

SCIENTIFIC MERIT AND ETHICAL REVIEW OF ANIMAL-BASED RESEARCH

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The following is a selection of frequently asked questions (and their respective answers) concerning the *CCAC policy statement on: scientific merit and ethical review of animal-based research* (CCAC, 2013).

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GENERAL CONSIDERATIONS

1. How are research proposals and animal use protocols linked?

Animal-based research work, as described in an animal use protocol prepared for an animal care committee, is typically conducted as part of a larger research project or program.

The animal care committee must receive confirmation from the principal investigator that the work described in a research animal use protocol is part of a research project or program that has been found to have scientific merit through independent, expert review, which should be confirmed by the research administration.

In turn, once the animal care committee has approved the protocol, it must confirm this to the research administration and principal investigator in order for funds to be released for the animal-based component of the research project.

2. Who is responsible for ensuring that research has scientific merit?

The organization's research administration is responsible for ensuring that research for which animals will be used has been independently reviewed by expert peers, and for ensuring that:

- peer reviewers are identified for each project that has not already been peer reviewed; and
- any concerns raised by the reviews are addressed before scientific merit is confirmed.

The person or persons with overall responsibility for research can be a vice-president of research, scientific director, research and development director, director-general, chief executive officer, dean, associate dean of research, or other persons in similar positions, depending on the type of organization.

Some institutions choose to establish a scientific committee, work with a scientific committee that has been established elsewhere or work with other institutions to establish their scientific merit review mechanism.

3. Who is responsible for ensuring that animal-based methods are appropriate for the proposed work?

Principal investigators and animal care committees are jointly responsible for ensuring that appropriate animal-based methods are selected and used.

Principal investigators are responsible for ensuring that appropriate methods are identified and explained within the context of their research objectives. They are encouraged to consider and include relevant replacement, reduction and refinement alternatives to live animal use as early as possible in their research program planning. In order to find, select and develop the most appropriate methods, investigators:

- are invited to consult the CCAC's Three Rs microsite;
- can choose to team with other research groups doing similar work to conduct thorough Three Rs searches in a given field every few years; and
- should work with their institutional veterinarians for live animal-based methods.

Principal investigators should provide complete information on their proposed methods to the animal care committee in animal use protocols. They may choose to append information such as brief, relevant grant proposal excerpts or scientific reviewers' comments to facilitate the protocol review process.

If animal use is described in a research proposal, it may be reviewed as a part of the scientific merit peer review process of the granting agency. Scientific reviewers may flag ethical/practical issues raised by the proposed animal use within a given research proposal. These should be conveyed to the research administration of the organization, which should ask the animal care committee to review them before approving any corresponding animal use protocols.

The animal care committee should review all of the information provided, ask questions of the protocol author as needed and discuss any further possible replacements, reductions or refinements of animal use. The animal care committee and protocol author should then agree on the final contents of the animal use protocol. In cases where there would be serious difficulties in adopting certain alternatives immediately but where they could be planned for and adopted in the longer term, the protocol author and animal care committee may agree to longer term implementation of alternatives.

4. Is animal use typically described in research proposals?

Depending on the nature of the research project or program and on the funding source's requirements, animal-based work may be referred to in a proposal, but the specifics of animal work are often absent from proposals. However, complete details on specific animal work, and on the animal-based methods chosen as part of the research, are included in animal use protocols submitted by principal investigators to the animal care committee.

There are several reasons why a description of the animal-based methods may be brief or absent in research proposals:

- the nature of the funding for which the researcher has applied and instructions with respect to the content of research proposals;
- grant review committee procedures; and
- difficulty in predicting that animal experiments will become necessary within a longer term research program.

In addition, where animal-based work constitutes a small part of the overall research program, it is less likely to receive focused peer review.

APPLICATION OF SCIENTIFIC MERIT REVIEW REQUIREMENTS

1. What kinds of projects need to be reviewed for scientific merit?

Basic and applied research must be reviewed for scientific merit. Scientific merit review does not apply to regulatory testing, teaching/training (except where students are being taught/trained as partners in research projects), animal health surveillance, or the production of animals or biologics for scientific purposes (except where production is part of a research project).

2. Does peer review of scientific merit need to be conducted on a yearly basis?

Research proposals are often funded for more than one year (generally up to five years) by sources with independent scientific peer review processes, and confirmation of scientific merit from these sources remains valid for the entire funding period. In these cases, scientific merit does not need to be reconsidered on a yearly basis.

In the case of research projects that are submitted to the institutional research administration for peer review, the author of the project should specify the proposed duration of the project, and the research administration should confirm the duration of the project to the animal care committee when it confirms that the project has scientific merit.

3. Who should determine whether a new study can be considered part of an existing research program?

The protocol author normally confirms to the animal care committee that a given study, as described in the protocol, is part of a given research program.

Where there are questions about whether a proposed new study is an extension of, or supplementary to, a peer-reviewed research program, the research administration is responsible for working with the principal investigator to determine whether or not the study is covered within an existing, peer-reviewed program, and for presenting its conclusions to the animal care committee.

4. Do pilot studies require peer review?

It depends on the nature of the study. If the purpose of the pilot study is to develop or evaluate a new method within the context of a peer-reviewed research program, a peer review of scientific merit is not necessary. However, if a principal investigator intends to use a pilot study to explore a new research direction that is not covered within the context of an existing peer-reviewed research program, the study should be peer reviewed for scientific merit.

5. Does animal-based research linked to start-up funds require scientific peer review?

Research that is undertaken with start-up funds requires scientific peer review unless it is associated with a previous project that has undergone scientific peer review. Where there are questions about whether a proposed new study is an extension of, or supplementary to, a peer-reviewed research program, the research administration is responsible for working with the principal investigator to determine whether or not the study is covered within an existing, peer-reviewed program, and for presenting its conclusions to the animal care committee. Generally, if a principal investigator intends to use start-up funds to explore a new research direction that is not covered within the context of an existing peer-reviewed research program, the study should be peer reviewed for scientific merit.

6. What if two reviewers have conflicting conclusion?

If concerns are raised by reviewers, the principal investigator should be given the opportunity by the research administration to address these concerns. If following this step, one reviewer concludes that there is scientific merit while the other does not, the CCAC's expectation is that each institution have a formal process in place to address this situation. It is the responsibility of the research administration to decide how to best manage conflicting reviews.

7. How should scientific merit be addressed for collaborative animal-based projects?

Collaborative animal-based projects can involve:

- one or more researchers working at a host organization's facilities; and
- a group of researchers from different organizations working collaboratively on different aspects of a shared project.

In all cases, the organizations involved are responsible for ensuring that animal-based research has been demonstrated to have scientific merit through a process that meets their standards, regardless of where the research takes place. The research administrations of the organizations involved should work together to ensure:

- that the project has been found to have scientific merit through independent reviews by expert peers; or
- that such a process will be applied (possibly by one organization on behalf of the others).

8. How should scientific merit be addressed for organizations with several sites, research stations or centres?

Organizations may be decentralized, with several sites, research stations, or centres that may be located in one area, across the country, or around the world. In these cases, the organization should normally decide on an overall strategy for scientific merit review – this may result in a centralized mechanism, a decentralized mechanism, or a combination of both. In all cases, these mechanisms should be well defined and should meet the [*CCAC policy statement on: scientific merit and ethical review of animal-based research*](#) (CCAC, 2013).

MECHANISMS FOR DETERMINING SCIENTIFIC MERIT IN DIFFERENT TYPES OF ORGANIZATIONS

1. How can academic institutions determine the scientific merit of basic or applied research?

Academic institutions rely in large part on funding sources that have publicly recognized peer review mechanisms. These sources, including federal and provincial granting agencies and some private (including charitable) organizations, use committees of expert peers (sometimes known as peer review committees or evaluation groups) to rate grant proposals and allocate funding. Confirmation of research funding through these types of sources provides organizations with evidence of scientific merit.

In cases where funding has not been awarded to a grant proposal that received above average ratings in the peer review process, an organization may choose to accept this positive rating (as determined by the funding source) as evidence of scientific merit.

Where members of academic institutions are funded through sources that do not have a mechanism for scientific peer review that meets CCAC policy, the research administration will need to ensure that the research project has scientific merit through a mechanism that involves independent peer review by at least two experts. When scientific merit is confirmed, the relevant animal care committee can choose to approve the corresponding animal use protocols.

2. How can government institutions determine the scientific merit of basic or applied research?

Research within government units (e.g., research stations, centres, or laboratories) can be funded by either the department's or agency's base funding (e.g., A base funding) or by other sources. For funding sources that do not have an independent peer review mechanism that meets CCAC policy, the government department or agency must be able to demonstrate that independent peer review by at least two experts has found that the research project has scientific merit before the relevant animal care committee can approve the corresponding animal use protocols. Animal care committees should expect to receive confirmation that a given project has scientific merit through this mechanism, and in no case should an animal care committee have to seek peer review itself or ask a protocol author to do so.

Some government departments and agencies have begun implementing scientific merit review policies and procedures under the responsibility of the senior research administration of the department or agency. This is particularly important for departments and agencies that have animal-based work taking place in a variety of units. Where several units operate within a department or branch, a coordinated approach to scientific merit is generally the most effective and efficient way to operate.

3. How can private organizations determine the scientific merit of basic or applied research?

Research conducted within private organizations, or funded by them, presents challenges related to guarding the privacy of information, patents, and other trade secrets in the peer review process. There are also challenges related to the size of the organization:

- within multinational private organizations, there are generally structured peer review processes that involve external expert advice at a higher organizational level than a specific research site; and
- for smaller organizations, a scientific advisory board, or equivalent, composed of external experts bound by confidentiality agreements can provide scientific merit reviews.

If this is not possible, the organization's research administration is responsible for defining a mechanism that involves at least two experts independent of the research group in question (preferably external or, at least, from one of the organization's other sites) who will review the work and provide the research administration with their conclusions. The research administration can then inform the animal care committee of the results.

Applied research undertaken on a candidate drug or device before moving into the regulatory testing phase may be undertaken by a contract research organization. Confirmation that the applied research has been found to have scientific merit should be provided to the contract research organization by the organization that has contracted it to undertake the animal-based work.

THE INSTITUTIONAL SCIENTIFIC MERIT REVIEW PROCESS

1. What tools can be useful in establishing organizational peer review processes?

Lists of Funding Sources

Organizations can compile lists of funding sources that have recognized peer review processes with appropriate independence and expertise. Principal investigators and the research administration can refer to these lists to check if a given research project has already been subjected to a peer review process that meets recognized standards, or if it will need to be peer reviewed through the organizational process. Organizations are invited to share these lists to assist each other in identifying all sources with sound peer review processes.

Databases of Reviewers

For projects that are either internally funded or that are funded by a source without a peer review mechanism with appropriate independence and expertise, it is recommended that the organization (or groups of organizations) establish a pool of reviewers with expertise in the fields in which the members of the organizations work.

2. What happens when a principal investigator's work is funded through a source that does not appear to have a recognized peer review mechanism?

In the case of animal-based research funded by a source that does not appear to use a peer review mechanism with appropriate independence and expertise, there should be communications between the principal investigator and the research administration about measures for ensuring scientific merit. The funding source may be able to demonstrate, to the research administration's satisfaction, that the project has been peer-reviewed by independent experts, and should be able to describe the process in writing.

Otherwise, the research administration should ensure that the scientific merit of proposed research is reviewed by at least two independent, expert peers. Any concerns raised by the review should then be addressed by the principal investigator, working with the research administration, before the animal care committee can receive confirmation from the research administration that the project has scientific merit.

3. What are the most important criteria in selecting reviewers?

Independence

To avoid any real or perceived conflicts of interest, reviewers must be independent of principal investigators whose project or program is being assessed. Conflicts of interest may arise from professional collaborations

or other relationships, past or present, personal or professional. Based on the criteria used by the federal granting agencies, scientists should not review a proposal when they:

- are from the same immediate department, institution, organization or company as the applicant, and interact with the applicant in the course of their duties at the institution;
- have collaborated, published or been a co-applicant with the applicant, within the last five years;
- have been a student or supervisor of the applicant within the last ten years;
- are a close personal friend or relative of the applicant;
- have had long-standing scientific or personal differences with the applicant;
- are in a position to gain or lose financially from the outcome of the application; and
- for some other reason feel that they cannot provide an objective review of the application.

Expertise

Reviewers should be recognized experts in the field in question.

4. How can these criteria be met?

To help ensure that the criteria of independence and expertise are met, the CCAC encourages all organizations – especially smaller institutions, where there are greater potential conflicts of interest among a limited pool of possible reviewers in each field of endeavor – to seek external reviews.

5. Who selects peer reviewers?

The persons selecting peer reviewers should have sufficient knowledge about the proposed areas of research, or have the research experience and judgment needed to seek appropriate expertise. Each organization needs to determine its own solution for selecting peer reviewers. Some examples that have worked well include:

- creating a scientific review committee with broad enough representation to identify appropriate peer reviewers in each field of endeavor;
- associate deans of research or scientific directors being responsible for selecting peer reviewers; and
- vice-presidents or associate vice-presidents of research working with other specialists to select peer reviewers.

In all cases, the research administration is ultimately responsible for the process. Most organizations can benefit from developing a database of reviewers that can potentially be used as a shared resource with other organizations. This database can be developed with suggestions from internal and external researchers.

Establishing a database and having independent persons with research expertise select reviewers and oversee the process will help to ensure that the process is appropriate and is independent from the project author and animal care committee, and that real or perceived conflicts of interest are avoided.

6. Can the animal care committee coordinator be involved in selecting peer reviewers?

Animal care committee coordinators can support the administration of the peer review process, once reviewers have been selected. However, they should not be involved in selecting reviewers.

Any concerns identified during the scientific merit review should be addressed by the principal investigator working with the research administration or institutional scientific committee.

7. What documents should be sent to reviewers? Is a completed animal use protocol form enough?

Reviewers should be provided with a project description that explains the objectives, hypotheses, potential contributions, and methodological approach of the study. Animal use protocols typically do not include all the necessary scientific information and are not structured to provide this information.

8. What should reviewers provide as evaluations of scientific merit?

Although organizations should determine the specific questions to ask reviewers, in general, reviewers should provide a written evaluation of whether the overall proposal has scientific merit and is likely to contribute to the body of knowledge within its field. The CCAC has developed a sample peer review form that can be used as a template.

RESPONSIBILITIES OF PRINCIPAL INVESTIGATORS

1. What can principal investigators do to help the animal care committee understand their proposed animal-based methods?

Principal investigators are responsible for:

- choosing the most appropriate methods for their work, in consultation with veterinarians and other experts as needed;
- detailing all animal-based methods in writing to the animal care committee within the animal use protocol forms provided for this purpose by the animal care committee;
- answering questions from the animal care committee on any aspect of animal-based work, including:
 - why animals cannot be replaced, if this is the case;
 - why the animal model and proposed numbers of animals have been chosen;
 - what refinements to animal use are proposed and what additional ones could be considered (in some specific cases, certain elements that would normally be refinements may not be appropriate, in which case the principal investigator should provide justification of the proposed choice); and
 - what can be learned from previous, similar work.

2. Can principal investigators forward information from grant proposals and information received through scientific merit reviews to animal care committees, in order to facilitate animal care committee review of animal use protocols?

Sections on animal-based methods from grant proposals and comments from peer reviewers are generally considered confidential, and can usually only be shared at the discretion of the principal investigator. However, principal investigators can choose to share this information with the animal care committee where the information is directly relevant to animal use, and the animal care committee should use this information in reviewing the relevant protocols and animal-based methods. When principal investigators share relevant grant proposal sections and peer reviewers' comments, it can reduce both the animal care committee's workload with respect to seeking information about animal-based methods and the principal investigator's workload in answering related questions from the animal care committee.

RESPONSIBILITIES OF THE ANIMAL CARE COMMITTEE

1. What can the animal care committee do to ensure that the proposed animal-based methods are appropriate for the work being planned, and that the Three Rs have been carefully considered and applied?

The animal care committee is responsible for:

- developing and implementing complete and appropriate animal use protocol review procedures (see the [CCAC guidelines on: animal use protocol review](#) (CCAC, 1997) and the [CCAC policy statement on: terms of reference for animal care committees](#) (CCAC, 2006));
- carefully reviewing the material forwarded by the principal investigator;
- checking with the research administration to ensure that the corresponding research project or program has received positive scientific peer review, and examining and using all relevant information, potentially including information and comments on animal-based methods from the grant proposal or the peer reviews;
- ensuring that animal care committee members (e.g., scientists and veterinarians) who are familiar with the field in question share their experience and expertise to help the animal care committee understand proposed methods and make informed decisions;
- asking the principal investigator any questions it has about the animal-based methods;
- ensuring that complete information is received from the principal investigator including (see the [CCAC policy statement on: terms of reference for animal care committees](#) (CCAC, 2006)):
 - why sentient animals must be used for the project;
 - why the animal model and numbers of animals proposed have been chosen;
 - what procedures are to be used on the animals and what refinements to animal care and use can be made; and
 - any other information considered important or necessary and pertinent, including information or results derived from any relevant previous work.

- considering consultations with independent experts to gain a better understanding of the methods, particularly where the pool of experts within an institution is small or where the work being proposed is new to the institution, followed by work with the principal investigator to arrive at the best possible methods for both ethical and scientific reasons;
- basing its decision on a protocol on:
 - all of the above information;
 - organizational policies and procedures; and
 - CCAC policy statements, guidelines documents and other CCAC-recognized standards.