
Issues for Institutional Animal Care and Use Committees (IACUCs)

Scientific Merit Review: The Role of the IACUC

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One of the most contentious issues facing each federally mandated institutional animal care and use committee (IACUC) is scientific merit review. To what extent, if any, should the IACUC review animal research proposals for scientific merit? Certainly, no reputable scientist would deny the validity of the ethical imperative that all animal research should be scientifically and ethically justified. In the past, however, scientists may have planned and conducted animal experiments in relative isolation with little pre- or post-experimental ethical accountability. The value and humaneness of animal research was generally assumed regardless of the source of funding and whether or not the research was reviewed by peers. The use of animals in research was largely a matter of individual conscience rather than discussion and debate. Contrary to the rhetoric of the animal rights movement, there is no evidence that this led to a significant amount of unjustified animal experimentation. Admittedly, there are cases of research with questionable merit and incidents of animal abuse in the name of science (Rowan, 1984), but these are extremely rare given the tremendous volume of animal research. Now, of course, researchers and institutions are not permitted to operate in an environment devoid of accountability for the humane care and use of laboratory animals.

Because the emphasis on accountability in animal research is relatively new, it is not surprising that there is disagreement about what accountability means and how it should be judged. On the one hand, there are the animal rights groups who claim that a great deal of animal research is unnecessarily duplicative or lacks scientific merit, regardless of whether the research was reviewed by peers at the institutional or funding agency level. In other words, peer review is considered by animal rights activists to be a "fraternity white wash." On

the other hand, there are a number of scientists who feel that the quality of their research speaks for itself and only reluctantly submit to merit review, particularly that which takes place at the institutional level. Whereas the right of an agency to perform scientific merit review may be acknowledged, particularly for funding priority, there is neither recognition nor acceptance of the right of anyone else to evaluate a research project's merit. Indeed, some investigators consider scientific merit review performed by the institution to be, at best, an unnecessary bureaucratic imposition and, at worst, an infringement upon academic freedom perpetrated by a committee devoid of the prerequisite scientific expertise to judge the research.

In general, society appears to support valuable animal research that is humanely conducted. Unfortunately, there is a widening credibility gap that the research community may be doing too little to close. Many polls have indicated that the public is increasingly concerned and suspicious about what actually happens behind closed laboratory doors. Recent public discussions of several cases of scientific misconduct, as well as the significant administrative improprieties regarding indirect costs at major research institutions, have contributed to these feelings. The activities of People for the Ethical Treatment of Animals (PETA) and other animal rights organizations have further unduly alarmed the public about the use of animals in research and thus have promoted a general distrust of biomedical science. One approach to addressing these concerns is to demonstrate prior to the initiation of a research project that the proposed work has intrinsic value and that the treatment of the animals is humane. Although the investigator, the institution, and funding agencies should be involved in this demonstration, the IACUC, we believe, has an important role, which it is the purpose of this paper to explore.

SCIENTIFIC MERIT

Webster (1979) defines *merit* as the "state of having worth, value or excellence." When the noun *merit* is combined with the adjective *scientific* it means of "scientific worth, scientific value, or scientific excellence."

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Gordon (1989) offers further clarification of the term *merit* in the scientific context of National Institutes of Health (NIH) grant applications by stating that, "The research should be based on a significant hypothesis and, if possible, oriented towards uncovering an important biological mechanism.... Typically, a valuable hypothesis gives insight towards a better understanding of normal physiology, biological mechanisms, disease processes, or the prevention or treatment of a disease or injury. The hypothesis should be testable (proved or disproved) by the proposed experiments."

RESPONSIBILITY FOR SCIENTIFIC MERIT REVIEW

Who has the responsibility for ensuring that animal research has an acceptable level of scientific merit? Is it the investigator, the institution, the IACUC, or the funding agency? In our opinion, it is all of these to one extent or another. However, there are conflicting views regarding who has the obligation and, indeed, the right to carry out scientific merit review. At some institutions, this lack of consensus is bound to lead to a proverbial "passing of the buck." It is our contention, however, that the buck stops at the institutional level. In other words, it is the institution that bears the ultimate responsibility for ensuring that animal research carried out in its laboratories has an acceptable level of merit.

The legal basis for the institution's responsibility for scientific merit review is grounded in the *Public Health Service Policy on Humane Care and Use of Laboratory Animals* (PHS Policy), which applies to all PHS-supported animal research (PHS, 1986a). Principle II of the nine *U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research and Training*, developed by the Interagency Research Animal Committee and implemented by the PHS Policy, charges the institutional official with ensuring that "procedures involving animals should be designed and performed with due consideration of their relevance to human or animal health, the advancement of knowledge, or the good of society" (PHS, 1986b). According to the NIH's Office for Protection from Research Risks (OPRR), which is responsible for developing, implementing, and overseeing compliance with the PHS Policy, institutional consideration of Principle II should reflect scientific merit in the broad context (Miller, 1991). The framers of the PHS Policy, however, wisely chose not to use the contentious and provocative term, "scientific merit." Instead, the less inflammatory term "relevance" was apparently used as a synonym for scientific merit.

The PHS offers further clarification of the institution's responsibility in Principle III, which states in part, "The animals selected for a procedure should be of an appropriate species and quality and the minimum number required to obtain valid results" (PHS, 1986b). Principle

VIII requires that "investigators and other personnel shall be appropriately qualified and experienced for conducting procedures on living animals" (PHS, 1986b). Finally, Principle IX states, "Where exceptions are required in relation to the provisions of these Principles, the decisions should not rest with the investigators directly concerned but should be made, with due regard to Principle II, by an appropriate review group such as the institutional animal care and use committee" (PHS, 1986b). One can interpret Principle IX to mean that the PHS considers the IACUC an appropriate review committee to determine if any exceptions should be granted. Whereas exceptions should be rare, when they occur, due regard must be given to Principle II, which means that considerations of "relevance" should not be compromised or waived.

In order for an institution to be qualified to receive PHS funds that will be used for animal research, the IACUC must provide the PHS with certification of approval of the protocol. This certification means that the IACUC has approved those components of the application related to the care and use of laboratory animals. We, along with Orleans (1987), interpret "care" to include all aspects of animal welfare and "use" to include scientific rationale, experimental design, and scientific merit. Specifically, certification means that the proposed research is in compliance with all provisions of the PHS Policy, including, as previously stated, the requirement that the research project have "...relevance to human or animal health..." (PHS, 1986a) (i.e., an acceptable level of scientific merit). If an institution does not have a separate peer review committee that is charged with reviewing scientific merit, we suggest that it is incumbent upon the IACUC to assume this responsibility. According to OPRR, the institution cannot defer scientific merit review to the NIH. Approval by an IACUC of a proposed activity, conditioned on successful peer review by the NIH, is not in keeping with the PHS Policy requirements. Such conditional action would not constitute the approval required by the PHS Policy prior to review by an NIH Initial Review Group (IRG) or Study Section (Miller, 1991). The NIH review of merit should, therefore, be viewed as additional assurance rather than the only assurance that the research has value.

Institutional review of scientific merit becomes particularly important in a situation where an investigator, using in-house funds, initiates a research project whose review is pending at the NIH. If the NIH finds the proposal substantially deficient in terms of merit, the institution will be informed only that the project is "not recommended for further consideration." Meanwhile, an ongoing project that may be unacceptable could continue unrecognized as such as long as sufficient funding exists at the departmental level. A much more common, but analogous, situation is a project that is funded entirely by departmental sources or small organizations that do not have rigorous scientific peer review. It should be noted that if the institution is one of 925 that have filed an

Assurance of Compliance with the OPRR, it is not uncommon that the provisions of the PHS Policy apply to all of the institution's animal research without restrictions based upon the source of funding.

It is interesting to note that the U.S. Department of Agriculture (USDA) Animal Welfare Regulations are for the most part silent with regard to the institution's responsibility for scientific merit review. In the comment section of the Animal Welfare Regulations, the USDA clearly states that it wishes "...to avoid any misunderstanding or implication that APHIS [Animal and Plant Health Inspection Service, a component of the USDA] intends to become involved in the evaluation of design outlines, guidelines, and scientific merit of proposed research" (USDA, 1989). In our opinion, this statement does not preclude a USDA-regulated research facility from fulfilling its ethical obligation for ensuring that its animal research is meritorious. In addition, the USDA indirectly addresses one aspect of scientific merit by stating, "The principal investigator has provided written assurance that the activities do not unnecessarily duplicate previous experiments" (9CFR2.31). Whereas the language used by the USDA does not specifically require the IACUC to determine that the research is not unnecessarily duplicative, certainly the intent of the regulations is to avoid unnecessary repetition of animal experiments. Based upon regulatory language, one may assume that the USDA was even less anxious than the PHS to take a concrete stand in writing on the issue of scientific merit. Of course, regulators understand that acceptance of controversial rules by the scientific community is often best accomplished by offering interpretation, clarification, and education after the rules are promulgated and their initial impact has been assimilated.

IACUC REVIEW OF SCIENTIFIC MERIT

The question of whether or not the average IACUC possesses enough expertise to perform a valid assessment of the scientific merit of all projects submitted to the committee has been raised by investigators and committee members alike. A properly constituted IACUC obviously should have a broad based expertise, but it probably will not include experts in every field of research. However, lack of IACUC expertise in the precise scientific field of research under review is not a reason for the committee to ignore merit and simply rubber stamp the proposal as "approved" solely because its procedures are judged to be humane. A properly constituted IACUC can perform a valid evaluation of scientific merit by asking investigators the appropriate questions. If a protocol involves particularly complex issues, the PHS Policy states, "The IACUC may invite consultants to assist in the review of complex issues (PHS, 1986a, P.8)." However, as per the PHS Policy "Consultants may not approve or withhold approval of

an activity or vote with the IACUC unless they are also members of the IACUC" (PHS, 1986a, P.8). The final decision rests solely with the IACUC.

At the University of Nebraska Medical Center (UNMC), the IACUC ensures that animal research protocols have an acceptable level of scientific merit. The committee addresses this responsibility by asking investigators to respond to a number of items, including six points of information that facilitate merit evaluation (Prentice et al., 1991).

1. State the specific scientific objectives (aims) of the research;
2. State the potential value of the study with respect to human or animal health, the advancement of knowledge, or the good of society. Identify the information gaps the project is intended to fill. If the research duplicates previous experiments, explain why the duplication is necessary;
3. Justify the species selection;
4. Provide detailed justification for the number of experimental and control animals requested. Include a brief description of the experimental design and state the number and species/strain of animals per group/subgroup in each experiment/procedure;
5. Describe sequentially, with a reasonable degree of detail, all procedures (surgical and nonsurgical) to be carried out on live animals. The end points of procedures and the time frame must be clearly defined; and
6. Address familiarity of all involved personnel with behavioral/physiological/anatomical characteristics of the selected species, and describe their experience with regard to the specific procedures to be applied to live animals.

We believe that there are two integrated levels of review for scientific merit: the fundamental level and the knowledge-based level. At the fundamental level, all members of an IACUC who are experienced scientists should be able to form basic judgements about the adequacy and appropriateness of the experimental design in terms of the testability of the hypothesis, use of controls, sample size, statistical analysis, and the training and experience of investigators. It is our contention that any trained biomedical scientist with an understanding of scientific methodology can judge the merit of a protocol at the fundamental level, given adequate responses to the six points above. Expertise in the precise area of the research is not necessary. Dresser (1989) is referring to this level of review when she observes that "...simply asking questions and demanding answers provides a crude merit evaluation. This consciousness raising function of the IACUC may serve to weed out some clearly unmeritorious protocols." On the other hand, judgements of merit at the knowledge-based level do require expertise because this level of evaluation requires that an assessment be made of the scientific importance of the study, that is, the

contribution of the research to the knowledge base. Such an assessment obviously requires the reviewer to possess an adequate background in the scientific discipline of the protocol under review.

The 20-member IACUC at UNMC utilizes a primary and secondary reviewer who are assigned principal responsibility for each review. These members of the IACUC, who are given review assignments based upon their expertise, are charged with making a preliminary assessment of provisions for animal welfare and those issues related to scientific merit. During full committee consideration of the protocol, it is customary for the two principal reviewers to explain the protocol and present the results of their initial review. It is incumbent upon the reviewers to clearly and succinctly explain the merits of the proposed research because not all members of the IACUC possess equal levels of expertise in any given area of research. In order to prepare for this task, it is often necessary for one or both reviewers to consult the literature and discuss the protocol with the investigator. The objective is to anticipate and answer questions and concerns of the other panelists and to help the entire committee develop a clear understanding of the merit related issues of the research. In this respect, the non-expert members of the IACUC function essentially like jurors who, using the reasonable person standard, form their own evaluations of the case based upon evidence and evaluations presented to them by experts.

During the course of the IACUC review, members often raise questions concerning merit and other issues that require a detailed written response from the investigator. Usually, the investigator's response adequately addresses the questions of the committee and the use of animals in the research proposal will be approved. Occasionally, however, a confidential consultation with expert investigators within the institution, but not on the committee, will be sought to resolve a problem. Only rarely has the UNMC IACUC found it necessary to seek peer review of scientific merit from a recognized expert outside the university to determine whether or not the proposal should be approved. Indeed, in the case of very controversial protocols, the IACUC has sought consultation from several outside experts, as well as from other OPRR-sanctioned IACUCs.

Using this procedure, peer review by an IACUC is possible within the general limits of adequacy necessary to ascertain that the proposed research has an acceptable level of scientific merit. In fact, the IACUC review of merit may have one advantage over reviews by external bodies. Because the IACUC regularly consults with the investigator regarding protocols, it may derive a more complete picture of the intended research than can be obtained from a written proposal alone. This may lend to the peer review process, an aspect called for in a recent paper by Horrobin (1990), namely, a protection of real creativity and innovation, while still controlling the quality of the research.

ETHICAL COST-BENEFIT ASSESSMENT

When the term "scientific merit" is applied to animal research, it is not sufficient to base justification for conduct of the research solely upon the existence of a valuable hypothesis that is testable. Because a living creature serves as the experimental model, it is necessary ultimately to justify the use of animals in terms of an ethical cost-benefit assessment. According to the UNMC Code of Ethics for Animal Research (Prentice et al., 1986): "When live animals are used in research or biological testing, there must be a reasonable expectation that such utilization will contribute to the enhancement of human or animal health, the advancement of knowledge, or the good of society. The relative value of the study is a particularly important consideration in potentially painful experiments where there is an ethical imperative that the benefits of the research clearly outweigh any pain, discomfort, and distress experienced by the animals." We believe this is an appropriate qualification of scientific merit in an animal research context because societal values demand that the review include a judgement that takes into consideration the ethical costs of the research in terms of animal pain, morbidity, and mortality. Granted, absolute limits are not specified and, theoretically, even very painful experiments may be acceptable if the potential value of the research is sufficiently great. Nevertheless, by inextricably linking ethical costs with scientific merit, animal research will not and should not be justified solely on the basis of whether or not the research is designed to pursue a significant and testable hypothesis. Undoubtedly, there are many experiments which could provide scientifically valid answers to important questions. Such experiments may have unquestioned scientific merit, but might not be justified because of the associated ethical cost.

Unfortunately, there are no mathematical algorithms or related computer programs that can be used by an IACUC to perform an ethical cost-benefit assessment of animal research. Instead, it requires the thoughtful judgement of men and women who, using individual values, must strike the right balance between the needs of science and fulfillment of a moral obligation to treat laboratory animals humanely. Unlike the Institutional Review Board (IRB), an IACUC cannot transfer the decision-making responsibility to human subjects who can decide for themselves whether or not they wish to participate in research. Animals are not autonomous and, obviously, cannot control their destiny in a research laboratory. Therefore, the cardinal responsibility of the IACUC must be to ensure the ethical costs of the research are justified. Whereas review bodies other than the IACUC can, and ideally should, be charged with scientific merit review, it is the IACUC that must render the ultimate judgement on the acceptability of the research in terms of scientific merit balanced against animal welfare. This judgement is not a recommendation for funding priority. Instead, it simply

acknowledges the appropriateness of the research using an animal model.

CONCLUSIONS

Optimally, a research institution should appoint one or more expert peer review committees who are specifically charged with scientific merit review. If, however, that is not possible because of the institution's size, bureaucratic complexity or other constraints, the obligation to perform scientific merit review falls by default to the IACUC. Despite the use of somewhat obtuse language, the PHS Policy unequivocally requires merit review by any institution that is the recipient of PHS funds. Even if there were no such federal requirements, it is clear that the value and humaneness of animal research could not simply be assumed. The public demands and deserves accountability in animal research. Institutions must be responsive to that demand in order to preserve their privilege to use animals in research for the benefit of humankind or animals.

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