

Guide to Ethics Committee Assessment of Project Applications under Scientific Animal Protection Legislation



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1 SCOPE

This guideline is intended to advise ethics committees on best practices to ensure a thorough, expert, robust and independent assessment is performed, prior to the submission of project applications to the HPRA. It also describes the evidence to be provided to the HPRA and included as supporting documentation as outlined in the 'Guide to Project Applications under Scientific Animal Protection Legislation'. It outlines the reasons why the HPRA values the input of ethics committees into the harm-benefit analysis and wishes to encourage their continuing role.

It is recommended that ethics committee members read the applicable legislation, and in particular make themselves aware of the role and duties of the animal welfare body, as well as retrospective assessment requirements, in order to establish or adapt their terms of reference so that they are appropriately aligned to the requirements of the legislation.

2 INTRODUCTION

The guidance in this document is intended to set out the parameters for what the HPRA considers to be a robust ethical review and to outline the requirements for making a project application to the HPRA. In framing this document, the HPRA has considered the wide diversity and size of establishments involved in the use of scientific animals in Ireland.

Ethical review is a process that aims to ensure that at all stages in scientific work involving animals, including their use for educational purposes, from initial planning, through study conduct and completion as well as the review of the study outcome, there is adequate, clearly explained 'ethical justification' for using and carrying out procedures on animals.

Ethics committees are responsible for reviewing the proposed use of animals at a local level. They have a role in ensuring that research conducted at the user establishment is in line with the ethos of that establishment. In the case of certain user establishments, they are also required to support the publication of research outcomes in peer reviewed literature. Ethics committees consider the study design, procedures planned and evaluate situations where there might be a risk that the use of animals could be in conflict with the best welfare interests of the animals involved. They are instrumental in ensuring that the 3R principles (~~replacement~~Replacement, ~~reduction~~Reduction and ~~R~~refinement) are applied in a meaningful manner. Therefore, they play a key role in ensuring high standards of animal welfare and in assessing the harm-benefit balance of any proposed study.

[Article 38 of Directive 2010/63/EU and Regulation 31 of the Regulations require the HPRA to perform an evaluation of every project application before issuing a project authorisation.](#)

The HPRA wishes to ensure that before new project applications are submitted to the HPRA for mandatory ~~and independent harm-benefit analysis~~project evaluation, that a preliminary ethical review has already been conducted. This is seen to be in the best interests of animal

welfare and ~~in-to improve~~ the overall efficiency of the process. There is no legal requirement in the legislation for a local ethical review process to be conducted. However, the HPRA is aware that a number of ethics committees already exist that carry out ethical reviews prior to submitting project applications. The HPRA considers that the review conducted by a user establishment/local ethics committee will continue to be of benefit, as it will be based on a sound understanding of the local context in which the user establishment operates, including governance arrangements for the envisaged project, as well as the facility infrastructure, knowledge of the project manager's resources and compliance record, and local animal husbandry and care arrangements. Such consideration is expected to complement the assessment of the project application conducted by the HPRA, e.g. as any issues with a project application that have already been resolved by an ethics committee are not likely to be queried again during the HPRA project evaluation. However, the HPRA must be made aware of these all issues during the application process and: a report outlining project queries that have been raised and addressed, or alternatively all correspondence between the ethics committee and the applicant should be submitted as part of the HPRA project application. The ethical review might be conducted either by each individual user establishment, or by a committee mandated to act on behalf of a group of user establishments. In the case of the latter, it would be necessary for the ethics committee to have a formal contract in place with the user establishments involved before protocol submission so that the recommendations and conclusions of the ethics committee are binding on the parties concerned.

It is appreciated that prior to and during study conduct, it might be necessary to make changes to the authorised project (i.e. study protocol) as either project amendments or project deviations.

- ~~Project amendments are intended and planned changes to the protocol, which are described, justified and approved in advance of the study conduct. This document does not address project amendments specifically, other than to advise that amendments that negatively impact on animal welfare should be reviewed by the ethics committee. This is a matter which should be considered by the ethics committee in its terms of reference.~~
- ~~Project deviations are unplanned changes which are necessary during the conduct of a study. In accordance with Regulation 63(1) and 63(3) of S.I. No. 543 of 2012, as amended by S.I. No. 434 of 2013 and S.I. No. 174 of 2014 (hereafter referred to as 'the Regulations') any deviations which negatively impact on animal health or welfare and which vary from the terms and conditions of a project authorisation must be recorded and provided to the animal welfare body of the user establishment concerned. The HPRA considers that this notification should happen within a reasonable period of time (within six weeks). The HPRA plans to review such records during its inspections of the user establishment. It is therefore recommended that in developing the terms of reference of the ethics committee that it also considers the position of the animal welfare body and the specific duties of that body. The HPRA is open to the integration of the ethics committee with the animal welfare body, or to other governance~~

~~arrangements such that both bodies work closely together for the benefit of animal welfare and are informed of each other's decisions (as relevant). Project deviations e.g. increasing the frequency of a procedure or an increased severity classification of a procedure will require a project amendment application. Refer to the 'Guide to Amendment and Renewal Applications for Projects under Scientific Animal Protection Legislation' for information on submitting amendment applications.~~

Article 38 of Directive 2010/63/EU and Regulation 31 of the Regulations require the HPRA to perform an evaluation of every project application before issuing a project authorisation.

There is no legal requirement in the legislation for a local ethical review process to be conducted. However, the HPRA is aware that a number of ethics committees already exist that carry out ethical reviews prior to submitting project applications. The HPRA considers that the review conducted by a user establishment/local ethics committee will continue to be of benefit, as it will be based on a sound understanding of the local context in which the user establishment operates, including governance arrangements for the envisaged project, as well as the facility infrastructure, knowledge of the project manager's resources and compliance record as well as local animal husbandry and welfare conditions. Such consideration is expected to complement the assessment of the project application conducted by the HPRA e.g. any issues with a project application that have already been resolved by an ethics committee are not likely to be queried again during the HPRA project evaluation; however the HPRA must be made aware of these issues during the application process. A report outlining project queries that have been raised and addressed or alternatively all correspondence between the ethics committee and the applicant should be submitted as part of the HPRA project application.

3 COMPOSITION OF ETHICS COMMITTEES

An ethics committee must contain sufficient members to ensure that there is a wide range of expertise and persons with different perspectives to facilitate a comprehensive and detailed review of the relevant factors in ethical evaluations. ~~While some of the functions attaching to the animal welfare body may duplicate those required for the assessment of harms and benefits, the HPRA considers that the ethics committee needs to reach its own judgment of the harm benefit analysis and must therefore be adequately constituted to undertake this task, regardless of animal welfare body involvement.~~ A diverse range of beneficiaries may also be needed in order to assess the potential benefits of the proposed study. The HPRA considers that for the committee to be in a position to consider project applications with the necessary objectivity, it must consist of at least six persons (but preferably substantially more to provide more robust scrutiny of proposed projects and to allow for occasional absences of members). All persons involved in the ethics committee are expected to be familiar with, and be able to provide evidence (e.g. signed and dated records of having read and understood relevant documents and reading material) that they fully understand the 3R principles.

This document does not detail the precise terms of appointment of members to an ethics committee, but the HPRA would suggest that members should be appointed to serve a three year term (renewable), with care being taken to ensure that the appointment of members is staggered over time. The committee should also consider having a vice-chair.

The expertise that an ethics committee would be expected to include are:

- the designated veterinarian [\(DV\) or expert](#) who is charged with advisory duties in relation to the well-being and treatment of the animals,
- the animal care and welfare officer(s) who is responsible for overseeing the welfare and care of the animals in the user establishment,
- one or more representative(s) of the research community, or those with current or recent experience in the conduct of procedures in animals,
- a public interest representative independent of the research being conducted at the user establishment (i.e. a 'lay' person), and
- a statistician or person with expertise in statistical analysis.

It is recommended that additional participants are included where possible to enhance the value of the ethics committee's assessment. Such members might include:

- an ethicist or member of an ethical review group for clinical trials in humans,
- a patient representative,
- a specialist in ~~a-the~~ particular animals species being investigated, ~~and/or suitably qualified expert and~~
- additional animal technicians or members of the research community.

Additional members may be temporarily appointed to the committee from time to time to provide specific expertise when necessary.

The chairperson should be a person of standing or with significant responsibilities in the institution, such as a president or vice-president of research, dean, professor, director or senior executive with a demonstrable track record in dealing with complex issues and the ability to chair meetings [and forge consensus](#) where different perspectives are being sought.

It is possible that a member of the ethics committee may have skills in more than one scientific discipline; this is acceptable provided consideration is given to each of the various perspectives as described above and that any conflicts of interest are declared and managed appropriately.

It is appreciated that not all facilities or establishments have access to the breadth of expertise for membership of the ethics committee described above. Where an establishment is not sufficiently large to have sufficient personnel available of the requisite background to form its own ethics committee, the HPRA considers it appropriate that it could engage the services of an ethics committee from another establishment to carry out the tasks described.

4 FUNCTIONS OF SPECIFIC COMMITTEE MEMBERS

4.1 Designated veterinarian

If projects relate to laboratory animals, the ~~designated veterinarian~~DV should be an individual with experience of and specialist training in laboratory animal medicine and ~~ideally will have specialist training in the area and in~~ the application of the 3R principles. This person would ideally be affiliated to the user establishment and have familiarity with the conduct of procedures being undertaken. In relation to projects involving farm animals, the person involved should have species-specific training in the 3Rs and ~~/or in the design of experimental trials~~experimental design. Likewise, in projects involving birds, fish or wild animals, the person involved should be educated in the 3Rs and have obtained specific training in the husbandry and welfare of the species involved and in the principles for the conduct of ~~trials~~projects in such animals.

The function of the ~~veterinarian~~DV is to uphold the welfare of animals, and ensure that the 3R principles are being correctly applied. The veterinarian should also be able to provide a view on the technical feasibility of the proposed project and the procedures to be conducted, and on the acceptability of the proposed humane end-points, the level of severity of the project and the adequacy of harm-mitigation measures, particularly the use of anaesthesia and analgesia.

4.2 Animal care and welfare officer(s)

The animal care and welfare officer(s) is expected to be the person(s) listed in the user establishment's authorisation. In practice, it is often ~~the a~~ senior technician involved in the care of the animals. This person is expected to be familiar with the practical conditions under which the animals are kept at the establishment or in premises where projects are to be conducted. They are expected to be knowledgeable about the husbandry and welfare of animals under study, ~~and be~~ educated in the 3R principles and familiar with the conduct of procedures.

The function of this person is to ensure that the 3R principles are being applied correctly and that the care and welfare of animals proposed for study takes into account the animals' natural behavioural needs ~~and that the 3R principles are being applied correctly~~. It is recommended that more than one such person should be nominated to the ethics committee where possible.

4.3 Representative of the research community

The representative(s) of the research community will have a scientific, life-science based qualification and experience of research involving animals and/or in the conduct of procedures in animals. They should be educated in the 3R principles.

This will be one or more persons, not directly connected with the project under discussion, who can comment on the validity of the proposed protocol, including the study design and procedures envisaged, and attest to the proposed benefits which may accrue.

4.4 Public representative ('lay person')

The public representative may be either an external person or an internal person from a discipline outside of the biological, medical, chemical, medical device or veterinary field. The person should not have a bio-medical or health professional background and should not work in scientific research. This person's role is to give a public or non-scientific view of the proposal. It is important that the individual has the ability to understand the sometimes complex issues involved in reaching ethical decisions, ~~and~~ is appropriately trained to contribute to the committee and feels able to ask pertinent questions. The function of this person is to ensure that the proposed study is merited i.e. the scientific gain envisaged outweighs the costs in terms of animal use and potential animal suffering. Examples of an internal lay person would include a professor of English, university librarian, accountant, personnel from human resources, ~~a member of an IT department, chaplain, retired lecturer in a discipline unrelated to scientific animal research~~ etc. Examples of an external lay person would include a ~~primary school teacher, a secondary school teacher other than a science teacher, a member of the army, police, clergyman, retired civil servant~~ etc.

4.5 Person with experience in statistical analysis

A person with experience in statistical analysis and statistical design is required for most bespoke research projects. ~~Their role is, in order~~ to ensure that the proposed study is adequately designed and planned to ensure that the ~~minimum possible~~ most appropriate numbers of animals are used. ~~This is important as it will, whilst still in order to maintaining~~ ensure the scientific validity and reliability of the results. Ideally this person should have prior training or expertise in the evaluation of animal studies. If this person

~~This person does not need to be a permanent member of the committee, but if they provide~~ input into the ethical review of any project, and ~~give their recommendation for a project's ethics application to be approved~~ approves the experimental design, evidence of their ~~ir~~ approval ~~of this statistical expert~~ must be provided to the HPRA, along with ~~in~~ the approval letter for new project and ~~amendment~~ project amendment applications, where relevant.

4.6 Other ethics committee members

4.6.1 Persons with special expertise

Specialists, such as animal-based ethicists, may also be required on occasion to [provide moral guidance and to](#) assist with [questions in relation to](#) the correct application of the 3Rs.

4.6.2 Researchers

Additional researchers or those with experience in the conduct of procedures on animals may be able to provide additional value to the discussion. However, researchers should absent themselves from any discussions or assessment of projects in which they have an interest e.g. projects submitted by their colleagues from the same user establishment on which they have a role as a direct collaborator.

The HPRA advises that the [research proposers/applicant](#) whose project is under review engage with the committee in the review process, as they hold the responsibility for what happens to the animals in practice. This does not mean they should be in attendance at actual deliberations by the ethics committee but some dialogue should be facilitated, to help clarify the submission where needed.

5 TRAINING FOR PARTICIPANTS OF THE ETHICS COMMITTEE

It is mandatory that all members of the ethics committee understand the 3R principles and [the Scientific Animal Protection Legislation](#). It is advisable that at least two members of the committee have completed an [HPRA](#)-approved [scientific](#) animal training course.

The HPRA [expects to may](#) examine the role profiles and training records of the members of the ethics committee as part of its inspections [of establishments](#) in order to verify that the committee members are aware of their duties and have the necessary skills to undertake them effectively.

6 WHAT THE HPRA EXPECTS FROM THE ETHICAL REVIEW PROCESS

The fundamental basis for ethical review is the harm-benefit [assessment/analysis](#), in which the potential harms likely to be caused to animals used in a [research](#) project are weighed against the likely potential benefits of the work. A key part of a harm-benefit [assessment/analysis](#) is the evaluation of the application of the 3Rs ([R](#)eplacement, [R](#)eduction and [R](#)efinement). This will involve ensuring that:

- (i) A scientifically satisfactory method or testing strategy, not entailing the use of live animals, is used instead of a procedure, where it is available,
- (ii) The number of animals used in projects is reduced to a minimum without compromising the objectives of the project, and

- (iii) Refinement of breeding, accommodation and care, and of methods used in procedures, eliminating or reducing to the absolute minimum any possible pain, suffering, distress or lasting harm to the animals is undertaken.

The harm-benefit [assessment-analysis](#) process involves the following three elements.

6.1 Assessment of the potential benefits of the project

The HPRA acknowledges that general guidance may not be suitable for all project applications but expects that a robust ethics review would consider the following questions:

- How will the results add to existing scientific and/or clinical knowledge? What practical applications, if any, are envisaged at this stage?
- What is the potential value of these insights and/or applications?
- Are the objectives of the study original in relation to previous or ongoing studies?
- Are the objectives timely (in relation to other studies) and realistic?
- If there is an element of replication of previous work? If so, how strong is the case for this replication and what efforts have been made to avoid mere duplication?
- If this is ongoing work i.e. a sub-project of a larger overall project, how does the present proposal relate to what has gone before? What progress was made in previous studies, and what scientific or other benefits have resulted that will contribute to the overall project objective?
- What is the relevance of this project to other studies in this field of research and what might be the implications for other areas of research, if any?
- How has the assessment of the potential value been determined or corroborated by evidence?

6.2 Assessment of the potential benefits being realised

The HPRA notes that the criteria in section 6.1 might not be demonstrable in every case. Where appropriate the assessment of the likelihood that the potential benefits will be achieved would address the following questions:

- Is there a realistic prospect that the results are achievable with the time and other resources that are available for the study conduct?
- Are the numbers and species of animals used and the use of controls appropriate and how well has this choice ~~has~~ been informed by statistical input or expert advice?
- Do those involved in the study have the necessary expertise or competence in the specific area of interest, and is appropriate training foreseen for new research workers and those involved in the conduct of the procedures?
- Can the envisaged work be completed at the establishment or in the facilities proposed?
- [Is there sufficient funding in place for the entire duration of the proposed project?](#)
- Can the project be completed within a reasonable period of time? Is the project complex and/or ~~expected~~ to continue for many years and/or ~~dependent~~ on the outcome of another project?
- Is a pilot study ~~is~~ needed before proceeding to the main project?
- Do those nominated as project managers (or deputy project managers) have the necessary expertise, time and resources to ensure its proper conduct and reporting?
- Do those nominated as project managers, as well as those carrying out procedures or euthanasia hold the necessary individual authorisations from the HPRA?
- Do those nominated as project managers have previous experience of managing projects and if so, have they ~~have~~ achieved their objectives in previous projects? This may require review of their publication history.

6.3 Assessment of the extent of any harm or suffering

In relation to the assessment of the harms caused to animals and possibilities for reducing these, the HPRA expects that a robust ethics review would address the following questions:

- Is there a need to use animals at all (have non-animal alternatives been considered or does the data exist from previously conducted studies)?
- Are the numbers of animals to be used reduced to a minimum without compromising the objectives of the project?
- Are the species, strain, [sex](#) and age of animal to be used the most appropriate?
- Is the severity of the potential harms in the proposed studies accurately described and have appropriate mitigation measures (e.g. anaesthesia, analgesia) ~~have~~ been taken to minimise them? This should also include consideration of the humane end-points proposed as well as any opportunities for refinement in the conduct of the procedures themselves, the duration of the procedures and any follow-up.

- Is the husbandry and welfare of animals prior to, during and following procedures, optimal (including consideration of the need for natural and social behaviour, environmental enrichment, etc.)?
- What is the fate of the animals at the end of the procedures, including any proposed reuse of animals, and the method of euthanasia proposed (if relevant), and is this appropriate?
- Do the individuals responsible for carrying out procedures have the necessary competence and if not, will they receive the required training?
- ~~Is~~ **Are** the choices of anaesthesia and analgesia and/or provision of other care ~~are~~ optimal?

It is important to note that carrying out a harm-benefit analysis is not a quantitative process. Assessments of harms and benefits are matters of judgment, informed by expert opinion. This is why an ethics committee should have members from a variety of perspectives, in order to ensure the integrity of the process and to achieve the best possible outcomes.

7 MEETINGS OF THE ETHICS COMMITTEE

Meetings of the ethics committee should be organised to allow members sufficient opportunity to voice opinions and engage in discussion. Such interactions are expected to help ensure that the ethical review is informed by, and responsive to, a range of different perspectives.

Meetings should be conducted in a formal manner, based on an agenda and relevant documentation circulated to members beforehand. A quorum should be established to ensure that the deliberations are sufficiently robust. Quorums are generally half the membership of a committee plus one. In the case of a committee of six persons, the HPRA would expect the quorum to be four. Within the quorum, the ratio of scientists to other members should remain balanced. The quorum should always include [a veterinarian and](#) an animal care and welfare officer, and it is strongly advised that ~~the designated veterinarian and the statistician is part of the quorum. However, where it is not possible for the designated veterinarian to consistently be a part of the quorum, at the very least they should always be present for the review of projects involving procedures classified as severe.~~

The HPRA is aware that it might not always be ~~necessary feasible to hold for~~ a face-to-face meeting ~~to be held but and~~ that opinions and decisions might also be taken by electronic means [on some occasions](#). This is acceptable to the HPRA as long as evidence is provided that the members concerned actively contributed (as evidenced ~~e.g.~~ by the existence of e-mail correspondence in respect of proposed projects). As the HPRA understands the effectiveness of decisions taken by a committee using remote tools (i.e. virtual meetings by teleconference) for proper interaction to take place, members should be familiar with each

other through prior face-to-face meetings. The HPRA would expect therefore that the ethics committee should meet face-to-face all together at least once annually.

The chairperson should manage the meeting to ensure that any potential conflicts of interests are declared and the members in question absent themselves from the relevant agenda items. The chairperson should manage discussions to ensure that all those present are encouraged to engage and give their opinions.

Whether the ethical reviews take place face-to-face or virtually, a record (i.e. minutes) must be taken. The minutes must document the following:

- The names of those who have participated.
- Whether any of those participants have a potential conflict of interest in relation to any project application.
- Whether any person with a declared conflict of interest was present or absent for the duration of the discussion and decision in relation to the relevant project(s).
- In relation to each proposed project, the following should be documented:
 - o The key points of discussion
 - o The decision and reasons for the decision
 - o Whether the decision was taken unanimously, or by majority or by consensus
 - o Whether there are any conditions ~~attaching~~ attached to the approval,
 - o Any other information likely to be relevant ~~to~~ for the HPRA's consideration.

8 OUTCOME OF REVIEW AND DOCUMENTATION REQUIRED BY THE HPRA

In order to verify the efficacy of the ethics review, the HPRA will expect to receive the following associated documentation in order to assess each project application:

- A copy of the project protocol as approved by the ethics committee.
- A copy of the letter of approval of the ethics committee that identifies any conditions for the conduct of the proposed project. ~~This should include a list of all ethics committee members and any additional persons (where relevant) that have reviewed and approved the project application.~~
- A report outlining project queries that have been raised and addressed. Alternatively, correspondence to and from the ethics committee relating to the project in which queries have been raised and addressed should be submitted.
- ~~Evidence of the input of a statistician, such as a signature on the approval letter. A signed letter of recommendation from a biostatistician, where relevant.~~
- ~~A letter of recommendation from the animal welfare body (only relevant where an increase in severity classification has occurred).~~

~~In addition to the information submitted with the project application, where several projects are to be submitted during the course of the year, a copy of the membership, qualifications~~

~~and individual roles of the ethics committee should be submitted to the HPRA once annually at the beginning of the year. If there are changes in the membership in the interim, these must be notified within one month.~~

~~During the conduct of the inspection of relevant user establishments, in order to be in a position to demonstrate that the ethics committee procedure has been sufficiently robust, the HPRA will expect to see the following documentation:;~~

- ~~- Terms of reference~~
- ~~- Membership and qualifications of participants~~
- ~~- Exemplary Copies of minutes or records of meetings, including records of participation (whether by physical presence or otherwise)~~
- ~~- Information on procedure for handling conflicts of interest of members~~
- ~~- Agendas of previous meetings~~

~~The HPRA will expect to have available records of meetings of the ethics committees (including agendas, minutes, participants, records of individual contributions) and will review them at time of inspection of the user establishment concerned. The HPRA expects that from these documents it can determine how the harm-benefit assessment was conducted and how the decision was made.~~

9 — HPRA ASSESSMENT CRITERIA

~~The HPRA will expect to see the following documentation during the conduct of the inspection of relevant user establishments in order to be in a position to demonstrate that the ethics committee procedure has been sufficiently robust:~~

- ~~— Terms of reference~~
- ~~— Exemplary minutes or records of meetings, including record of participation (whether by physical presence or otherwise)~~
- ~~— Information on procedure for handling conflicts of interest of members~~
- ~~— Agendas of previous meetings~~

109 CONCLUSION

The HPRA is conscious that, as the competent authority under the legislation, it has a duty and legal responsibility to perform its own independent project evaluations. However, the HPRA ~~understands the values of~~ the role of ethics committees and wishes to encourage their continued involvement in the future.

The proper conduct of a harm-benefit analysis can be quite complex with no specific mathematical formula available to deliver a decision. The assessment of harms and benefits are matters of opinion, informed by experts, where the eventual decision involves careful

consideration and a balanced judgement. Moreover, the mitigation of certain identified harms and risks might be addressed by the establishment of specific and bespoke conditions ~~attaching-attached~~ to the conduct of the project. These are intimately linked to the design of the proposed project, as well as those personnel responsible for its management, ~~and~~ conduct and other logistical factors related to the setting involved, ~~and~~ the operation of the establishment. Accordingly, the HPRA wishes to benefit from the prior review of the ethics committee before reaching its own judgment. However, for the HPRA to fully carry out its duty, it must ensure that the ethics committee process has been truly thorough, independent, expert, and robust.

The HPRA will review the application of this guidance periodically based on ongoing experience.