

Introduction

Reviewing protocols involving the use of animals is one of the most important responsibilities of the IACUC. Although the format employed for this review varies across institutions, the criteria used in reviewing and approving protocols should be as consistent as possible. Consistency of review is a particularly important consideration with regard to animal welfare issues, such as the use of nonanimal model alternatives and the application of refinement techniques to reduce animal pain, discomfort, and distress. The purpose of this chapter is to present general concepts of protocol review that will help IACUC administrators, IACUC members, AVs, and other interested individuals gain an appreciation for how IACUCs conduct protocol review. Particular attention is given to issues such as scientific merit review, prereview, use of consultants, designated-member review versus full-committee review, and IACUC actions. Because the answers to the questions posed in this chapter are designed to be as succinct as possible, the reader is encouraged to consult the PHS Policy, the AWAR, and the *Guide*.

9:1 What guidelines do the AWAR, the PHS Policy, and the *Guide* provide with respect to IACUC review of protocols?

Reg. PHS Policy (IV,C,1,a–IV,C,1,g; IV,D,1,a–IV,D,1,e) and the AWAR (§2.31,d,e) specify criteria that must be met before an IACUC can approve a proposed research protocol. These requirements address issues such as:

- Avoidance or minimization of discomfort, distress, and pain to the animals.
- Appropriate living conditions for species used in the project.
- Availability of medical care to be provided by a qualified veterinarian.
- Euthanasia consistent with the recommendations of the American Veterinary Medical Association Panel on Euthanasia.¹
- Qualifications of personnel conducting procedures on the species being studied.

PHS Policy (IV,A,1) requires that Assured institutions also base their IACUC review of protocols on the *Guide* and that they comply with the AWAR which apply to APHIS/AC-regulated species.

The AWAR (§2.31,d,i–2.31,d,xi; §2.31,e,1–2.31,e,5) list a total of 16 requirements that must be met before the IACUC can approve a protocol. Some of the requirements mirror the PHS Policy, whereas others are not found in the PHS Policy. For example, the AWAR require an investigator to consider alternatives to painful procedures and to describe the methods and sources (e.g., electronic literature search) used to determine that alternatives are not available. The AWAR also require the investigator to provide written assurance that the animal-related activities do not unnecessarily duplicate previous experiments. The PHS Policy requires that the PI consider alternatives, but does not require a description of the methods and sources used.

The PHS Policy also includes the nine U.S. Government Principles for the Utilization and Care of Vertebrate Animals that provide additional guidance concerning

the concepts of Replacement, Reduction, and Refinement (3 Rs). Of particular note is Principle II which states 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.” Principle II represents the scientific and societal justification for using animals in research.

Opin. It should be noted that neither the PHS Policy nor the AWAR provide specific guidelines in all areas of protocol review. It is, therefore, left to the institution to develop specific guidelines for implementation of federal requirements. Many institutions have, therefore, developed investigator handbooks that include information concerning local policies for anesthetics, analgesics, blood sampling, tail sampling, antibody production, pre- and post-operative care for non-rodent animals, and other aspects of animal research.

Finally, it should be mentioned that NIH periodically publishes guidance on selected topics, in “Dear Colleague” letters and in notices in the NIH Guide for Grants and Contracts that provide information concerning NIH/OLAW’s interpretation of the requirements of the PHS Policy.² In a somewhat similar vein, APHIS/AC issues its Animal Care Policy Manual that provides further guidance for IACUCs.

9:2 What are some useful pathways to disseminate protocols for review once they have been submitted to the IACUC?

Reg. PHS Policy (IV,C,2) requires that each IACUC member be provided with a list of proposed projects to be reviewed, and that written descriptions of projects be available to all IACUC members. The AWAR (§2.31,d,2) have the same requirement.

Opin. There are many methods used to disseminate protocols for review. Most IACUCs meet in a common location to review protocols, but some committees communicate by fax, electronic mail, phone, or video conferencing (see 6:11). It is common practice for IACUCs to assign each protocol to a primary and secondary reviewer (chosen based upon their expertise in the subject matter of the protocol) who are given principal responsibility for in-depth review. With this method, all members of the IACUC receive either a complete copy of the protocol or a protocol summary for review. Some IACUCs, particularly at institutions that have a large amount of research using animals, utilize a pre-review system where protocols are clarified and modified as necessary prior to full-committee review (see 9:5, 9:6). Many IACUCs also utilize a designated-member review system, (also referred to as “expedited review”, although the use of this term is strongly discouraged by the USDA, PHS and AAALAC), which in turn helps to decrease the workload during full committee meetings (see 9:22). In general, the method used to disseminate protocols for review is dictated by the size and specific needs of the institution.

9:3 What are the IACUC and institutional obligations for reviewing a protocol for an internally funded project?

Reg. If an institution has elected, in its NIH/OLAW Assurance, to apply the requirements of the PHS Policy to all activities (regardless of the source of funding), then the IACUC obligations for reviewing internally funded projects do not differ from those obligations under the PHS Policy.

Opin. Internally funded projects may pose special problems for the review process, particularly with respect to scientific merit review. Even IACUC members who maintain steadfastly that the committee has no responsibility or right to review scientific merit agree that the IACUC has some obligation to do so when the proposal will not be subjected to external peer review. At least a minimal level of merit that justifies animal use must be assured before such protocols are approved. Needless to say, animal welfare considerations should be the same, and the same rigorous review process with regard to regulatory compliance must be uniformly applied to both internally and externally funded projects.

9:4 At what point in the review of a protocol are consultants best brought in?

Reg. PHS Policy (IV,C,3) and the AWAR (§2.31,d,3) allow the use of consultants for the review of a protocol. Consultants may not vote with the IACUC, and the IACUC remains responsible for its actions and decisions.

Opin. The use of consultants is highly variable among IACUCs. In some institutions, it is common practice for IACUC reviewers to use colleagues within the institution as consultants for clarification of issues raised during prereview of a protocol (see 9:5, 9:6). This prereview clarification can greatly speed the final review process. Outside consultants are seldom used unless there is disagreement among the IACUC members as to the merit of a given proposal or if unresolved concerns exist with regard to animal welfare. Consultants also are useful if an investigator asks the committee to reconsider its decision (see 9:55, 9:56, 29:30).

9:5 What is meant by prereview of a protocol?

Opin. Prereview refers to review of a protocol by one or more individuals prior to formal review by the IACUC. Neither the PHS Policy nor the AWAR make any specific mention of the term or concept of prereview, although many institutions find it useful. The AWAR (§2.31,d,1,iv,B) require veterinary consultation during the planning of a procedure that might cause more than momentary pain or distress. (See 9:6, 16:4.)

9:6 What are the reasons for a prereview of protocols?

Opin. Protocols are sometimes incomplete when they are submitted for IACUC consideration. Information that the IACUC needs in order to effectively review the protocol might be absent or unclear. For example, the investigator may be proposing to use a method of anesthesia involving injectable agents without specifying the dose. Clearly, this information must be provided before the IACUC can approve the protocol. Prereview saves the IACUC time, because IACUC members do not have to read protocols that are obviously not ready to be reviewed. Prereview also should be helpful to the investigator in terms of speeding up the review process, because the protocol is less likely to be tabled and carried over to the next IACUC meeting pending further information and clarification.

9:7 Is prereview of protocols required by any regulation or policy?

Opin. Prereview of protocols is not a PHS Policy requirement, but the AWAR (§2.31,d,1,iv,B) require PIs to consult with a veterinarian when potentially painful procedures are planned. Prereview of the protocol by a veterinarian is one way that such a consultation can be provided. (See 9:5.)

9:8 Can the prereview team be an IACUC subcommittee composed of IACUC members, non-IACUC members, or a combination of these?

Opin. Because prereview is not a mandated function of an IACUC, the prereview process can be structured in a way that is most helpful to the IACUC and investigators. Prereview can be carried out by designated IACUC members, qualified IACUC office staff, campus veterinarians, or any other experienced individuals who are able to adequately review the protocol.

9:9 What is a workable mechanism for the prereview of protocols?

Opin. The best mechanism depends on the institutional structure and the composition of the prereview team. For example, an institution with multiple vivaria may choose to have incoming protocols immediately sent to a prereviewer. Each prereviewer handles all of the submitted protocols from the particular vivarium on the campus, so the prereviewer becomes very familiar with the investigators, facilities, and types of research conducted in that unit. The prereviewer reviews the proposal, notes any points of inadequacy in the document, and communicates with the PI. The prereviewer may be able to suggest minor corrections or suggest adding clarifications to the protocol (for example, changing the route, dose or type of anesthetic agent) or suggest adding a sentence to the protocol (for example, indicating the volume of blood to be withdrawn). In the case of more substantial corrections, the prereviewer discusses the problems with the PI and may recommend that the investigator rewrite the protocol and submit a corrected version. There is the potential problem that the PI may interpret prereview as actual committee review, and changes made may be interpreted as IACUC approval. The PI should clearly understand that prereview is not full-committee review and that additional changes may be required by the IACUC.

9:10 What should the PI do following prereview?

Opin. Assuming that the prereviewer suggests changes that are in accordance with IACUC policies and concerns, it is in the PI's best interests to make the necessary corrections before the IACUC meeting so that the protocol is suitable for review.

9:11

What happens to a protocol after it is prereviewed?

Opin. After a protocol is prereviewed, it must be processed for formal review by the IACUC. This may be accomplished by either a designated reviewer (see 9:21-9:26) or review at a fully convened meeting of the IACUC.

9:12 Are the results of the prereview presented to the full IACUC? If so, by whom?

Opin. In institutions that still use paper submissions, the IACUC may be presented with a completely revised application form including all of the changes made by the PI as a result of the prereview process. Alternatively, the changes may be presented as a separate document along with the original application form. The former method is preferred because it yields a “clean,” complete protocol application, which is a benefit to both the IACUC and the investigator and his staff. In institutions that use electronic submissions, the PI can simply alter the online form, especially if the submission software is able to track all the changes. Unfortunately, not all of the commercial software packages allow such tracking. There are, however, separate software packages that provide this capability. From the point of view of minimizing the workload of the IACUC it is preferable to have a single document for review.

9:13 Are prereview comments binding on investigators?

Opin. No. Prereview is simply a method for giving investigators advice on their protocols. A possible exception may arise when the AV determines during prereview that a particular anesthetic or surgical procedure is not appropriate (AWAR §2.33,b,4). Investigators may occasionally disagree with the prereviewer’s suggestions and choose to provide an explanation and send an unmodified or a partially modified protocol to the IACUC for formal review. However, an investigator who insists on presenting an inadequate document to the IACUC is likely to find that the IACUC will not approve the protocol, and the protocol will be returned for modifications or clarification for the same reasons identified by the prereviewer. This will result in unnecessary delays in obtaining IACUC approval of the project.

9:14 Should the IACUC review protocols for scientific merit? Do the AWAR or the PHS Policy specifically require (or prohibit) review of scientific merit?

Opin. In our experience, many IACUCs review protocols for “scientific merit” or “scientific relevance.” It is not clear, however, that these terms have the same or similar meaning to all IACUCs. Whether IACUCs should perform such review is open to debate. Prentice et al.³ and, more recently, Mann and Prentice⁴ reviewed the PHS Policy, in which the term “scientific merit” is not used. Rather, it refers to “relevance” in U.S. Government Principle II, in a manner that strongly suggests the terms are synonymous. The PHS Policy (IV,D,1,d) also uses the terms “sound research design” (IV,C,1,a) and “scientifically valuable research.” When all of these terms are considered together, they support the position of NIH/OLAW that an IACUC should at least consider the scientific relevance of a proposal.⁵ Indeed, NIH/OLAW⁵ has written:

“. . . The primary focus of the IRG is scientific merit, whereas the primary focus of the IACUC is animal welfare. It is evident, however, that there is some overlap of function between the two bodies.

“Although not intended to conduct peer review of research proposals, the IACUC is expected to include consideration of the ‘U.S. Government Principles for the Utilization and Care of Vertebrate Animals in Testing, Research and Training . . .’ in its proposal review process. Principle II calls for an evaluation of the relevance

of a procedure to human or animal health, the advancement of knowledge, or the good of society. Other references (sections IV,C.1 and IV,D.1) include language such as ‘consistent with sound research design,’ ‘rationale for involving animals,’ and ‘in the conduct of scientifically valuable research,’ which presumes that the IACUC will consider in its review the general scientific relevance of the proposal. The presumption is that a study that could not meet these basic tests would be inherently invalid or wasteful and, therefore, not justifiable.”

The AWAR appear inconsistent in their reference to “scientific merit review.” In the Public Comment Section of the regulations, APHIS/AC states, “we added the term ‘animal care and use procedure’ ... to avoid any misunderstanding or implication that APHIS intends to become involved in the evaluation of the design, outlines, guidelines, and scientific merit of proposed research.”⁶ On the other hand, the AWAR (§2.31,e,4) like the NIH/OLAW, make reference to “scientifically valuable research.” Also, the AWAR (§2.31,a) and the AWA itself (§13,a,6,A,i-ii) state that “except as specifically authorized by law or these regulations, nothing in this part shall be deemed to permit the Committee or IACUC to prescribe methods or set standards for the design, performance, or conduct of actual research or experimentation by a research facility.”

It appears that NIH/OLAW and APHIS/AC do not want to explicitly commit themselves to require IACUC review of scientific merit. Nevertheless, according to NIH/OLAW,⁷ an institution cannot defer scientific relevance review to the funding agency. IACUC approval, using criteria stated in the PHS Policy, must (in the original policy statement;⁵ not under the just-in-time criteria noted below) precede NIH peer review. Therefore, approval by an IACUC of a proposed activity that is conditional upon successful peer review by the funding agency would not be in keeping with the PHS Policy requirements. Such conditional action does not constitute IACUC approval required by the PHS Policy prior to review by the NIH Initial Review Group (IRG) or Study Section. The NIH review of merit should, therefore, be viewed as additional assurance rather than the only assurance that the research has value.^{3,7} Based on this, Prentice et al.³ concluded that the IACUC does have a responsibility to review the scientific relevance of animal projects that are subject to the requirements of the PHS Policy. There is not, however, general agreement with this conclusion. Black⁸ argues that merit and relevance are not the same thing; that IACUC review does not constitute peer review, the consequences of IACUC review are different from those of external review, and IACUC review may constitute a violation of researchers’ academic freedom. Prentice et al.⁹ and Mann and Prentice⁴ offer counter arguments. Clearly there is not general agreement.

The advent of just-in-time certification of IACUC approval of research proposals (see 8:22) seems to add another level to the arguments above. It would seem that the NIH now allows the IACUC to refrain from reviewing scientific merit or relevance. On the other hand, referring to the just-in-time process, the NIH wrote, “The fundamental PHS Policy requirement that no award may be made without an approved Assurance and without verification of IACUC approval remains in effect. This change only affects the timing of the submission of the verification of that review.” Given this, it seems that the PHS still expects the IACUC to do reviews for scientific merit or relevance.

9:15 Can the IACUC approve judicious use of animals without consideration of scientific merit?

Opin. See 9:14 for a general discussion. Prentice et al.³ note that there are two levels of review for scientific merit. They refer to a “fundamental level” of review in which scientists form “basic judgments about the adequacy and appropriateness of experimental design in terms of the ability to test the hypothesis, use controls, sample size, statistical analysis, and the training and experience of investigators.” This first-level merit review is necessary for the IACUC to approve the judicious use of animals. The other level of review, “knowledge-based level,” requires “an assessment be made of the scientific importance of the study.” An assessment of merit at the fundamental level could be made by any appropriately constituted IACUC, even in the absence of special expertise in the topic of the protocol. It would seem that a judgment of the merit at the knowledge-based level would be necessary to determine the appropriateness of the proposed animal use. Of course, the latter judgment requires that the IACUC have suitable expertise in a range of subject matters.

9:16 The AWAR (§2.31a) states that the IACUC shall not prescribe methods or set standards for the design, performance, or conduct of actual research or experimentation by a research facility. What does this actually mean since the IACUC has the authority to approve or withhold approval of animal research activities?

Reg. Actually that section reads, “Except as specifically authorized by law or these regulations, nothing in this part shall be deemed to permit the Committee or IACUC to prescribe methods or set standards for the design, performance, or conduct of actual research or experimentation by a research facility.”

Opin. This apparent contradiction in the AWA was discussed in detail by Prentice et al. (1992)³ and Mann and Prentice (2004)⁴. Consider an animal use protocol that did not contain suitable controls. One could argue that if such a protocol contained no animal welfare issues, it should be approved by the IACUC because the quoted text above seems to say that scientific merit should not be considered. On the other hand, §2.31e.3 says that a protocol should contain “A rationale for involving animals and for the appropriateness of species and numbers to be used.” In this case, the numbers would be inappropriately low because of the missing controls, and the IACUC should not approve it.

It seems that the phrase “Except as specifically authorized by law or these regulations” is critical. The IACUC should not “prescribe methods or set standards for the design, performance, or conduct of actual research or experimentation” except as specifically stated in the AWA itself or other relevant laws. (See 9.14 and 9.15.)

9:17 Is it appropriate for the IACUC to use consultants to review scientific merit?

Reg. (See 9:4.)

Opin. If the IACUC assesses the scientific merit of a study (see 9:14, 9:15), then it is appropriate for the IACUC to use consultants, particularly if the IACUC does not have

the requisite expertise to assess scientific merit. Also, outside reviewers would likely be most useful when there is disagreement among the IACUC members as to the scientific merit of a protocol or if an investigator can appeal the decision of the IACUC (see 9:55, 9:56, 29:30). Indeed, the IACUC could seek advice from consultants with regard to any aspect of the project that is problematic.

9:18 What types of consultants might be useful for review of scientific merit? Who picks them?

Opin. Consultants can be

1. Experts on the topic of the protocol under review or
- 2) Experts in the use of animals, with respect to a particular procedure proposed in the protocol or,
- 3) Both

An example of the former is an expert who is asked to review a protocol because the IACUC is uncertain whether the use of the ascites method for making monoclonal antibodies is required in a particular project as the PI claims. Or, the consultant can be asked to judge whether any useful information will be forthcoming once the antibody is made. An example of the second use is an expert in primate behavior and care who is asked to review a protocol because the IACUC is uncertain whether a rhesus monkey may reasonably be restrained continuously for more than 24 hours. Or, the expert can be asked whether any useful information could be derived from the experiments that require the monkey to be restrained for that period of time.

Consultants should be selected by the IACUC, but it may also be reasonable to allow the PI to suggest possible experts. This allows the committee to maintain objectivity in the review process while allowing the PI to feel that his or her point of view is being presented. Some institutions require the consultant to sign a CDA (Confidentiality Disclosure Agreement) to protect the proprietary nature of the proposed study. The CDA will be useful in terms of protecting anonymity of the consultant and the confidential nature of the study.

9:19 Should the identity of consultants be kept anonymous to the investigator?

Opin. The same arguments apply to anonymity of consultants and to the anonymity of grant proposal reviewers. It has been argued that reviewers refrain from making negative comments about a protocol if their identity is known to the investigator and may fear reprisals. It also is possible to argue that reviewers may make unfair statements about a protocol because their identity is withheld. Whether this will happen probably depends upon who the reviewer and investigators are. In any case, if the reviewers of a protocol remain anonymous, then certainly consultants should as well. On the other hand, anonymity may be difficult if the investigator is allowed to suggest possible experts.

9:20 An IACUC retains the services of a consultant to help evaluate a complex protocol. Based in part on the consultant's recommendation, the protocol is approved. The IACUC subsequently learns that the consultant was a former

student of the PI who submitted the protocol. Should the IACUC revisit the protocol's approval?

Opin. Clearly the PI should have informed the IACUC of this consultant's former relationship. But, even if consultants are used in the review process, it is still the IACUC that must make the decision for approval. In this case, the IACUC must have determined that the protocol should be approved. The occurrence of the conflict of interest would not change the fact that the IACUC had found the protocol acceptable. Therefore, it would be unnecessary to revisit the protocol's approval. On the other hand, if the protocol had not been approved based on the consultant's input, then the IACUC might well want to revisit the withholding of approval.

9:21 What is "designated-member review" and what is its intent?

Reg. Both the PHS Policy (IV,C,2) and the AWAR (§2.31,d,2) recognize a method of "designated-member review" that is widely implemented by research institutions.¹⁰ Some institutions refer to this review process as "expedited review," but "designated-member review" is the appropriate term. Designated-member review must conform to the following process: written descriptions of research projects that involve the care and use of animals must be made available to all IACUC members, and any member of the IACUC must have the opportunity to request full-committee review of those research projects. "If full committee review is not requested, at least one member of the IACUC, designated by the chairperson and qualified to conduct the review, shall review those activities, and shall have the authority to approve, require modifications in (to secure approval), or request full committee review of any of those activities." (PHS Policy IV,C,2; AWAR §2.31,d,2).

Opin. Although the exact procedures frequently vary between institutions, the designated-member review process can enable IACUCs to review and approve protocols faster than those presented for full-committee review. It's important to mention, however, that designated-member review in no way implies that the quality of review is less stringent than a protocol reviewed by the full committee. A successful designated-member review process allows institutions, particularly larger institutions that process a large number of protocols, the opportunity to reduce the workload of the IACUC at convened meetings, thereby, allowing members to focus on protocols that may warrant more time and attention. (See 11:9.) It should also be noted that the designated-member review process does not reduce the IACUC office staff workload that may include follow-up reminders to the designated reviewer, correspondence with the PI, etc.

There is no regulation that limits the number of protocols that may be reviewed by the designated-review process. It is expected that an IACUC will meet in a convened meeting at least twice per year to approve the semi-annual program review and inspections. However, there is no required number of meetings. Clearly, progressive IACUCs meet on a regular basis to conduct whatever business is appropriate to the program. This is most often spelled out in the PHS assurance.

In the designated-review process, the members of the IACUC do not vote. A member who is not assigned as a designated reviewer may only refer it to the full committee for review. If a full-committee review is not called for, the designated reviewer has the authority to approve a protocol, require modifications to secure approval

or refer it to the full committee. If there is more than one designated reviewer, they must agree on a course of action or refer the protocol to the full committee.

9:22 Under what circumstances might a protocol be assigned to a designated-member review process?

Reg. A protocol may be assigned to one or more designated reviewers only after all IACUC members have been provided the opportunity to call for full-IACUC review (PHS Policy IV,C,2; AWAR §2.31,d,2). (See 9:21.)

Opin. Because the AWAR and the PHS Policy do not define the criteria for assigning protocols to the designated-member review process, each institution must develop an internal policy, tailored to the individual institution's needs and idiosyncrasies. Even if an institution develops criteria to determine the kinds of activities or protocols that it will permit this review method, all IACUC members must still be provided with the opportunity to call for full-IACUC review of each individual project.

An institution should first decide whether it needs to establish a designated-member review process. Then, the IACUC should create a list of well-defined criteria to determine the types of protocols qualifying for designated-member versus full-committee review. For example, some institutions restrict designated-member review to protocols involving noninvasive or acute procedures that do not cause more than momentary or slight pain or distress to the animals (e.g., the procedures only involve euthanizing the animals in order to harvest tissues), or to protocol amendments that involve minor changes to an approved study.

If an institution elects to adopt a designated-member review process, the IACUC should document the assignment criteria and the procedures for processing the protocols. The IACUC should develop a set of SOPs in order to ensure that the designated-member review process is not misused. The SOPs should be included in the institution's Animal Welfare Assurance, approved by NIH/OLAW, and included in the institution's IACUC Policy and Procedures Manual.

9:23 Under what circumstances is the designated-member review not appropriate?

Opin. Although each institution must determine the criteria appropriate for its own program, designated-member review may be unacceptable under many circumstances, including the following:

- IACUC members are not provided with sufficient information concerning the proposed research activities.
- IACUC members are not given an opportunity to call for full-committee review prior to the approval of the proposed protocol via designated-member review process (PHS Policy IV,C,2; AWAR §2.31,d,2; OLAW "Dear Colleague" letter of 5/21/90).¹⁴
- If any IACUC member requests full-committee review (PHS Policy IV,C,2; AWAR §2.31,d,2).
- One or more members of the subcommittee authorized to conduct designated-member review and to approve research activities has a conflict of interest (PHS Policy IV,C,2; AWAR §2.31,d,2).

- The proposed protocol does not meet the requirements for designated-member review delineated in the institution's NIH/OLAW-approved Animal Welfare Assurance or the institution's IACUC Policy and Procedures Manual. For example, the invasive nature of the research may not permit the protocol to be reviewed by the designated-member review method according to the institution's policies and its Animal Welfare Assurance.

9:24 Should the entire IACUC be involved in the designated-member review process or can a subcommittee conduct designated-member review?

Reg. (See 9:21, 9:22.)

Opin. The entire committee must have the opportunity to review the information provided on each designated-member protocol review list and to request full-committee review. A subcommittee of two or more members who are qualified to review the protocol (e.g., the chairperson and the AV) can be assigned to review the protocol in its entirety. Questions and concerns raised by any member of the subcommittee should always be addressed prior to approval.

9:25 What is required for approval of a protocol via the designated-member review?

Reg. The designated reviewer(s) must use the same criteria that are applicable to protocols undergoing full-IACUC review.

Opin. Although the intent of the designated-member review process is to conduct rapid review of protocols, by no means does this process require less information than the full-committee review process. The designated reviewer(s) must ensure that the review method and criteria for approval is in full compliance with all of the applicable requirements of the PHS Policy (IV,C,1,a–g; IV, D,1,a–e) and the AWAR (§2.31,d,1,i–xi; §2.31,e,1–5). Before approval may be granted via a designated-member review process each member of the IACUC must have the opportunity to review the protocol and the opportunity to request full-committee review. If a subcommittee is being utilized for this review process, all designated reviewers *must* agree on the decision; it is not acceptable to use a majority vote.²⁰ If one of the reviewers disagrees, the protocol should be referred to the full committee for review.

9:26 What is an effective means for administering a designated-member review?

Opin. One significant difference between designated-member review and full-committee review is that the designated-member review process does not require a fully convened meeting of the IACUC. Despite this fact, after a protocol is assigned to designated review, at least one or two IACUC members should review the entire protocol with the same degree of thoroughness that is given to a protocol reviewed by the full committee.

Another difference between the two processes involves the way in which protocol information can be disseminated to the IACUC members. Unlike the full committee protocols, the information pertinent to protocols presented for designated

review can be more easily disseminated through the use of electronic means (e.g., fax or e-mail) in order to facilitate the most expeditious type of review. (See 6:11.)

The following is an example of a designated-member review process. This particular example goes beyond the requirements of the AWAR and PHS Policy in that it requires a summary to be sent to all members and documentation of each designated reviewer's decision with regard to designated-member review:

- The IACUC administrator reviews the protocol submitted to the committee and decides whether it qualifies for designated-member review based upon the IACUC's predetermined criteria.
- A summary of the protocol qualifying for designated-member review (including title of project; species, number of animals requested; type of experimental procedures) is forwarded to members of the IACUC via postal mail, fax, or email (see 6:11). In some instances, additional information may be included (e.g., supporting grant materials or parts of the original protocol).
- Each IACUC member reviews the summary and, if necessary, requests a copy of the complete protocol to determine whether clarification or changes are needed, and has the opportunity to call for full-committee review.
- If no member calls for full-committee review in a reasonable, specified time period, a subcommittee, composed of the IACUC chair and the AV, is authorized to review and approve the protocol. In a case where the chair or the AV has a conflict of interest (e.g., is personally involved in the project), he must be replaced by another member qualified to conduct the review (PHS Policy VI,C,2; AWAR §2.31,d,2). (See 6:8.) In our experience, a week is a sufficient time for the designated reviewer process to occur. The protocol can be reviewed and either approved or referred to the full committee.
- Documentation, including review sheets, is maintained as evidence of each designated reviewer's decision with regard to these protocols. The designated reviewer sheets are kept in the protocol file in the event the designated-member review of a protocol is ever questioned. *No matter what process an institution adopts, the designated-member review procedure must be documented from assignment to approval each time it is used.*

9:27 An IACUC chairperson appoints designated-member reviewers. Can an IACUC member who was not chosen as a designated reviewer demand to be made a designated reviewer?

Reg. Both AWAR §2.31,d,2 and PHS IV,C,2 specify that one member of the IACUC is designated *by the chairperson* and qualified to conduct the review.

Opin. There is no requirement for the chairperson to honor such a request. Although this may be an unusual request, an IACUC chair would be wise to find out why an IACUC member has made this demand and perhaps refer the protocol to full-committee review.

9:28 What is “full-committee” review?

Reg. Full-committee review of an IACUC protocol is one that is conducted by a quorum of the IACUC at a regularly scheduled or specially convened meeting (PHS Policy IV,C,2; AWAR §2.31,d,2).

Opin. Due to the volume of protocols reviewed at many institutions, a good portion of the actual work involved in protocol review may be done before the meeting via a mechanism such as prereview (see 9:5 to 9:13). Thus, at the meeting, the committee members are able to concentrate on the proposed protocol, its “scientific merit,” and the care and use of laboratory animals without the necessity of obtaining clarifications related to incomplete information and/or confusing points.

9:29 What is the purpose of a full-committee review?

Opin. The purpose of full-committee review is to have all IACUC members involved in reviewing and making decisions regarding the disposition of protocols during an interactive meeting. This in turn allows the IACUC to utilize the expertise of its members in a discussion-based format, thus facilitating the resolution of protocol-related issues.

9:30 When is full-committee review of a protocol appropriate?

Reg. Full-committee review is appropriate at any time and required when requested by any member of the IACUC (PHS Policy IV,C,2; AWAR §2.31,d,2). Each member must have the opportunity to review any protocol before approval may be granted.¹⁰ There are no other federal requirements specifying when a protocol should receive full-committee review or the type of protocol that should receive full-committee review.

Opin. Many IACUCs have developed criteria to determine the types of protocols requiring full-committee or designated-member review. Items to be considered in developing such criteria include:

- Invasiveness of procedures.
- Level of pain or distress.
- Species and number of animals requested.
- Experimental design.
- The nature of the animal use, e.g., research project versus educational use
- “Controversial” procedures, e.g., death as an endpoint.
- Procedures that request exceptions to regulations, e.g., multiple survival surgeries; that require appropriate justification, and for which the IACUC may want to review only at the time of a fully convened meeting
- Whether the protocol will receive peer review by the funding agency or other group prior to funding.

9:31 What is an effective full-committee review process?

Opin. Each IACUC should establish SOPs regarding conduct of full-committee review of protocols. One effective method of full-committee review includes the following process:

- Prereview (see 9:5 to 9:13).
- Review by IACUC staff or designated member of the committee for completeness of the application and compliance with information requirements, as indicated in PHS Policy (IV,C,1,a–g; IV,D,1,a–e; AWAR §2.31,d,1,i–xi; §2.31,e,1–5).
- Review by the AV in addition to the consultation required during design of the study (AWAR §2.31,d,1,iv,B).
- Review by outside consultants if the IACUC members do not possess relevant expertise.
- Review by committee members assigned as primary and secondary reviewers.
- Primary and secondary reviewers communicate with the investigator prior to the meeting, during which the reviewers may recommend modifications in the protocol (PHS Policy IV,C,2; AWAR §2.31,d,2).
- Presentation of the protocol to either a protocol review subcommittee or the full committee by the primary and secondary reviewers followed by a general discussion of the protocol.
- If reviewed by a subcommittee, it is recommended that a synopsis of that group’s deliberations be presented to the full committee to allow for any additional comments.
- Every member of the committee should be provided with a copy of the protocol, or, at a minimum, a summary of the protocol to be reviewed at the meeting.
- Following discussion at a convened quorum of the committee, a vote is taken to determine final disposition of the protocol.

9:32 What are the PHS Policy and AWAR requirements for approval of a protocol by full-committee review?

Reg. The PHS Policy and AWAR require:

- Each member of the IACUC must be provided with, at the minimum, a list of protocols to be reviewed (PHS Policy IV,C,2; AWAR §2.31,d,2).
- Both the PHS Policy (IV,C,1,a–g; IV,D,1,a–e) and the AWAR (§2.31,d,1,i–xi; §2.31,e,1–5) have specific requirements about information that must be included in the protocol as well as the items the IACUC must consider. These are described below.
- No member of the IACUC may participate in the review or approval of a research project in which the member has a conflict of interest (e.g., is personally involved in the project) except to provide information requested by the IACUC (PHS Policy IV,C,2; AWAR §2.31,d,2). Some IACUCs require this member to leave the room during final discussion and voting on the protocol in question.
- Approval of a protocol considered by the full committee “may be granted only after review at a convened meeting of a quorum of the IACUC and with the approval vote of a majority of the quorum present” (PHS Policy IV,C,2). The AWAR (§2.31,d,2) have the same requirement.
- A member who has a conflict of interest in a protocol under review may not contribute to the constitution of a quorum (PHS Policy IV,C,2; AWAR §2.31,d,2). This person may not vote on the protocol in question.

- Institutions must maintain written documentation of committee deliberations (PHS Policy IV,E,1,2; AWA §2.35,a,1,2). Whereas most IACUCs include this information in the minutes, such documentation can be maintained instead on file with the protocol. Filing records of deliberations along with the protocol is of importance to institutions subject to state open records laws. It is up to the IO, IACUC chair, or IACUC staff to explain to either APHIS/AC, NIH/OLAW, or AAALAC the rationale for the institution's recordkeeping methods. This should be documented in the PHS Assurance and in the institutional Policy and Procedures Manual.
- Both the investigator and the institution must be notified in writing of the committee's decision (PHS Policy IV,C,4; AWA §2.31,d,4).

9:33 What constitutes "administrative review," and when may it be used?

Reg. The PHS Policy (IV.C.1) states that "In order to approve proposed research projects or posed significant changes in ongoing research projects, 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." It goes on to say that such review must use either the designated-reviewer or full-committee review method. But, the policy does not say what should be done if there are non-significant changes. The USDA regulations (§2.31,c,6-2.31,c,7) contain essentially the same requirements. Neither the PHS Policy nor the AWR uses the term "administrative review" or discusses anything to which the term could reasonably be applied.

In the June 6, 2003 NIH Dear Colleague Letter,¹¹ it is stated that "IACUCs may, by institutional policy, classify certain proposed additions or changes in personnel, other than Principal Investigator, as 'minor' provided an appropriate administrative review mechanism is in place to ensure that all such personnel are appropriately identified, adequately trained and qualified, enrolled in applicable occupational health and safety programs, and meet other criteria as required by the IACUC."

Opin. According to the PHS, administrative review is possible in some cases provided the process and its application are documented. It is essential that the IACUC establish an SOP for the application of administrative review and that this be documented in both the institutional Assurance and the Policy and Procedures Manual.

When can it be applied? Clearly, it is inappropriate for initial review of all animal projects. It is also inappropriate for all continuing review.¹² Such administrative review may be applied to requests for change that are not significant. This would include changes in personnel other than the PI, as indicated above. NIH/OLAW has no written endorsement of these, but it seems that replacement of a small number of animals due to a technical, vivarium or vendor-related problem; a slight increase in the amount of blood to be drawn; correction of the dosage of pain relieving drug; or a change in a procedure that occurs after terminal anesthesia but before euthanasia could all be approved by administrative review. (See 10:3.) NIH/OLAW has indicated that changes in the objectives of a study; proposals to switch from non-survival to survival surgery; changes in the degree of invasiveness of a procedure or discomfort to an animal; changes in species or in approximate number of animals used; changes in anesthetic agents, use or withholding of analgesics or methods of euthanasia; and changes in the duration, frequency or number of procedures performed on an animal would not qualify for

administrative review.¹³ Wolff et al.,¹³ speaking for NIH/OLAW, have clearly stated that administrative review may not be used to grant continuance to a project the approval for which has expired because the investigator failed to seek continuing review in a timely fashion.

Administrative review, when it is appropriate, may be performed by the IACUC chair or administrator, by the AV or by an IACUC member designated by the IACUC chair.

9:34 An IACUC protocol was properly approved. Can an investigator begin research with animals based on an oral approval from the IACUC office or must there be written documentation of the approval?

Opin. Once approval of the protocol has been documented in the IACUC records, which can mean written in the IACUC minutes by the recording secretary, recorded on a summary check sheet or some other process approved by the IACUC, oral notification can be given to the investigator and the research may begin though an official approval letter has not been issued to the investigator. However, the official approval letter, with the same date as the oral approval, is required for the establishment of a paper trail.

9:35 Is it important for the IACUC to know whether a protocol is new or a resubmission with a change in title?

Opin. If a protocol is submitted and disapproved or tabled (approval withheld), it should be treated as a new protocol upon resubmission regardless of whether the title or funding source is changed or not. It should be handled as a new protocol, reviewed by either designated-member review or full-committee review as specified in the PHS Assurance or institutional Policy and Procedures Manual. If a protocol has been previously reviewed and approved, then the title or funding source may be changed without re-review if it is the policy of the institution to handle changes in title administratively.

9:36 What procedures can the IACUC use to determine if a protocol is new or a resubmission with a change in title?

Opin. If a protocol is determined to be a resubmission with a change in the title only, the IACUC may decide to verify this by comparing the resubmission with the previously approved protocol on file. Investigators sometimes inadvertently modify protocols during the course of resubmission without recognizing that the IACUC must approve all proposed significant changes (PHS Policy IV,B,7; AWAR §2.31,C,7). It is perhaps a better procedure to make changing the title of a protocol a separate process with its own form or treat it as just one of several types of amendments to a protocol. That way the changes in the protocol would be obvious.

For IACUCs that use electronic submissions of amendments, it is possible to detect changes in the protocol electronically through use of software with this dedicated purpose.

9:37 Should IACUC decisions be influenced by the source or size of a research grant?

Reg. The IACUC must review grants under the requirements of PHS Policy IV,C,1, regardless of the size of the grant. Non-PHS-supported research may or may not be covered by the PHS Policy, depending on the statement of applicability in the institution's Animal Welfare Assurance.

Opin. On reflex, most IACUC members would probably answer "no" to this question. In general, all protocols should be reviewed with the same rigor regardless of how much money is involved or the source of funding. Whereas political pressures for IACUC approval of large or prestigious grants are real, studies should be approved based on appropriateness of the proposed research. Certainly, animal welfare should never be compromised in the interest of increasing grant funds. Nevertheless, in one study¹⁵, results of a survey indicated that IACUC deliberations potentially can be influenced by the size of a grant as well as by pressure and perceptions that the committee may not even recognize. IACUCs must be constantly vigilant for inconsistencies in their deliberations and decisions, especially those affected by such pressures or perceptions.

9:38 Should the decisions of the IACUC be influenced by the potential scientific importance of a project proposed in a protocol?

Reg. The IACUC has the authority to approve a proposed project. NIH/OLAW and APHIS/AC have stated that under no circumstances is an IACUC required to approve a project against its will.¹⁶ (See 16:9.)

Opin. IACUC decisions should not be influenced by the investigator, species, funding source, or "hotness" of the research topic. Review should be based on animal welfare issues in consideration of the regulatory requirements. Nevertheless, both the dollar value of the grant, as well as a species-specific view of an animal's societal worth potentially could but should not affect IACUC deliberations.¹⁵

9:39 If a protocol is completely novel and contains untested surgical or experimental procedures, how could such a protocol be reviewed and approved when the procedures cannot be referenced?

Opin. Few protocols actually contain untested surgical procedures. Those that do can be handled in one of two ways. In some cases, the IACUC could recommend that a pilot study be conducted involving only the part of the protocol using the untested procedures. With these pilot data derived from successful use of the previously untested procedures, the investigator could then obtain IACUC approval for the complete protocol. Pilot studies must be reviewed and approved by the IACUC.

Alternatively, the IACUC could approve the protocol as submitted but with a reduced number of animals, the remainder being approved when the investigator has tested the new procedure. Both of these actions allow the researcher to proceed with the study while the animal subjects are being protected. (See 13:6, 13:9.)

9:40 What are some possible actions an IACUC can take with respect to protocols that have been reviewed?

Reg. Both the PHS Policy (IV,B,6) and the AWAR (§2.31,C,6) allow the IACUC to review and approve, require modifications in (to secure approval), or withhold approval of proposed activities related to the care and use of animals.

Opin. In determining the disposition of a protocol submitted for review by the full-committee review method, an IACUC has several options including:

- Approval
- Require modifications to secure approval (see 9:42)
- Tabling the protocol with a request for major revisions
- Withhold approval

When the designated-member review method is used, the only options open are:

- Approval
- Refer to full committee for review
- Require modifications to secure approval

9:41 What constitutes “approval” of a protocol? Does this action necessarily mean that no further changes or information are needed?

Reg. For PHS Policy and the AWAR, IACUCs either approve, require modifications in (to secure approval), or withhold approval of protocols (AWAR §2.31,c,6; PHS Policy IV,B,7). Designated reviewers may approve, require modifications to secure approval, or request full-committee review. Anything short of final approval is not adequate for initiation of animal activities or submission of an IACUC approval date to the NIH as part of a grant application.

Opin. Generally, an approved protocol is one that contains all the required information and has been judged by the IACUC to be acceptable.

9:42 What constitutes “approval with conditions?”

Reg. (See 9:41.)

Opin. The IACUC may require modifications of a protocol in order for a PI to secure approval when it is determined that no major revisions or clarifications are required. Often, the chair or the AV is assigned to review the PI’s response or revised protocol, and is empowered by the IACUC to approve the protocol without further review by the full committee. However, depending upon the conditions imposed, the entire committee may wish to see the response to conditions or a subcommittee may be formed and empowered to review the response and approve the protocol. Conditional approval does not, however, mean that the study can be initiated. The PI must first comply fully with all conditions arising from the IACUC’s review, and then final approval can be granted. The reader is cautioned that terms such as “conditional approval,” “provisional approval,” or “approved pending clarification” frequently cause confusion. NIH/OLAW and APHIS/AC prefer that IACUCs either avoid these terms or describe them in sufficient detail to be fully understood. (See 9:47.)

IACUCs might determine that a protocol is approvable, contingent on receipt of a specific modification (e.g., receipt of assurance that the PI will conduct the procedure in a fume hood). The IACUC can handle this modification (or clarification) as an administrative detail that is documented in the protocol record. On the other hand, protocols that are missing substantive information necessary for the IACUC to make a judgment (e.g., justification for withholding analgesics in a painful procedure) are incomplete. If the protocol is incomplete, it is not possible to satisfy the protocol review criteria. NIH/OLAW and APHIS/AC recommend that IACUCs devise effective ways of differentiating between substantive omissions and administrative issues.¹⁷

9:43 What constitutes a “tabled” or “postponed” protocol?

Opin. The “tabling” or “postponing review” of a protocol are terms often used interchangeably by IACUCs, but are not used as outlined in the more formal structure of Roberts’ Rules of Order. (See 6:4.) The IACUC may “table” or “postpone” further review of a protocol pending receipt of additional substantive information or a significant revision of the protocol. The action of tabling a protocol is generally used during the process of full-committee review when the IACUC decides it is necessary for the whole committee to re-review the protocol before further action can be taken. Tabling a protocol is usually reserved for proposals that do not contain sufficient information or those in which the IACUC has identified a serious animal welfare concern.

9:44 What might cause a protocol to be “disapproved” (approval withheld)?

Reg. Approval may be withheld if any of the PHS Policy (IV,C,1) or AWAR (§2.31,d,1; §2.31,d,2,e) criteria are not met.

Opin. Withholding approval of protocols is infrequent. Generally, approval is withheld when the PI and the IACUC cannot agree on fundamental aspects of the proposed study such as the protocol design, animal welfare issues, or the PI will not agree to comply with the IACUC’s requirements.

Both the PI and the IO must be notified in writing of the committee’s decision. This written notification should include a statement of the reasons for the decision and provide the PI with an opportunity to respond in person or in writing (PHS Policy IV,C,4; AWAR §2.31,d,4). The IACUC may want to seek outside review in the case of an appeal by the PI of withholding of approval for a protocol but perhaps only if it feels that it lacks expertise to make a decision.

9:45 How should an investigator respond to questions or conditions from the IACUC?

Opin. Responses from the PI to questions or concerns raised by the IACUC should be in such a format as to result in a protocol that contains a complete, easy to discern description of the proposed activities. The response from the PI should clearly answer each issue raised. This can be achieved via a point-by-point letter that serves as a means for the PI to respond to the Committee’s questions and concerns accompanied by a revised protocol which incorporates all required changes and clarifications. Requiring the PI to provide a revised protocol has the advantage of ensuring that a complete and up-to-date master protocol is embodied in one document. Copies of the final, approved IACUC

protocol should be maintained in the IACUC administrative office, in the animal facility, and in the investigator's laboratory. This master protocol also has the advantage of facilitating the management of the protocol by the animal care staff and for compliance review purposes.

9:46 Should there be a time limit to receive responses to queries raised by the IACUC?

Opin. Establishment of time limits and other constraints should be considered when the IACUC develops an SOP. Specific time constraints and deadlines can be of benefit to both the investigator and the committee when the expectations are known. Ironclad deadlines and inflexible staff, however, can present a major point of contention for faculty already juggling multiple projects and attempting to comply with much paperwork and many deadlines.

9:47 Once a response from an investigator is received, can the IACUC chair or his designee approve protocols if conditions are met?

Opin. Generally, this should be determined when the decision is made to grant "conditional" approval. That is, approval is granted on condition that the PI meet certain requirements, and the committee agrees that the assigned reviewers or the chair can determine if the conditions have been satisfactorily met, subsequently granting approval (PHS Policy IV,C,2; AWAR §2.31,d,2). It should be noted that "conditional approval" is not mentioned in either the AWAR or PHS Policy. Technically, the IACUC should initially "withhold approval" and then grant approval via the designated-member review process. A distinction should be made between conditions based on administrative details and information that has a bearing on the IACUC's decision. (See 9:41, 9:42.)

9:48 Is a majority vote required for any IACUC actions related to protocol approval?

Reg. Approval of a protocol considered under guidelines for full-committee review "may be granted only after review at a convened meeting of a quorum of the IACUC and with the approval vote of a majority of the quorum present" (PHS Policy IV,C,2). The AWAR (§2.31,d,2) has the same requirement. (See 9:21 for designated-member review considerations.)

Opin. These regulations represent the minimum requirements, and an institution may implement more stringent requirements. These should be clearly stated in the PHS Assurance and in the institution's Policy and Procedures Manual.

9:49 At a full-committee meeting of a 20-member IACUC, 15 members are present. Six vote to approve a protocol, six abstain, and three vote against approval. Is the protocol considered approved according to the AWAR and PHS Policy?

Opin. No. In this example, the 15 members present constitute the quorum. In order to approve a protocol, a simple majority of those members present, i.e., eight, would have to vote for approval of the protocol. Because only six members voted to approve, the vote

count fell short by two votes, and the protocol cannot be approved according to the AWAR and PHS Policy.¹⁸ (See 9:48.)

9:50 How should the IACUC handle minority opinions to IACUC actions on the review of protocols?

Reg. PHS Policy (IV,E,1,d) requires institutions to maintain copies of minority views of semiannual reports (not protocol reviews), but does not specify how the IACUC should handle them. There is also a PHS Policy (IV,F,4) requirement that minority views filed by IACUC members be forwarded (via the IO) to NIH/OLAW along with the annual report to NIH/OLAW (but again, this does not refer to protocol reviews). If the minority views relate to an IACUC action that is required to be reported promptly (PHS Policy IV,G,3), they should be provided to NIH/OLAW at that time. The AWAR (§2.31,c,3; §2.35,a,3) also require maintaining records of semiannual reports, including minority views.

Opin. Because neither the PHS Policy nor the AWAR address this issue relative to specific IACUC protocols, it should be considered when the IACUC develops an SOP. A common practice is to record dissenting opinions in the minutes. However, another option is to allow the dissenter to write a letter expressing her or his opinion. This is then filed along with the IACUC protocol.

9:51 A protocol has been approved with changes requested by the IACUC. The protocol is associated with a grant application to the NIH. Does the approval letter sent by the Research Administration Office to the NIH have to detail the changes made in the animal use portions of the grant?

Reg. The original PHS Policy (IV,D,2) requires “verification of approval (including the date of the most recent approval) by the IACUC of those components related to the care and use of animals. ... If verification of IACUC approval is submitted subsequent to the submission of the application or proposal, the verification shall state the modifications, if any, required by the IACUC.” For competing applications or proposals, verification of IACUC approval may be filed at a time not to exceed 60 days after the proposal application deadline (PHS Policy IV,D,2).

Opin. In 2002, this policy was amended to allow verification of IACUC approval to be submitted upon request from the PHS (just-in-time verification). (See 8:XX.) The PHS issues the request when it determines that a grant proposal is likely to be funded. Institutions are not required to use just-in-time and may still follow the original requirements as stated above.

Whereas, the original 60-day grace period and the new just-in-time verification may reduce workloads of both the PI and the IACUC, it may create a situation in which the IACUC requires changes to a protocol that would result in a change in the grant proposal after the proposal has been approved. As pointed out by Mann and Prentice,⁴ it is not clear what the granting agency will do then.

9:52 Should the IACUC review just the IACUC protocol or should the IACUC also review the animal care and use sections of an associated grant proposal?

Reg. Verification of IACUC approval submitted to the NIH means that the IACUC has reviewed and approved those components of the grant application related to the care and use of animals. “Applications or proposals (competing and non-completing) covered by this Policy from institutions which have an approved Assurance on file with OLAW shall include verification of approval . . . by the IACUC of those components related to the care and use of animals.” (PHS Policy IV,D,2). The signature of the institutional representative on the PHS 398 form is a legally binding statement that the IACUC has approved all animal activities covered in the grant application. The submission of just-in-time verification also constitutes a binding statement.

Opin. If the IACUC protocol accurately reflects the information contained in the grant application, then the verification is obviously valid. The IACUC, however, cannot be assured of such validity unless it also reviews the animal care and use sections of the associated grant application. With the advent of the just-in-time review and approval in 2002 (see 8:22), review of the grant proposal need not take place until it appears that the proposal will be funded. This delay may have as yet unknown consequences for funding.⁴

Many institutions do not review the grant proposals at all. They simply rely upon a statement by the PI that the protocol accurately reflects what is in the grant proposal. However, if the PI’s certification is inaccurate the resulting institutional verification to the PHS will be invalid.

9:53 Should the IACUC accept an approval statement from an IACUC at another institution?

Reg. An IACUC may accept the approval of an IACUC at another institution if that institution has an approved NIH/OLAW Animal Welfare Assurance. This practice is normally limited to collaborations or subgrant/subcontracts involving performance sites outside the awardee institution. In most instances, the IACUC of the performance site assumes responsibility for animal activities in its facilities. Both institutions should have a clear understanding of what their respective responsibilities are in this situation, particularly if one IACUC agrees to abide by the determinations of another IACUC.¹⁹ (See 8:11.)

Opin. This is an area for which the IACUC should establish an SOP. The IACUC should have some “comfort level” about the other institution, its committee, and the quality of its research. To avoid problems, a collaborative protocol approved by an IACUC at another institution should probably receive at least the equivalent of designated-member review by the local IACUC. In some instances, full-committee review is warranted. Issues to consider in accepting an approval statement from an IACUC at another institution include:

- Does the institution have an approved NIH/OLAW Animal Welfare Assurance?
- Is the institution a USDA-registered research facility?
- Is the institution accredited by AAALAC International?

For example, this situation may arise when an institution's faculty conducts research at a nearby Veterans Administration (VA) facility. Because the VA facility may not apply for or receive funding from other federal agencies, the grants must be made to the investigator's home institution. The problem is created because VA-IACUC-approval must be granted before research is initiated at the VA facility. The home institution has jurisdiction by virtue of receiving the grant. Thus, either redundant application or this kind of "external" approval is necessary.

Acceptance of an external IACUC review and approval also includes the responsibility for continuing review. The external institution should agree to supply all continuing review documents relative to the protocol as they are reviewed and approved. Failure to do this can result in withholding a notice of approval to the granting agency and possible loss of grant funds. In some cases the home institution's sponsored programs office may require an assurance of continuing IACUC approval for the grant funds to be released. This can be another source of problems for the PI's research.

9:54 Can an investigator receive "conditional approval" for a protocol approved at another institution until the IACUC can review and approve the protocol? What should be the conditions and limitations for this conditional approval?

Reg. (See 9:41.)

Opin. An IACUC may choose to grant conditional approval for a protocol approved by a different institution. However, any conditions regarding acceptance of an approval statement from an IACUC at another institution should be described in the IACUC's written policies. For example, in order to facilitate research, an IACUC may choose to allow animals to be purchased or transferred to its institution, but procedures that involve animals cannot be performed until the local IACUC has unconditionally approved the protocol. (See 9:42.) Because local institutional requirements vary, automatic approval is not advisable.

9:55 An investigator subcontracts part of a research project to another institution where animals will be used. What oversight and paperwork responsibilities does the primary institution have relative to the PHS Policy and the AWAR?

Reg. NIH/OLAW requires that any subcontracted work involving animals that is supported by PHS funds be conducted only at other NIH/OLAW-Assured institutions (PHS Policy V,B). If the performance site (collaborating institution or subcontractor) is not NIH/OLAW-Assured, then NIH/OLAW requires that an assurance for the performance site be negotiated in order for the work to go forward (PHS Policy V,B). Alternatively, an institution can choose to accept responsibility for the work under its own assurance with a written agreement between the institutions. It should, however, be recognized that the latter arrangement means that the NIH/OLAW-Assured institution assumes full responsibility for ensuring that all the animal work conducted at the collaborating institution is in full compliance with the PHS Policy and the AWAR. This arrangement necessitates that the NIH/OLAW-Assured institution's IACUC conduct semiannual program reviews and facility inspections of the collaborating facility. (See 8:11.)

Opin. When an institution subcontracts part of a research project to another institution, there should be a clearly defined written agreement concerning the responsibilities of each institution to comply with the PHS Policy and AWAR regardless of whether both institutions have approved Assurances on file with NIH/OLAW. If a serious compliance problem arises at a subcontract site, it will likely impact the primary institution. However, if the subcontract site is registered with APHIS/AC and is the facility whose IACUC approved the protocol, that site would be held primarily responsible. Written agreements can help minimize and resolve potential problems.

9:56 Can an investigator appeal the decision of the IACUC relative to a protocol review decision?

Reg. The PHS Policy (IV,C,4) and the AWAR (§2.31,d,4) require that written notification of withheld approval include a statement of the reasons for the decision, “to give the investigator an opportunity to respond in person or in writing.” Nevertheless, IACUC decisions to withhold approval may not be overturned by a higher authority (PHS Policy IV,C,8; AWAR §2.31,d,8).

Opin. The above regulatory information suggests that a reconsideration by the IACUC should be an option. Furthermore, the “Supplementary Information” that accompanies the August 31, 1989 Federal Register containing 9 CFR Parts 1, 2, and 3 Final Rules (page 36132), states that “on the basis of the response, the committee may reconsider its decision.” This is another area for which the IACUC is advised to establish a written SOP.

9:57 What is an appropriate and effective mechanism for appeal of IACUC decisions. (See 9:56, 29:30.)

Opin. Some suggestions to consider in developing an SOP for appeals include:

- Assignment of IACUC members to work with the investigator to facilitate the process.
- Assignment of an IACUC member to be a “hearing” officer.
- Involvement of the “Dean for Research” or institutional equivalent as a “hearing” officer.
- Participation of the IO as a “hearing” officer.

In any case, the SOP must include a reconsideration of the protocol by the IACUC in light of the findings of the “hearing” officer. According to both the AWAR and PHS Policy an institutional official may not overturn a decision of the IACUC. (See 9:56.) Therefore, the IACUC must alter its own decision, which it can do (according to the AWAR) by a vote of a majority of a quorum at a convened meeting or via the designated member review process, although the latter method may not do justice to an appeal that really should be considered by the full committee.

9:58 Can a protocol for which approval has been withheld be resubmitted with modifications?

Reg. Yes, neither PHS Policy nor the AWAR precludes resubmission.

Opin. Resubmission of a modified protocol should be encouraged. A resubmission provides the investigator an opportunity to respond to the IACUC's review as allowed by PHS Policy IV,C,4 and the AWAR §2.31,d,4. The IACUC also may consider assigning a member to work with the investigator to develop a protocol that can be approved by the committee and allow the investigator's research program to progress. (See 9:56.)

9:59 Is there any institutional authority that can reverse the decision of the IACUC?

Reg. No. The AWAR (§2.31,d,2) state that "officials of the research facility ... may not approve an activity involving the care and use of animals if it has not been approved by the IACUC." The PHS Policy (IV,C,8) is nearly identical. (See 9:56, 29:32.)

9:60 At times, PIs who do drug testing may receive a test drug, but the manufacturer does not want to reveal what the drug is. Can the IACUC approve the use of the drug in animals?

Opin. It is not uncommon that a pharmaceutical company contracts testing of a new drug to an investigator in a research institution. Because such drug development is highly competitive, the company may not want to divulge the exact identity of the drug. This poses a problem for the IACUC charged with evaluating the effect of the drug on the welfare of animals. In order to approve the use of the drug, the IACUC must know at least the general class of the drug as well as its dose and route of administration, and any known risks to the animals. With this much information it is possible for the IACUC to approve use of the drug. However, a binding confidentiality agreement signed by all IACUC members may obviate this problem. (See 9:61.)

9:61 Sometimes PIs do not know which of a class of drugs they will use, either because there are many or because they don't know which will be available. Can the IACUC approve the use of a class of drugs in animals?

Opin. Sometimes an investigator wants to use a particular class of drug in a study, but he or she is unsure if or when a given drug will be used. The IACUC can approve the use of a general class of drugs if a list of drugs that might be used along with dose and route of administration for each one is provided. It would also be good to know the conditions under which each would be used. The IACUC may also require that the PI notify the Committee of which drugs are actually used either at time of continuation or in a special interim report. (See 9:60.)

9:62 The IACUC has a responsibility for initial review and continuing oversight of animal research projects. Sometimes projects involve adverse events or unexpected problems. What actions should the IACUC take, if any, when notified of these adverse events?

Opin. If the unexpected problem results in the deaths of animals, the IACUC may require the PI to submit interim reports, i.e., to report more often than annually as required by AWR and PHS Policy. The nature and duration of such reporting would be determined by the severity of the problem and its frequency. The IACUC may be required to increase its frequency of oversight when a federal agency determines that such increased oversight is necessary to ensure animal health and welfare.

9:63 An IACUC member requests that the IACUC reopen the discussion of a previously approved protocol. He was away when the protocol was approved, and he has concerns that were not considered during the review process. Can an IACUC re-examine the approval of a protocol under these circumstances?

Opin. The IACUC is charged with continuous oversight of research and teaching projects using animal subjects. Therefore, the IACUC *can* re-examine a protocol at any time it thinks it is necessary. If an absent IACUC member raises valid concerns that were not addressed at the time of initial or continuing review, these should be brought before the full IACUC. It should be noted, however that the project may have already been started and therefore the IACUC should include this fact in their reconsideration of a project.

9:64 Can an IACUC develop and/or accept SOPs in lieu of the investigator describing procedures in detail within a protocol? What special concerns might be generated by doing so?

Opin. The animal welfare regulations do not specifically preclude the use of SOPs. Nevertheless, there are some issues that should be considered. First, if the SOP is to be part of an animal use protocol, then it should be specifically reviewed together with the protocol that references its use. This is an important facet of the review process and clarifies what will happen to an animal from the beginning to the end of the study. If not, then all aspects of the protocol have not been reviewed by the IACUC. Secondly, when the SOP is modified, this would constitute a change in every protocol that references its use, and all associated protocols should be amended each time the SOP is modified. In addition, every investigator who uses the SOP should be aware of the change and adopt it. Changing an SOP without adoption by the investigator might well have the effect of putting him or her into non-compliance.

It might be possible for the institution to maintain different versions of the same SOP, but it seems to us that keeping track of which version goes with which protocols seems a difficult process.

9:65 For commonly used, well established clinical procedures, such as taking a blood sample from a dog's cephalic vein, should the IACUC request details of how the procedure itself will be performed?

Opin. The IACUC should ask for information about preparation of the skin for the sample, the volume of blood to be drawn, and the frequency of draws. It would not be necessary to ask for the angle of needle insertion and such items unless the IACUC was not convinced that the person doing the blood draw knew how to do it. Training should be required if personnel lack sufficient expertise.

9:66 Rather than providing details of an experimental procedure on an IACUC form, a PI provides literature references that clearly describe the details of what he will do. Should the IACUC consider approving this study with just the literature reference or should the actual procedure be part of the IACUC protocol?

Opin. The actual procedure should be part of the IACUC protocol so that it is clear what will be done as part of the experimental procedures. As necessary, the IACUC reviewer may choose to read the literature references.

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