a useful trigger to initiate a conversation with students and trainees about standards for conducting and reporting work with human or animal subjects. Even if a more serious issue is identified that leads ultimately to rejection and/or sanctions, it is far preferable to relay this to one's institution in a timely fashion, such that corrections to process can be made and any liability for repayment of federal funds that may have supported unapproved research can promptly be addressed without penalties. Certainly, those charged with research compliance within an institution, if not the authors themselves, should be grateful for an early warning of looming problems.

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