Ethical Review of Animal Experiments: Current Practice and Future Directions

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Summary

Over the last 20 years, ethical review of animal use in research, testing, and teaching, has developed significantly across the world. However, the expectations and outcomes of the process can vary widely. This is not surprising, given that interpretations of ethics and ethical review processes, as well as ethical values and judgments, inevitably differ between individuals, roles, and research institutions, between societies, cultures, and legislative contexts, with differing historical precedents and timelines. Some countries have long experience with ethical review processes; some are just beginning to embrace the principles. It would seem beneficial and timely, therefore, to start to work toward harmonized, worldwide, "guiding principles." This presentation will discuss ways in which the ethical review process is, or could be, designed to achieve specific outcomes, drawing on available guidance from around the world.

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1 Introduction

Over the last 20 years, ethical review of animal use in research and testing has developed significantly around the world. Some countries have long experience of carrying out ethical review; others are only beginning to embrace the principles. It seems beneficial and timely, therefore, to start to work towards worldwide harmonized "guiding principles and good practice guidelines" that could be used within the context of different legislation, cultures, and traditions.

Harmonization within this field is likely to be an ambitious aim. This is partly due to the nature of ethics and ethical review. In "doing ethics" we move beyond consideration of what is *possible* to do and make choices about what *ought* and ought not be done. These choices are matters of judgment that, by their nature, are contestable and likely to vary between individuals, roles, and establishments; between societies, cultures, and legislative contexts; with differing historical precedent; and over time (Smith and Boyd, 1991). It is, therefore, entirely reasonable to anticipate variations in attitudes, expectations, and outcomes of ethical review, which may make a harmonized approach difficult.

There are also differences in the interpretation of the terms "ethical review" and "ethical review process." For some people, both refer solely to the weighing of harms and benefits of a research project, whereas others regard "the ethical review process" as a wider system of oversight of animal use, covering ethical review of projects but also addressing on-going issues relevant to the establishment as a whole, such as working to promote and enhance implementation of the 3Rs, considering issues arising in animal husbandry and care, and needs for staff training[1]. It is the latter, broader interpretation – the ethical review process as a system of oversight – that this paper will address.

Similarities and differences between processes of ethical review

There are already many good statements of principle (e.g., ICLAS, 2010) and detailed documents describing organizational aspects of ethical review processes (e.g., from Australia, Canada, Europe, New Zealand, and the US[2]). These include many points of agreement on the structure and functions of effective ethical review processes, as well as many similarities in the information input required for the ethical evaluation of research involving animals.

Of course, there are also differences between countries in, for example, the level of authority of the ethical review process and its scope of interest. The name also differs. Some processes explicitly recognize the ethical review aspect of their role in the name: for example, Animal Ethics Committees (AECs, Australia and New Zealand), Ethical Review Processes (ERPs, UK). Others emphasize the animal care role, for example Institutional Animal Care and Use Committees (IACUCs, USA) and Animal Care Committees (ACCs, Canada), although these processes also have a role in ethical review. Internationally, the greatest difference probably is whether the ethical review proc-

[1] Note that "ethical review" is sometimes reduced just to application of the 3Rs. This is convenient for those who want to avoid debate over the balance between harms and benefits, but is not its proper meaning.

[2] See: Australian Government National Health and Medical Research Council (2004); Canadian Council on Animal Care (2006); Europe: FELASA (2007); New Zealand Ministry of Agriculture and Forestry (2000); and US: ARENA and OLAW (2002).

ess operates at an institutional, regional, or national level, and whether it is one part of the regulatory process (as in the UK, for example) or, in itself, forms the regulatory process (as in Australia, Canada and New Zealand).

Even within a country there are likely to be differences in the structure and working practices of ethical review processes, particularly where these operate at the institutional level. This is inevitable given that establishments differ in size, the number and nature of projects (e.g., goals of the work, numbers and types of animals and procedures used, and the severity of adverse effects caused to the animals), and culture (e.g., degree of business or academic freedom for staff, type of management structure, level of senior management support for the review process and for animal care and veterinary staff, the "drive" of key players in the process, and the importance placed on training and communication).

2 Developing harmonized guidance

Despite these differences, it is clear that there is sufficient agreement on the *underlying principles* of ethical review processes (as set out in existing documents such as ICLAS, 2010) to facilitate harmonization in this respect. Translating established principles into workable and worthwhile practical review systems that have similar expectations and can achieve equivalent outcomes is likely to be more problematic, since it is the expectations and outcomes of ethical review that vary. This is where development of harmonized guidelines could most usefully be focussed, providing encouragement for people to focus more on what ethical review should achieve and developing easily accessible *practical* guidance to help in doing so.

The question remains of whether to harmonize to a minimum standard or to current best practice[3]. Existing well-developed systems for ethical review may not, at least initially, translate easily to countries that have regulatory systems or research processes at an earlier stage of development. Clearly, implementing good ethical review processes will not always be easy, but the many advantages (for both science and welfare) are widely accepted, so we would argue that it is best to aim high – for universal "best practice."

2.1 Harmonizing the aims and scope of ethical review processes

As a first step, it is important to develop a common understanding of what the aims and objectives of an ethical review process should be so that a harmonized aim and scope, applicable to all types of ethical review process, can be defined. A number of documents are helpful in this respect. The UK Home Office (2000) summarizes the aims of the local ethical review process (ERP) as providing: "*a local framework acting to ensure that all use of animals is carefully considered and justified; that proper account is taken of all possibilities for reduction, refinement and replacement; and that high standards of accommodation and care are achieved*."

This aim is echoed in other guidelines, for example by CIOMS-ICLAS (2011, in press), which emphasizes the educational and awareness-raising role of review processes in developing "*a culture of care and conscience*" within the institution. FELASA also makes this point, stating that "*Ethical review processes should not be merely* "*committees for review of particular projects" but should aim to permeate and influence the ethos of every institution in which animals are used – creating an appropriate "culture of care" and providing advice and resources to ensure proper consideration of ethical aspects and application of the Three Rs in all scientific work involving animals*."

The ethical review process, therefore, can be viewed as a vehicle to stimulate greater awareness of ethical, welfare, and societal issues such that everyone plays their part in practicing "ethical science." Adding this aspect to the Home Office statement would provide a clear and concise overarching aim for ethical review processes around the world, showing that they are a valuable asset *at an institutional level*, whatever the nature of the regulatory system. This was another point recognized by FELASA in its report on ethical review in Europe (FELASA, 2007), in which it emphasized that: "*ethical review should be based on a sound understanding of the local context in which the procedures are performed*." A key tenet of harmonized guidance, therefore, should be to emphasize the importance of developing ethical review processes at an institutional level.

2.2 Harmonizing the functions of ethical review processes

Despite all of the above, much of what is written about ethical review at the moment focuses on procedures for project (or protocol, or program, depending on terminology) evaluation and the factors that need to be taken into account. However, the broader aim defined above applies not only to project evaluation but to animal use within an institution more generally, and it can be broken down into a set of specific functions (of which project evaluation is one). Thus, "ensuring that all use of animals is carefully considered and justified" encompasses both prospective project evaluation and interim and retrospective review (see Jennings and Howard, 2005 for further discussion). Specific tasks identified are: ensuring that high standards of animal care and accommodation are met and that proper account is taken of all possibilities for implementation of the 3Rs. Additional functions could include:

[3] The new EU Directive 2010/63 provides an example where only minimum standards have been applied. The need for evaluation of projects (i.e., the prospective harm/benefit aspect of ethical review) is well set out in the new legislation, but the concept of an institutional ethical review process was diminished during the drafting to an Animal Welfare Body, albeit with responsibilities for 3Rs advice and housing and care, but with no explicit role in ethical evaluation of projects, and a requirement for only two members – "the person or persons responsible for the welfare and care of the animals and, in the case of a user [establishment], a scientific member" (European Commission, 2010). This is disappointing given the many good examples of ethical review processes throughout Europe (FELASA, 2007).

– working to reduce animal wastage and encourage the sharing of tissues and organs;
– ensuring that the most humane methods of killing are used;
– ensuring that staff undertake appropriate education and training and have access to appropriate advice on matters related to ethical issues, legislation, and the welfare of animals in their care; and
– providing a forum for discussion and communication on issues relating to the use of animals that arise both internally and externally.

"Ensuring compliance with legislation" could also be added to the list, but that would depend on the regulatory context. FELASA, states that: "*For effectiveness and credibility, it is vital that all ethical review processes have means of ensuring that their decisions and recommendations actually are implemented in practice. The power to stop animal studies when, for example, authorizations are exceeded or unexpected adverse events occur that prejudice their justification, should be built into the process*."

Project evaluation

All the major ethical review systems, whether regulatory or supplementary to legislation, have similar documentary requirements, particularly with regard to *information input* but also with regard to many of the administrative or operational issues. All require information on scientific objectives, species, and numbers of animals, experimental design, the 3Rs, and adverse effects, and most have some requirement for ongoing or retrospective review, so in a sense, there is already a harmonized approach to information input.

However, there are some significant differences in how the information is used. There are different views on whether ethical review should involve assessing the scientific benefits of a research project and the likelihood that these will be achieved in practice. In the USA, for example, there is debate about whether and how far IACUCs should consider scientific merit in protocol review, what "scientific merit" means in practice, and whether it is acceptable to delegate scientific merit review solely to funding agencies. The USA legislative and policy guidelines seem unclear on the matter. Some commentators argue that IACUCs lack appropriate expertise and that their consideration of scientific merit is a "violation of academic freedom." Others conclude that IACUCs do have a responsibility to review scientific merit, at least at the level of experimental design, but observe that "the jury is out" on whether they should examine the scientific importance of studies so as to weigh them against harms (Silverman et al., 2006, pp. 112-114; Mann and Prentice, 2004).

Elsewhere, where consideration of reasons for using animals and weighing against harms is part of the review process, there may still be debate about whether and how far animal ethics committees should consider scientific merit and potential benefits, especially when work has already been peer reviewed for funding. Arguments "for" consideration of potential benefits are that ethical review is different from peer review, which does not look at animal procedures in detail nor perform an ethical weighing, and that researchers ought to be able to convince the review process (and the public) that their work has sufficient value to justify the use of animals, not just the funding. We support this view and believe that harmonized guidance should advocate this approach.

Practice also differs in the assessment of harms to animals and whether this is seen solely in terms of harms caused by procedures, or whether the cumulative suffering over the lifetime experience of the animal is also considered, taking into account issues such as transport, handling, and housing. The latter view is gaining more weight and, we believe, should be advocated as good practice.

Perhaps the biggest difference, however – and this is between individual institutions as much as between different countries – is in how the harms and benefits are actually weighed; how willing people are to question custom and practice; what limits they set on justifiable benefits and harms; and whether they are ever prepared to say no. This is probably one of the most difficult areas to achieve harmonization. Inputs and operational issues can be harmonized, but can ways of "thinking" ever be so? To what extent is this desirable?

Other functions

Aside from the prospective and retrospective review of projects, there seems to be little information in regulatory documents and guidelines on what ethical review processes are expected to achieve, and on how, in practice, they might address their functions. Consider, for example, the requirement in UK Home Office guidance to "promote the development and uptake of the 3Rs and ensure the availability of relevant sources of information." How should the local ethical review process in a large multi-department university do this? What outcomes are expected and what are the criteria for "success" in fulfilling this function? This is the kind of information that is missing from most existing guidance.

For an ethical review process to be effective, it is vital that everyone involved is clear about the aims and objectives of each of its functions. Harmonized guidance on interpreting each of the functions, therefore, would be extremely useful. A report produced jointly by the Royal Society for Prevention of Cruelty to Animals (RSPCA) and the Laboratory Animal Science Association (LASA) (RSPCA/LASA, 2010) aims to do this for the UK by bringing together examples of good practice from a wide range of UK local Ethical Review Processes in industry and academia, and translating these into concise practical principles for addressing the functions and evaluating outcomes. Though designed for the UK, the report incorporates the principles set out in the 2007 FELASA report on ethical review of animal experiments across Europe, and it is widely applicable to most systems of review. This approach could perhaps provide a basis for a more international guidance document, which could take each function separately, define what it should aim to achieve, and provide practical examples of successful approaches, together with actual examples or activities to illustrate what others have done successfully in their establishments.

2.3 Membership issues

The success and effectiveness of ethical review processes depends critically on the people "round the table." As the UK Institute of Medical Ethics working party on the ethics of research involving animals observed 20 years ago, "*the quality of ethical judgements depends on the approach of those who make them, and in particular, whether and how far they have been responsive to all the relevant factors and interests involved*" (Smith and Boyd, 1991). A similar point was made by the UK Animal Procedures Committee in its report on the harm/benefit assessment (Animal Procedures Committee, 2003). This emphasized that ethical review "*is an evolving process and should not rest with the status quo*," and that those involved should engage in "*critical, creative, and imaginative thinking*." The more recent CIOMS (2010) guidance document makes a similar contribution, stating: "*Decisions regarding the welfare, care, and use of animals should be guided by scientific knowledge and professional judgement, (and) reflect ethical and societal values*."

If it is to be taken seriously, ethical review requires input and discussion between people who bring a range of perspectives and expertise to the process. This means that systems that have very few participants (in some countries there may be only one or two people responsible for decisions) will be less effective than those with a wider range of inputs.

Most of the guidance on ethical review process membership, including that from Australia, New Zealand, Canada, the UK, and the USA, focuses on the role of the individual, with minimum membership requirements, generally comprising a vet, an animal welfare representative, a scientific member, and an unaffiliated member (variously described as lay, public, or community member). This provides a basic minimum.

However, it is important to go beyond a list of job titles and think more carefully about who is involved, considering both the competencies and personal qualities required. This is the approach taken in the RSPCA/LASA guidance document. It sets out the key competencies that, together, are needed to address the many issues encompassed by the ethical review process, including competencies in: the relevant science, experimental design and statistics, animal husbandry and care, health and welfare assessment, humane endpoints, each of the Three Rs, education and training, ethical issues and dialogue, and "uninvolved," external and/or public perspectives. It may not be necessary for all these people to be present at every formal meeting, but this is the expertise that needs to be available within the review process.

The personal qualities of those who participate are also a vital consideration. We and our colleagues have experienced members who make no contribution to discussions even when they are concerned about an issue, and this is frustrating. Participants need to have the confidence to contribute to discussions and to challenge custom and practice where necessary. They need to be open-minded, fair and, impartial. They must also be prepared to listen, to respond to different views and not be defensive, to "think outside the box," to have realistic expectations of what can be achieved and the time and commitment to take an active role. Without these qualities, it is difficult to see how ethical review can be effective.

In summary, there is already concordance in many guidelines on the minimum membership requirements. These focus on job roles, however, and to harmonize to a higher standard, other factors such as competencies and personal qualities need to be considered. Institutions, therefore, need to be encouraged to think very carefully about the participants in their process. Other relevant membership issues are the need for an effective chair and for an enthusiastic person to drive the process with energy.

2.4 Operational issues

No one wants to waste time and resources on fruitless activities, or those that repeat what others are doing, so operational issues are another key topic for guidance, with the emphasis on procedures that can help to ensure that the ethical review process really "adds value" to any other system (local or national) already in place. This should include guidance on efficient organization of the process, the need for sufficient resources (both time and administrative support), clear "user-friendly" guidelines on the information requirements of the process, early planning and advertisement of timetables for meetings, and fast track systems for project evaluation where appropriate.

Effective communication is another important principle. All staff members need to know what the ethical review process is, what it is for, why it is important and how it actually affects them. The review process must be responsive to the needs of users, consulting with those whose activities it affects, in order to identify and solve concerns and to celebrate and capitalize on achievements. It therefore needs to engage in constructive dialogue with researchers rather than merely being seen to "sit in judgment" on them. Periodic re-evaluation of the aims, outcomes, and efficiency of the process – with input from, and feedback to, staff – is also important.

3 Moving thinking on

Of course, agreement on principles and practice for ethical review can go only part of the way towards ensuring ethical conduct in practice. It is the attitudes, care, and approach of the people and institutions involved that really make the difference. So, how do people develop their thinking on what is or is not acceptable? How do different ERPs compare in their outlook and actual outputs? How does any individual know they are doing the "right thing" for welfare, science, or social mores? Can there be a harmonized vision of what is acceptable to do to animals and for which purposes? How can we fast track people towards good practice when they are just starting out?

Enabling people from individual ethical review processes to interact with and compare ideas with others would therefore be our final principle. Forums for discussion between people from different ethical review processes are beneficial, so that people working in different contexts (nationally and internationally) can learn from and discuss approaches with one another and thereby work more closely towards desired outcomes. This in-

teraction can take place within countries, such as at the annual IACUC conferences organized by PRIM&R (Public Responsibility in Medicine and Research) in the USA[4]. It is also important between countries, especially those that are at different stages in developing their review processes and/or that operate in different social and cultural contexts. Providing training for participants is another highly beneficial step.

While it is in the nature of ethics that the outcomes of review will continue to vary between processes, the very fact that the people involved are making time and space to think about the ethical questions arising in animal experiments can have value in moving thinking forward. Among other things, "doing ethics" in the ways advocated above should enable those involved to:

– make sure that the arguments on which their decisions are based take into account all the relevant perspectives and features of the situation;
– engage in debate with people who hold different views and, by pin-pointing exactly where the arguments differ and are similar, learn from each other, identify any common ground and move towards consensus; and
– eventually, at the end of all their thinking, feel more confidence in the soundness of the decisions they have made, in the knowledge that, at least, they have done their very best to identify the most morally acceptable standpoint or solution to a problem (see Smith and Jennings, 2009, pp.54-57 for further discussion).

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