

PRINCIPLES AND PRACTICE IN ETHICAL REVIEW OF ANIMAL EXPERIMENTS ACROSS EUROPE

**A report prepared by the FELASA Working Group on
Ethical Evaluation of Animal Experiments**

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December 2005

This report is available on-line at: <http://www.felasa.org/recommendations.htm>
A summary has been submitted to *Laboratory Animals*.

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KEY POINTS

This report describes and explores a set of principles for the conduct of ethical review of laboratory animal use, drawing on the findings of a questionnaire that elicited information on how each of twenty countries represented in FELASA currently handles such review.

Responses to the questionnaire suggest that, although local practices differ, there is an emerging consensus on the key elements that any ethical review process should involve.

Key points are as follows:

1. Ethical review should aim to ensure that, at all stages in scientific work¹ involving animals², from initial planning, to completion of the studies and review of the outcomes, there is adequate, clearly explained 'ethical justification' for using animals, which is subjected to on-going, critical evaluation. This will involve consideration of:
 - a) the possibility that the objectives might be achieved by alternative means, not involving the use of animals;
 - b) the balance of the predicted (or actual) benefits of the work over the harms caused to the animals involved;
 - c) whether and how far, given the experimental design, facilities and expertise involved, there is reasonable expectation that the objectives of the work will be achieved in practice and the likely benefits will be maximised; and
 - d) whether and how far animal suffering is minimised and animal welfare enhanced, by implementation of the Three Rs, optimisation of standards of animal husbandry and care, and effective training, supervision and management of all personnel involved.
2. FELASA recognises that the *existence* of an effective ethical review process for scientific uses of animals should be mandatory in every European country. Further than this, over-arching European regulations and codes of practice should set out *principles* for effective ethical review, which, in order to meet local needs, allow for variation in how these principles are implemented in different countries. Similarly, national laws should allow sufficient flexibility of approach to ensure that ethical review can be organised efficiently and effectively in the range of different contexts and institutions in which animals are used.
3. For effectiveness and credibility, it is vital that all ethical review processes have means of ensuring that their decisions actually are implemented, and their recommendations given due weight, in practice. The power to stop animal studies, when, for example authorisations are exceeded or unexpected adverse events occur that prejudice their justification, should be built into the process.
4. All uses of animals in regulated procedures for regulated scientific purposes, as defined in relevant pan-European regulations, should be subject to comprehensive ethical review. This includes all uses of animals that fall within the definitions given in the EU Directive and that require prior notification and/or authorisation, including the use of animals in legally-required studies; and also the use of animals for the additional purposes listed in the European Convention, i.e., education and training, basic scientific research, and forensic enquiries.

¹ See point 4 re the scope of 'scientific work' that should be subject to ethical review.

² The term 'animal' is used to encompass, at a minimum, all animals covered by EU Directive 86/609 (currently under review).

5. 'Initial' ethical review should be carried out when authorisation to use animals is requested; and mechanisms should also be in place to ensure that there is 'on-going' review of ethical issues throughout the duration of the work involved – that is, from initial idea to publication of the results.
6. In addition to comprehensive ethical review of all scientific uses of animals that require notification and/or authorisation under the relevant pan-European regulations, FELASA also recommends that ethical review processes should have oversight of issues arising in the killing of animals by humane methods, and should implement strategies to ensure that harms to animals are minimised and best use made of the animals that are killed.
7. Ethical review should also involve consideration of wider standards of husbandry and care of animals, quality of facilities and competence of personnel (including their training, experience and management), all of which can have impacts on the harms caused to animals and the scientific value of scientific studies involving animals.
8. It is FELASA's view that in general initial ethical review should be at the project level³. This should enable an appropriate balance to be achieved between oversight of the ethical justification (or otherwise) for the programme of work as a whole, and detailed scrutiny of the particular procedures that will be carried out on the animals, particularly with respect to possibilities for implementing the Three Rs.
9. Ethical review processes should involve a diversity of participants who hold a variety of perspectives on the issues and encompass a range of relevant expertise. Opportunities should be provided for the different participants to *engage in discussion*, and so ensure that the ethical review is informed by and responsive to a range of different perspectives, and that ethical thinking can evolve with experience rather than merely rest with the *status quo*.
10. When one-person ethical review is required by national legislation, additional review processes that bring other perspectives and expertise to bear are also recommended.
11. All ethical review processes should include local elements, so that the review can be responsive to local factors, such as quality of facilities, standards of animal husbandry and care, and expertise of personnel involved. As part of this, participants in ethical review processes should be permitted and encouraged to visit animal facilities and to 'see for themselves'.
12. When local (institutional) review is the sole reviewing process, there is a need for an over-arching process within each country (or region) that can act as an 'independent' monitor of the performance of the more local processes and set standards; and to which the local processes can refer difficult cases and/or appeals can be made.
13. Ethical evaluation of scientific projects involving animals should include not only assessment of the harms likely to be, or actually, caused to the animals, and the possibilities for reducing them, but also the quality of the justification for such a use of animals, in terms of the objectives of the project, the necessity to use animals at all, or in the manner proposed, and the potential and likely benefits of the work. That is, such ethical evaluation should take the form of a harm-benefit assessment.

³ "A coherent programme of work aimed at meeting a defined scientific objective or objectives and involving a combination of one or more procedures" (TEWG 2003b), and with a limited period of authorisation – e.g. five years maximum.

14. In order to promote confidence in ethical evaluation of scientific projects involving animals, it is important that the factors to be taken into account are well known and widely agreed (see also the report of an Institute of Medical Ethics Working Party, Smith and Boyd 1991 and APC 2003). Drawing on a number of published schemes, a list of key, general factors that are important in ethical evaluation of scientific projects involving animals is presented in Table 2, page 16 of this report.
15. Agreed lists of 'factors for consideration' can be very valuable in guiding ethical review, particularly in encouraging and facilitating comprehensive identification and evaluation of the key aspects that impact on the balance of benefit over harm in scientific projects involving the use of animals. Such lists should be used as aide-memoirs, to assist thinking. They should not be used in a mechanical way, as 'check-lists' or quantitative 'scoring schemes', which would belie the complexity of the judgements involved and give a false sense of certainty and permanence in the conclusions that are drawn.
16. Whenever scientific proposals to use animals are reviewed, it is vital that applicants provide adequate information and argument on which to base the ethical review. Furthermore, since the application process itself can be an important prompt to encourage and assist applicants in thinking about ethical aspects of their proposed use of animals, it will usually be helpful to have special application forms that are designed to promote appropriate thought.
17. The ethical review process will be enhanced when applicants are required to describe their own harm-benefit assessments.
18. The information provided should be accessible and meaningful to all participants in the ethical review process. Experience suggests that non-technical summaries can be valuable for *all* participants in the ethical review (whether these participants are labelled 'lay' or not), and optionally for public information purposes.
19. Applications to the ethical review process should be named (i.e. not anonymous), so that issues relating to who will carry out the work and where it will be carried out can be identified and considered in the review.
20. Effective on-going review should be incorporated into the ethical review process, via:
 - (i) on-going monitoring and evaluation by everyone involved, including locally competent people, such as animal care staff, veterinary staff, animal welfare officers (and similar) and/or inspectors, in dialogue with researchers themselves; and
 - (ii) more formal process(es), such as:
 - formal interim review of projects (e.g. halfway through) to provide an opportunity for re-consideration of ethical issues arising in the work, including re-evaluation of the harm-benefit assessment in light of the actual harms and benefits arising, identification of possibilities for better implementation of the Three Rs, and any needs for training or expert advice; and
 - retrospective review when studies are completed, in order to help inform future ethical evaluations and learn from experience.
21. Ethical review processes must involve a wide enough range of expertise and perspective to facilitate comprehensive and detailed review of the factors that are relevant in the ethical evaluations. However, this does not (indeed cannot) mean that participants will be able to provide 'all the answers', but should mean that they have sufficient relevant understanding and insight to ask pertinent questions and know where

to go for further expert advice. Some competencies will be needed at all times in ethical review; other relevant expertise and perspective should be called upon when required.

22. All ethical review processes should include specific competence in animal welfare relevant to the species in question. Moreover, it is vital that veterinarians and animal care staff are directly involved in ethical review of animal research. These people should not be merely 'in attendance', but should be full, and key, participants.
23. Scientific expertise is also of vital importance in ethical review - to assist, for example, in evaluating the scientific justification for, and ethical conduct of, procedures on animals, asking pertinent questions that can help to guide thinking, and helping to provide advice to researchers. Moreover, participation of practising scientists helps to emphasise that ethical review involves, and is not separate from, the scientific community.
24. Inclusion of uninvolved, 'lay' perspectives (i.e. people who are not involved in animal research and testing and have no technical expertise related to the scientific use of animals) and preferably external perspectives can add value to the ethical review process. Such participation is recommended.
25. Ethical review should be carried out in dialogue with the researchers involved, recognising the researchers' responsibility for what happens to the animals in practice.
26. It should be ensured that participants in ethical review processes understand their role in the process, the reasons for requiring ethical review, and how their own ethical review process is organised; and, further:
 - appreciate the wider legal context in which the review process operates;
 - are aware of the general ethical principles involved; and
 - feel able to ask relevant and suitably challenging questions when necessary.
27. FELASA would be well placed to collate and disseminate resources and promote dialogue to support and assist participants in ethical review across Europe.
28. 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.
29. Effective ethical review processes can advance and facilitate such educational outcomes by, for example:
 - providing, in themselves, a 'forum for discussion' of issues arising in laboratory animal use;
 - supplying on-going advice and resources to support researchers;
 - promoting awareness-raising activities, such as seminars on contentious or difficult issues in animal use; and
 - being open, by explaining their work both to people both within and without the institutions concerned.
30. It is vitally important that efforts are made to develop common ethical goals and outputs as well as common processes of ethical review – both within and between countries – and, as part of this, to ensure that all involved are aware of developments in laboratory animal science and advances in application of the Three Rs.

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This report describes and explores a set of principles for the conduct of ethical review of laboratory animal use, drawing on the findings of a questionnaire that elicited information on how each of twenty countries represented in FELASA currently handles such review.

Responses to the questionnaire suggest that, although local practices differ, there is an emerging consensus on the key elements that any ethical review process should involve. These are identified and discussed below.

Preamble

At present, relevant European rules (EU Directive 86/609 and Council of Europe Convention 123, 1986) contain no specific requirement for prior ethical review of proposed animal studies.⁴ Nevertheless, it is now widely agreed that, if the conduct of animal experiments that have the potential to benefit humans and other animals is to be ethically defensible, an ethical review process that commands the confidence of wider society is needed. Current work by the European Commission to amend Directive 86/609 intends to accommodate this.

Early in the process of amendment of the Directive, a Technical Expert Working Group (TEWG) was established to give advice to the Commission. This comprised four sub-groups, one of which covered ethical review. At the same time, the Federation of European Laboratory Animal Science Associations (FELASA) independently established a Working Group on Ethical Evaluation of Animal Experimentation, with the aim of providing unified guidance on how best to conduct the ethical review process within different institutions and countries in Europe, in light of wider societal demand and interest in the subject.

The TEWG Ethical Review report was published on the web in December 2003 (TEWG 2003a). It focuses on defining the objectives of ethical review and the competencies needed to help to achieve those objectives. The present FELASA report provides a more detailed analysis of current processes for ethical review across Europe, and includes a wide range of recommendations intended to guide future practice. It draws on the findings of a survey of ethical review processes in FELASA member countries, the initial results of which were shared with an EU-funded survey (as yet unpublished) and fed into the TEWG discussions

Method of working

The FELASA Working Group was asked to "describe practical guidelines on how a responsible ethical evaluation is to be performed". It began this task by examining how ethical review is currently organised and carried out in the different FELASA member countries, by means of a detailed questionnaire completed by carefully chosen representative(s) of each country – that is, people with intimate, practical understanding of

⁴ Except, perhaps, in the case of regulated scientific uses of animals which "subject an animal to a procedure in which it will or may experience severe pain which is likely to endure", which "must be specifically declared and justified to, or specifically authorised by, the responsible authority" (Article 9 in Council of Europe Convention 123, 1986; the text of Article 12 in EU Directive 86/609 is similar).

ethical review in that country, as recommended by the FELASA Board. The questions are listed in Appendix 1 to this report.

In this way, the Working Group gained 'snap-shots' of experiences of ethical review from the following twenty FELASA member countries: Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Ireland, Italy, Latvia, Lithuania, Netherlands, Norway, Poland, Spain, Sweden, Switzerland, and UK. The questionnaire findings are not, therefore, 'nationally approved' responses. They have, however, been subject to additional scrutiny by FELASA Board members who represent the relevant national/regional LAS organisations, and wherever possible double-checked against other, published accounts.

This information and comment, together with reviews of relevant published and on-line literature, enabled the Working Group to consider the advantages and disadvantages of a range of different approaches to ethical review, and, from this, to draw up FELASA's recommendations, in the form of a series of principles for the conduct of effective ethical review in practice, which have been agreed by the FELASA Board.

The **principles that emerge** from responses to the questionnaire and FELASA's analysis are presented in bold type below, along with supporting argument, further comment, and relevant examples of current practice from the questionnaire responses. For clarity, the questionnaire findings are presented in grey boxes.

Definitions: the objectives of ethical review

To begin, it is important to be clear what is meant by 'ethical review'. This is best described by reference to the objectives of the process, which emerge from consideration of the range of responses to the FELASA survey. That is:

Ethical review should aim to ensure that, at all stages in scientific work⁵ involving animals⁶, from initial planning, to completion of the studies and review of the outcomes, there is adequate, clearly explained 'ethical justification' for using animals, which is subjected to on-going, critical evaluation. This should involve consideration of:

- a) **the possibility that the objectives might be achieved by alternative means, not involving the use of animals;**
- b) **the balance of the predicted (or actual) benefits of the work over the harms caused to the animals involved;**
- c) **whether and how far, given the experimental design, facilities and expertise involved, there is reasonable expectation that the objectives of the work will be achieved in practice and the likely benefits will be maximised; and**
- d) **whether and how far animal suffering is minimised and animal welfare enhanced, by implementation of the Three Rs, optimisation of standards of animal husbandry and care, and effective training, supervision and management of all personnel involved.**

To achieve these goals, effective ethical review processes will need not only to subject particular scientific uses of animals to initial and on-going ethical review, but also to consider more general ethical issues and concerns, common to many different areas of biomedical research and testing, such as standards of animal husbandry and care, management of

⁵ The scope of 'scientific work' that should be subject to ethical review is considered later in this report.

⁶ In this report, the term 'animal' is used to encompass, at a minimum, all animals covered by EU Directive 86/609 (currently under review). We note that some countries extend this definition to include certain fetal or embryonic forms and/or certain species of invertebrate.

animal work, communication, and the training, experience and resulting competence of personnel.

Ethical review processes will also have wider educational and awareness-raising impacts, which are vitally important in helping to develop and maintain a culture conducive to achieving all of the above objectives.

Legal requirement for ethical review

Although not yet a requirement of European law, respondents from 16 out of the 20 FELASA member countries surveyed confirm that they already have in place national, mandatory controls that require prior ethical review of all regulated scientific uses of animals. These controls may be exercised via the statute itself, via obligatory administrative provisions issued by the relevant competent authority, or a combination of the two.

At the time of writing, there is no national, mandatory requirement for prior ethical review of all regulated uses of animals in France, Ireland, Italy or Spain – but regional legislation applies in the autonomous Spanish regions of Catalonia, Aragon and Andalusia. However, respondents from all four countries report that they are moving towards national legislation or binding administrative provision that requires such ethical review. In Spain, recently enacted national law now requires the creation of ethical review processes in all State (but not other) research centres, and it is widely believed that the example set by Catalonia, Aragon and Andalusia will be followed by the other autonomous regions.

Note, however, that in the countries and regions in which a legal requirement for ethical review currently does not apply across the board, other mechanisms, such as peer review by funding bodies, or institutional policy, often result in local ethical review of animal studies

For example:

In France, although not required in law, both public and private research institutions have set up ethics committees for animal experimentation.

Public research organisations have created 22 regional committees gathering National Institutes of Research, Universities, Veterinary Schools and any other public structures concerned with animal experimentation. Each organisation has to sign a charter and a convention to be member of a regional committee. The special application form a researcher has to complete is established at a national level.

Similarly, private research centres have organized an inter-professional group (GRICE), to which approximately 30 institutions belong. A charter has to be signed by the managing bodies of these private centres, and each has its own committee with a minimum of 3 members (depending on the size of the organisation), one of whom is not a scientist.

In Ireland, all the major academic institutions have internal rules that require ethical review and the State funding agency, the Health Research Board, requires ethical review as a grant award condition.

A mandatory requirement for ethical review is important in helping to ensure that:

- (i) all relevant animal studies (see below) actually are subject to effective ethical review and the process is taken seriously; and

- (ii) the process, and the people involved in it, have the necessary status and power in law to *require* that the recommendations arising from the review are implemented in practice.

Beyond this, however, care should be taken to ensure that the law does not unnecessarily proscribe or restrict the way in which the ethical review process can discharge its duties. The practical organisation of such a review process has to meet local needs, and, because these needs differ between countries and institutions, there is the potential for a diversity of effective approaches.

FELASA recognises that the *existence* of an effective ethical review process for scientific uses of animals should be mandatory in every European country. Further than this, over-arching European regulations and codes of practice should set out principles for effective ethical review, which, in order to meet local needs, allow for variation in how these principles are implemented in different countries. Similarly, national laws should allow sufficient flexibility of approach to ensure that ethical review can be organised efficiently and effectively in the range of different contexts and institutions in which animals are used.

For effectiveness and credibility, it is vital that all ethical review processes have means of ensuring that their decisions actually are implemented, and their recommendations given due weight, in practice. The power to stop animal studies, when, for example authorisations are exceeded or unexpected adverse events occur that prejudice their justification, should be built into the process.

The necessary monitoring could be carried out by a separate, independent inspectorate and/or by elements of the ethical review process itself, such as local Animal Welfare Officers or other Competent Persons, who will need to have adequate information, statutory (legal) powers and strong management support in order to discharge their duties effectively.

Scope of ethical review

Background

At present, there is variation between countries in what is counted as a 'scientific use of animals' that is, or might be, subject to ethical review. Respondents to the FELASA survey report that, at a minimum, and in accordance with the definitions in EU Directive 86/609⁷, 'a scientific use of animals' is taken to encompass the use of:

- live, adult non-human vertebrates, or their free-living and/or reproducing larval forms;
- in procedures that may cause the animals pain, suffering, distress or lasting harm, including any course of action intended to, or liable to, result in the birth of an animal in such a condition (termed *regulated procedures* in this report), but excluding the least painful methods accepted in modern practice (i.e. 'humane' methods) of killing or marking an animal, and non-experimental agricultural or clinical veterinary practices; and

⁷ All countries represented in FELASA, with the exception of Switzerland and Norway are members of the European Union. As already noted, at the time of writing EU Directive 86/609 is undergoing revision. This includes re-consideration of which animals are covered by the legislation, and which scientific uses of such animals require specific authorisation.

- for experimental or other scientific objectives, which fall into one or more of the following categories of *regulated purpose*:
 - (a) the development, manufacture, quality, effectiveness and safety testing of drugs, foodstuffs and other substances or products:
 - (i) for the avoidance, prevention, diagnosis or treatment of disease, ill-health or other abnormality or their effects in man, animals or plants;
 - (ii) for the assessment, detection, regulation or modification of physiological conditions in man, animals or plants;
 - (b) the protection of the natural environment in the interests of the health or welfare of man or animal.

Beyond these minimum criteria, responses to the FELASA survey illustrate a range of national variations in the scope of 'scientific uses of animals' that are, or might be, subject to ethical review:

Extension of the definition of 'animal', to include:

- (i) vertebrate embryos and fetuses in some countries (e.g. Norway includes embryonic forms and foetal stages with the exception of fertilised eggs; the UK includes embryos and fetuses from halfway through gestation or incubation) and/or
- (ii) some invertebrate species (e.g. Switzerland includes decapods and cephalopods; Norway includes decapods; the UK includes *Octopus vulgaris*).

Extension of the definition of a 'regulated procedure', to include:

- (i) killing protected animals by approved (humane) methods, without any other regulated procedure being performed, in order to obtain tissues and organs for *in vitro* studies (i.e. *ex vivo* work). For instance, in Germany, the killing of protected animals by approved methods for use *in vitro* work or other scientific purposes must first be announced to the local Animal Welfare Officer (AWC), indicating the purpose of the work, the number of animals involved, the method that will be used and the competence of those carrying out the killing. The AWC can refer any such proposal for further consideration by a regional ethics committee. Similarly, in the Netherlands, the killing of a protected vertebrate animal for the aforementioned purposes is regarded as an animal experiment in all its aspects, and thus has to undergo the full ethical review process;
- (ii) scientific uses of protected animals that do not cause pain, suffering, distress or lasting harm e.g. some behavioural, dietary and field studies. For instance, in Switzerland such experiments are reviewed by local authorities and the numbers of animals involved are reported in national statistics.

Addition to, or variation in interpretation of, 'regulated purposes':

- (i) addition of purposes that are covered in the European Convention, but not the EU Directive, including the use of protected animals in regulated procedures for education and training purposes and forensic enquiries;
- (ii) exclusion of the use of protected animals in regulated procedures carried out for safety or efficacy tests that are required under local or international legislation. Germany and Austria specifically exempt such legally-required uses of animals from 'authorisation and ethical argumentation';
- (iii) there is also room for debate about whether and how far EU law covers the use of animals in basic scientific research that is not directly related to the development and use of drugs, foodstuffs and other substances or products or for protection of the natural environment. The European Convention, by contrast, explicitly lists "scientific research" as a regulated purpose.

FELASA's general conclusion

All uses of animals in regulated procedures for regulated scientific purposes, as defined in relevant pan-European regulations, should be subject to comprehensive ethical review. This includes all uses of animals that fall within the definitions given in the EU Directive and that require prior notification and/or authorisation, including the use of animals in legally-required studies; and also the use of animals for the additional purposes listed in the European Convention, i.e., education and training, basic scientific research, and forensic enquiries.

All of the uses of animals encompassed in this statement can raise ethical concerns, which should be identified and addressed. This includes consideration of:

- whether and how far the intended outcomes could be achieved by means that do not involve the use of animals; and, if not,
- how far the overall balance of likely benefit over harm in the studies can be considered acceptable; in light of
 - the nature of the harms likely to be caused to the animals and whether these are of a degree and/or kind that should not be caused at all, and/or have been minimised as far as possible; and
 - the value of the potential outcomes of the studies and the likelihood that these benefits will be realised in practice.

'Initial' ethical review should be carried out when authorisation to use animals is requested; and mechanisms should also be in place to ensure that there is 'on-going' review of ethical issues throughout the duration of the work involved – that is, from initial idea to publication of the results.

Legally-required scientific uses of animals

We have noted that some countries specifically exclude legally-required scientific uses of animals from ethical scrutiny. It is our view that, although a legal requirement to carry out a particular animal test according to a standard protocol might seem at first sight to provide sufficient ethical justification to perform the study, important ethical questions can still be raised (see our general conclusion above). These would include:

- whether there are possibilities for better application of the Three Rs (e.g. use of hierarchical testing strategies that aim to cut to an absolute minimum the use of protected animals, and better implementation of humane end-points); and
- whether and how far, in relation to the nature and potential benefits of the substance being tested, the studies are scientifically valid and the particular use of animals considered justified.

Scientific uses of animals not currently regulated in pan-European law

It is also clear that ethical questions and concerns can be raised in the case of scientific uses of animals that are not considered to cause suffering directly, and so are not 'regulated', but which might involve indirect, contingent harms, and/or killing animals.

(i) Killing animals for scientific purposes, without performing any other regulated procedure, in order to obtain tissues and organs for in vitro studies:

Under European law, this will be a regulated procedure if the method of killing is not by an accepted humane method, and (according to the statement above) should therefore be

subject to detailed ethical review. However, even when animals are killed by approved methods which are exempt from specific authorisation in many countries, ethical issues still arise. For example, in order to minimise animal suffering, it should be ensured that all personnel who kill animals are competent to do so, and, in order to maximise benefits, efforts should be made to ensure that the fullest possible use is made of the organs and tissues of animals that are killed. FELASA also considers that the death of an animal is a harm in itself, and therefore that the number of animals killed for such purposes is of moral concern, and should be kept to the minimum necessary to achieve the scientific objectives.

(ii) Killing animals bred within scientific institutions that are surplus to requirements:

Similar considerations apply. Although such killing is highly unlikely to require specific authorisation in law, there is again a need to ensure that the personnel involved are competent in the methods of killing. Moreover, strategies should also be in place to minimise the breeding of surplus animals in the first place, and to ensure that fullest use is made of any surplus animals that unavoidably have had to be killed.

In addition to comprehensive ethical review of all scientific uses of animals that require notification and/or authorisation under the relevant pan-European regulations, FELASA also recommends that ethical review processes should have oversight of issues arising in the killing of animals by humane methods, and should implement strategies to ensure that harms to animals are minimised and best use made of the animals that are killed.

(iii) Scientific uses of animals that, in themselves, can be considered to cause no discomfort but which may involve contingent harms:

Ethical considerations may also apply in the case of non-regulated scientific uses of animals (e.g. issues relating to husbandry and care of animals used in dietary and behavioural studies). For scientific studies of animals in the wild, in particular, steps need to be taken to ensure that disturbance is kept to a minimum. In such cases, guidelines are needed to illustrate the point at which the procedures involved would be considered to cause harms sufficient for them to become regulated, and so require more formal ethical review.

(iv) Wider context in which laboratory animals are used:

More generally still, wider standards of laboratory animal husbandry and care, the quality of facilities for carrying out regulated procedures, levels of competence (including training and awareness, experience and standards of management) of the personnel involved, can all influence the scientific quality of animal studies and the harms caused to animals, and therefore can have significant ethical impact.

Ethical review should also involve consideration of wider standards of husbandry and care of animals, quality of facilities and competence of personnel (including their training, experience and management), all of which can have impacts on the harms caused to animals and the scientific value of scientific studies involving animals.

'Level' of ethical review

The 'level' at which initial ethical review should be approached is difficult to proscribe. Ethical review needs to be at a sufficiently detailed level to enable consideration of ethical aspects of study design and possibilities for implementing the Three Rs; yet also requires an overview of the programme of work in which individual experiments and procedures will be performed, in order to assess the likely scientific benefits and harms to animals involved and to weigh these, one against the other. Striking an appropriate balance between detailed *versus* oversight review can be difficult.

Our survey reveals that, at present, practice in this regard varies considerably between (and sometimes within) FELASA member countries – e.g. in whether review is at the 'study protocol', 'experiment', 'procedure' and/or 'project' level. Matters are further complicated because the definition of these terms also varies. The terms 'project' and 'procedure' are defined in UK legislation, and for clarity similar definitions have now been adopted by the Technical Expert Working Groups for the revision of Directive 86/609 (TEWG, 2003b) and will be used in the remainder in this report – that is:

Project: A coherent programme of work aimed at meeting a defined scientific objective or objectives and involving a combination of one or more procedures. (And, FELASA would add, with a limited period of authorisation – e.g. five years maximum – after which, if the project is not yet complete, further application for authorisation would be required.)

Procedure: A combination of one or more technical acts carried out on an animal for an experimental or other scientific purpose and which may cause that animal pain, suffering, distress or lasting harm – where examples of 'technical acts' would include gavage, injection, laparotomy, withholding of food/water.

[Note that the Council of Europe Convention 123, 1986 also refers to "procedures" (with a definition similar to that above), but that the current EU Directive 86/609 refers to "experiments" – a term which is not clearly defined, and which excludes the use of animals in routine 'production' e.g. of biological products (such as serum, antibodies and other blood products) and maintenance of tumours and infectious diseases.]

It is FELASA's view that in general initial ethical review should be at the project level⁸. This should enable an appropriate balance to be achieved between oversight of the ethical justification (or otherwise) for the programme of work as a whole, and detailed scrutiny of the particular procedures that will be carried out on the animals, particularly with respect to possibilities for implementing the Three Rs.

Beyond this, it may be judged necessary in certain cases to require ethical review on an experiment-by-experiment, test-by-test, or procedure-by-procedure basis – e.g. when there are special concerns about the harms likely to be caused to the animals.

FELASA's view that there should be an *upper* limit on the duration of a 'project' so defined, with a suggestion of a 5 year *maximum*, would not preclude a more limited duration – which might vary between countries according to local requirements and context. The important point is that there should be an appropriate balance between detailed scrutiny and oversight ethical review, that enables all relevant ethical issues to be addressed throughout the duration of the project, without imposing unnecessarily burdensome bureaucratic requirements that could stifle the research process itself.

Provided that there are adequate mechanisms in place to ensure on-going monitoring of work in progress after initial authorisation is granted (see further discussion on pp.21-22), then *routine* ethical review and prior authorisation of individual experiments, tests or procedures conducted within projects is likely to be overly bureaucratic in relation to the additional benefits of this more frequent review, and might not be in the interests of animal welfare or science if this means that there is less time or fewer personnel available for monitoring and caring for the animals (including seeking opportunities for better application of the Three Rs in studies in progress). There is also concern that, in some countries where

⁸ Note that, in this context, the term 'project' is used only as specifically defined above. In particular, it is not synonymous with the kind of 'scientific project' that is peer reviewed for funding. Ethical review of animal use 'at the project level' is not intended to replace or duplicate the scientific peer review process, but to complement it.

review is test-by-test and implementation of Freedom of Information legislation requires reports on each of the separate reviews to be made public, the volume of work involved in preparing the reports will paralyse the review process.

Principles for the organisation of ethical review

General comments

As in other areas of ethical concern and debate, the *method* by which ethical review of scientific uses of animals is approached is of crucial importance in determining the quality of, and trust in, the judgements, advice and other outputs of the process. 'Doing ethics' usually involves exploring and arriving at judgements and decisions which, by their nature, are often difficult and tend to provoke disagreement. Confidence in ethical judgements therefore largely depends on the approach of those who make them: that is, on whether the *process* of review is seen to result in sensitive, balanced and informed decisions and judgements that are responsive to all reasonable perspectives on the issues (report of an Institute of Medical Ethics Working Party (Smith and Boyd, 1991); see also Donnelly (1990) for further discussion).

This will entail:

- taking into account all the different features of the proposal or situation that are relevant to the judgement;
- involving all the necessary expertise, and as wide a range of views and perspectives on the issues as possible;
- recognising that decisions and advice resulting from such reviews are 'interim' judgements that may change as the work progresses and with scientific advance, and so should be subject to on-going review and re-evaluation; and
- being *seen* to do these things.

As will be generally accepted, it is also important that the overall organisation of ethical review meets both national and local needs and enables the processes to operate effectively within the various wider legal and political structures of each country.

Organisation of ethical review processes in FELASA countries

Table 1 (overleaf) summarises the general organisation of ethical review processes in FELASA member countries whose representatives responded to our questionnaire. It is clear that there is a diversity of general approaches to ethical review of animal experiments within Europe. These include:

- national committees;
- regional committees;
- institutional committees;
- other – e.g. review by government inspector or official veterinarian; and
- combinations of any of the foregoing approaches, sometimes with the addition of a national advisory committee.

The differences seem, in part, to be related to the size of the country and volume of animal studies carried out, as well as political considerations to do with, for example, the organisation of government, the wider regulatory climate within the country and the way in which science is funded and managed. Some approaches to ethical review, respondents suggest, are more effective than others.

Table 1: General organisation of ethical review of laboratory animal use: FELASA survey responses

COUNTRY	MANDATORY PROCESSES*	VOLUNTARY PROCESSES
Austria	For academic institutions: National committee of the Ministry of Education, Science and Culture. Industry: Official veterinarian .	Institutional committees in some facilities
Belgium	Institutional committees (which can be shared between institutions) and Government inspectors (who are members of the local committees) and a National committee when difficult issues arise	
Czech Republic	Institutional committees ; two National committees : representing (i) all Ministries involved in animal experiments and (ii) the Academy of Sciences; final authorisation by a Government committee , the Central Commission for Animal Welfare and the Environment	
Denmark	Review by National committee appointed by the Minister of Justice which directs a Government inspectorate	Four institutional committees
Estonia	A National licensing committee was established at the Estonian Ministry of Agriculture in May 2004. The committee reviews applications and grants permits for animal experiments; meetings take place according to the number of applications received	
Finland	At the time of writing, institutional committees (some are shared between institutions). Changing to a National Committee as a result of a change in the law in 2006	
France	<i>Applications for licences are approved and given by the Ministry of Agriculture. Government veterinary inspectors from the local Veterinary Service in each Prefecture check compliance (field of research, training and competence of researchers). Painful protocols must be declared to the local Prefecture, and an additional licence and evaluation is required for use of non-domestic animals. A National Ethical Committee oversees the good functioning of the ethical committees (but there is not as yet a legal requirement for researchers to submit their work for ethical review by these committees).</i>	Regional committees for public research (22); Institutional committee in each industrial firm #
Germany	Review by institutional Animal Welfare Officer (a veterinarian, medical doctor or zoologist), then by Regional committee (c. 40) advising the government authorities	
Greece	Official veterinarian from the Local Veterinary Service in each Prefecture, who may take advice from scientists in the relevant field of work.	Institutional committees in Medical Faculties and some research institutions
Ireland	<i>Applications for licences must be approved by the Minister for Health and Children. A local nominated competent person (preferably a veterinary surgeon) must review each application and declare that he/she does not envisage any practical difficulties on welfare grounds and specify any reservations.</i>	Institutional committees in most institutions
Italy	<i>A review by a special Commission at the National Institute of Health is required only for: procedures involving cats, dogs, non-human primates and/or endangered species; procedures without anaesthesia; and those for education and training.</i>	Institutional committees in most research centres
Latvia	National committee , at the Latvian Council of Science	
Lithuania	National committee of the State Food and Veterinary Service	Institutional committees in some facilities
Netherlands	Local (mostly institutional) committees , plus a National committee which acts as a 'court of appeal' when a local committee has rejected a proposal (very rare). The law permits the outsourcing of ethical review, so that 'institutional' committees can advise more than one institution, and there can also be independent committees (there is one at present), whose services can be hired by institutions do not have their own	
Norway	Local 'competent person' and National committee (National Animal Research Authority - for review of cases which the local competent person finds too controversial to make a decision, or is involved in, field experiments, and painful experiments where painkillers are withheld (very rare)) A new Animal Welfare Act is currently being drafted.	Institutional committees in some facilities
Poland	Regional committees (18) set up by the National Ethics Committee on Animal Experimentation (NEC/AE) which oversees their work as an appeal authority.	
Spain	<i>Regional committees in Catalonia, Andalusia and Aragon; institutional committees in all research centres in Catalonia and Aragon. From October 2005, a new national law requires institutional committees in all State (but not other) research centres, and sets up a State Ethical Commission of Animal Welfare which must approve and supervise high severity procedures</i>	Institutional committees in most other research centres in the remaining regions
Sweden	Regional committees (7)	
Switzerland	Regional committees (10), which advise the Cantonal Authority whether or not experiments should be authorised; plus a National committee to advise the cantons in controversial cases and more general matters. The Federal Veterinary Office has the right to appeal.	Institutional committees in some facilities
UK	Institutional committees and other local processes review project licence applications as well as more general matters pertaining to the care and use of laboratory animals within institutions. Applications then forwarded to Government inspectors who, having weighed the likely welfare costs against the potential benefits, advise the Secretary of State for the Home Office whether or not they should be granted. There is also a National committee (the Animal Procedures Committee) for general advice on the operation of the law and ethical review of certain classes of licence application.	

* *Italics* indicate countries in which there is not yet a national, mandatory requirement for prior ethical review of all regulated scientific uses of animals

Although not legally-required, the organisations involved sign a binding commitment to submit work to these processes for ethical review.

One-person review processes cf. wider involvement in ethical review

As Table 1 shows, in Greece generally, in industry in Austria, and for most studies in Norway, mandated review is carried out by one person (though there may be voluntary local ethics committees in some institutions).

For example: At present, in Norway, a local competent person, appointed by the National Animal Research Authority, has delegated authority to approve or turn down applications from researchers to carry out animal experiments. There are around 70 such people in Norway, each running one of Norway's animal facilities.

A similar situation exists at the time of writing in Ireland, though here the government department responsible for licensing animal use expects to see evidence of local ethical review, which 'should' include review 'by an ethics and/or scientific committee in a university or research centre', but is not a legal requirement (see Table 1).

One-person review processes may be expedient and flexible, particularly in countries or institutions in which there is a small volume of animal work. However, although the individuals involved may well consult with others, it is clear that one-person review is unlikely to be as responsive to as wide a range of factors or perspectives as processes that directly involve a range of participants.

Ethical review requires *discussion*; in order, for example, to clarify the concepts and arguments involved and to explore a variety of points of view, and so to work towards consensus judgements or other responses/ways forward (see for example Higgs 1997 for further discussion). Moreover, one-person review clearly invests a great deal of responsibility in one individual, who will require very strong, senior management support in order to perform effectively. Processes that involve a wide range of participants are likely to lead to outcomes that engender greater confidence than the more easily contested 'opinions' of an individual.

Ethical review processes should involve a diversity of participants who hold a variety of perspectives on the issues and encompass a range of relevant expertise. Opportunities should be provided for the different participants to *engage in discussion*, and so ensure that the ethical review is informed by and responsive to a range of different perspectives, and that ethical thinking can evolve with experience rather than merely rest with the *status quo*.

More detailed discussion of participants in ethical review follows later in this report.

When one-person ethical review is required by national legislation, additional review processes that bring other perspectives and expertise to bear are also recommended.

That this is already the case in some institutions is also shown in Table 1.

National, regional and/or local (institutional) review

Most FELASA member countries already have, or are developing, *local* (institutional) review, often in addition to other processes which might involve regional, national and/or one-person review. Respondents report that, at the time of writing:

- (i) in 5 countries (falling to 4 in 2006, because of a change in the law in Finland – see Table 1), local review is mandatory (by virtue of statute or other binding requirement) and so *all* institutions in these countries carry out such local ethical review – though sometimes the committees are shared between institutions;
- (ii) in the remaining 15 countries (rising to 16 countries in 2006) there is no legal or other administrative requirement for local ethical review – although in Spain there is such a requirement in three administrative regions and, nationally, in all State research centres, and in at least 9 of the other countries ethical review processes are voluntarily established in some institutions.

Regional or national review has the clear advantage of 'distance' from the personnel and work at hand and hence brings a measure of disinterestedness and independence to the ethical review process. However, it is also important that the ethical review should be based on sound understanding of the local context in which procedures will be performed and wherever possible should involve local personnel with experience and responsibilities relevant to the work under consideration.

Importantly, by involving key local personnel with expertise relevant to the use of animals local processes can also provide *support and advice* for researchers preparing and submitting applications for more formal approval and performing on-going ethical evaluation. Furthermore, involving local participants in ethical review will add to the awareness-raising effect of the review process within institutions.

All ethical review processes should include local elements, so that the review can be responsive to local factors, such as quality of facilities, standards of animal husbandry and care, and expertise of personnel involved. As part of this, participants in ethical review processes should be permitted and encouraged to visit animal facilities and to 'see for themselves'.

National 'oversight'

Table 1 shows that 4 of the 5 countries in which local, institutional review committees are mandatory also have national other processes which can 'oversee' the local review and, in some cases, act as final arbiter in decisions whether or not to authorise the work.

For example:

In Belgium, a Government Inspector is an obligatory member of each local ethics committee, which allows him to compare the way the committees function and to advise on needs for operational changes as appropriate.

In the Czech Republic the Animal Protection Act requires that experiments on living animals are approved by a Central (government) Commission for Animal Welfare and the Environment; in practice, the proposals should first be reviewed by local ethics committees and then by a special committee of the appropriate Ministry or Academy of Sciences, before final consideration by the government committee.

In the UK, government (Home Office) inspectors, in addition to other roles, review all licence applications approved by local ethical review processes and advise the government's Secretary of State for the Home Office whether or not licences should be granted.

Of course, local institutional review also brings with it the possibility for variations in depth and quality of ethical deliberation between different institutions, and also the possibility of 'bias' in the process. It is in the nature of ethics that, at times, opinions will differ and that, on occasion, there will therefore be differences in judgement between different reviews, whether these are 'local' or not. This makes it especially important to ensure that the *processes* of review are consistently conscientious and rigorous and give balanced attention to all the different factors that are important in arriving at decisions.

When local (institutional) review is the sole reviewing process, there is a need for an over-arching process within each country (or region) that can act as an 'independent' monitor of the performance of the more local processes and set standards; and to which the local processes can refer difficult cases and/or appeals can be made.

Factors for consideration in ethical review

Requirement to carry out harm-benefit assessment

Accepting that there might be at least *some* acceptable uses of animals in scientific studies (an assumption that is sometimes contested – see, for example, Nuffield Council on Bioethics (2005) for further discussion of ethical positions), a 'justification' for the use of animals will rest on whether and how far the potential, likely and (later) actual benefits of that use can be regarded as 'sufficient' in light of the potential, likely and (later) actual harms that will be caused to the animals – i.e. a weighing of the benefits of a given project against the harms caused to the animals. This ethical weighing is often referred to as a cost-benefit analysis. However, so as avoid inappropriate quantitative or economic implications it is preferable to call the process a **harm-benefit assessment**.

Beyond this weighing of harm and benefit, certain **ethical limits** may also be identified, in that:

- (a) individuals, institutions and/or countries may judge that certain reasons for using animals are unacceptable, however mild the harms caused, because the purpose itself is judged insufficiently serious and/or suitable alternatives exist; and, similarly,
- (b) certain procedures may be judged unacceptable, however great the likely benefits, because the harms are judged too severe and/or suitable alternatives exist.

The relevant Council of Europe Convention and EU Directive 86/609 set out certain ethical principles relating to the harms caused to protected animals in scientific studies. In brief, these relate to:

- steps that have been, and can be, taken to minimise pain, distress and other suffering to animals – including application of all Three Rs;
- competence of personnel and quality of facilities; and
- quality of experimental design.

In addition, the European Convention, but not the EU Directive, limits the purposes for which protected animals may be used, but only in the most general terms, so permitting a very wide range of particular purposes and potential benefits under the general headings. As noted, however, at the time of writing the Convention and Directive contain no specific requirement for prior ethical review of proposed animal studies (except perhaps in the limited case of severe and enduring pain, but the terms of the 'justification' required in this instance are not made explicit in the regulations) and a harm-benefit assessment is not a requirement of pan-European law.

As might be expected, ethical review processes in countries surveyed by FELASA all seem to involve consideration of the key factors that can impact on the harms caused to animals, as enshrined in the Council of Europe Convention 123, 1986 and in Directive 86/609 (see above).

All respondents to our survey report that their ethical review processes consider the aims and necessity of the animal work under review. However a small but significant number of respondents suggest that their ethical evaluations do not include consideration of the balance of likely benefit over harms of the studies.

At the time of writing, ethical review in 5 of the countries surveyed does not appear to include a requirement to perform such an ethical weighing of benefits against harms, thus focusing only on the harms and how these can be minimised.

Ethical evaluation of scientific projects involving animals should include not only assessment of the harms likely to be, or actually, caused to the animals, and the possibilities for reducing them, but also the quality of the justification for such a use of animals, in terms of the objectives of the project, the necessity to use animals at all, or in the manner proposed, and the potential and likely benefits of the work. That is, such ethical evaluation should take the form of a harm-benefit assessment.

Carrying out harm-benefit assessment in practice

Although most respondents to our survey have told us that the ethical review processes in their countries carry out harm-benefit assessments, it is difficult to gauge what this actually involves in practice, without sitting in on the committees and processes in which the weighing is done. However, it seems probable that the way in which the evaluation is approached varies both between and within between countries – particularly given the variation in the *people* (and therefore competencies) involved in the review processes, and also the *level* at which the review is currently carried out.

Respondents from 9 FELASA countries (just under 50% of replies) say that they have particular guidelines and/or lists of factors, which set out principles for performing ethical evaluations. Rather rarely does this guidance seem to be established at a national level, such as the detailed criteria provided by the Swiss Federal Veterinary Office (2005a). However, 18 (out of 20) respondents also report that the information about proposed animal studies that has to be submitted for ethical review is either set out in law and/or associated guidelines and/or there are special national or local application forms for researchers to complete – and that, therefore, this information in itself sets an 'agenda' for the ethical review.

As noted, confidence in judgements about ethical questions, such as those related to the use of animals in scientific studies, depends in large measure on the approach of those who make those judgements and, in particular, on how far they have shown themselves to be responsive to all the different factors and interests involved (Smith and Boyd 1991).

In order to promote confidence in ethical evaluation of scientific projects involving animals, it is important that the factors to be taken into account are well known and widely agreed (see also the report of an Institute of Medical Ethics Working Party, Smith and Boyd 1991 and APC 2003).

Worldwide, a variety of schemes intended to assist in harm-benefit assessment of animal research and testing have been published, including those described by: the Canadian Council on Animal Care (1997), Delpire *et al.* (1999), Institute of Medical Ethics (Smith and Boyd, 1991), Mellor and Reid (1994), Prentice *et al.* (1990), the Swiss Federal Veterinary

Office (2005a and 1994) and the UK Animal Procedures Committee (2003)⁹. See also a UK regulator's perspective in Home Office (1998).

Such lists of factors could be said to play an *educational* role, and might be of particular value to researchers who are new to the use of animals in science, and/or new members of ethical review processes – see, for example, a Resource Book for Lay Members of Local Ethical Review Processes (Smith and Jennings, 2003) prepared in response to lay members' requests for resources to support their (and other members of the review processes') thinking on the weighing of harms and benefit, including lists of factors to think about and suggestions for questions that ethical review processes might address.

Some other schemes, such as those of Porter (1992; see also Boisvert and Porter, 1995) and Stafleu *et al.* (1999) employ quantitative 'scores' for harms and benefits, which, the authors suggest, should be used to assist in the ethical weighing. It is our view that although a semi-quantitative assessment of animal suffering is sometimes possible, the use of simple ethical 'scores' for other factors, such as quality of experimental design and potential benefits, belies the complexity of the judgements involved. Moreover, when such scores are combined, there is the misguided impression that a 'poor' score on one factor can be compensated for by a 'good' score on another factor. The aim should be to make the design of studies as 'good' as possible on all factors rather than off-setting one against the other in this way. Ethical reasoning is a qualitative, multi-faceted and context-specific process, which relies on the sensitivity, integrity and competence of everyone involved, and cannot be reduced to the mechanical use of a set of scores that are added (or otherwise manipulated) to arrive at a decision.

Drawing on a number of published schemes, a list of key, general factors that are important in ethical evaluation of scientific projects involving animals is presented in Table 2.

Lists of questions such as those shown in Table 2 are 'starting points' that can be edited and tailored by particular review processes to suit their circumstances and the kinds of issues that their work raises. Such guidance can play an important *educational* role in ethical review, and might be of particular value to researchers who are new to the use of animals in science, and/or new members of ethical review processes

Agreed lists of 'factors for consideration' can be very valuable in guiding ethical review, particularly in encouraging and facilitating comprehensive identification and evaluation of the key aspects that impact on the balance of benefit over harm in scientific projects involving the use of animals. Such lists should be used as aide-memoirs, to assist thinking. They should not be used in a mechanical way, as 'check-lists' or quantitative 'scoring schemes', which would belie the complexity of the judgements involved and give a false sense of certainty and permanence in the conclusions that are drawn.

⁹ See also guidance provided by the Australian Government's National Health and Medical Research (NHMR) Council (2004) and the New Zealand National Animal Ethics Advisory Committee (2002); also the US IACUC Guide (published by ARENA and the Office of Laboratory Animal Welfare at NIH, 2nd edition, 2002) and American Association for Laboratory Animal Science (AALAS, 2002). These focus mainly on the application of the Three Rs in protocol review.

Table 2: Outline scheme for the assessment of benefits and harms in scientific projects involving animals*

Assessment of potential benefits of the project

**How will the results add to existing scientific and/or clinical knowledge and how might they be used?
What practical applications, if any, are envisaged at this stage?
And what is the potential value of these insights and/or applications?**

- Are the objectives of the project:
 - original, in relation to previous or on-going studies
 - timely, in relation to other studies that might be done (what is the need to do *this study, now?*)
 - realistic, in that they are achievable with the time and other resources available?
- If there is an element of replication of previous work, how strong is the case for this, and what efforts have been made to avoid mere duplication?
- If this is on-going work, 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?
- 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?

Assessment of likelihood that the potential benefits will be achieved in practice

Is there is a reasonable expectation that the potential benefits will be achieved in practice, given the:

- choice of animal model and scientific approach
- validity of experimental design (e.g. use of appropriate number of animals involved, appropriate use of controls) and whether and how this has been informed by statistical or other advice
- competence of researchers and other staff, including their training, supervision, experience and expertise
- appropriateness and quality of facilities
- researchers' plans for communicating and using and/or building on the findings of the project?

Assessment of the harms caused to animals and possibilities for reducing these, in terms of

- the need to use animals *at all* (what efforts have been made to seek suitable alternatives to the use of animals in regulated procedures? has as much information as possible already been gained from *in vitro* or other *ex vivo* work?)
- optimisation of the numbers of animals that will be involved (neither too many nor too few to achieve a meaningful scientific result) and quality of experimental design – again, what advice has been sought?
- the severity of the potential harms in the proposed studies, considering *all* potential adverse effects, psychological as well as physical, and their duration, in relation to:
 - the species and strain of animal used
 - the effects of the procedures themselves
 - wider factors, such as: the source of the animals (including, where relevant, their breeding conditions) and where relevant, the conditions of transport to the laboratory; and arrangements for their husbandry and care, including provision of environmental enrichment
 - the fate of the animals at the end of the experiments – will they be used in another procedure, killed (by what method?) or re-homed or released? And
 - how all of these factors will be influenced by the competence of researchers and other staff, and the quality of the facilities involved
- possibilities for refining the impact of the study on the animals so as to cause less harm to the animals whilst achieving a valid scientific outcome, e.g. by
 - using a different species or strain
 - obtaining animals from a different source
 - adapting or enriching animal housing and care
 - modifying the techniques involved
 - enhancing the monitoring of the animals and implementing humane end-points
 - better use of anaesthesia and analgesia and/or provision of other special care

* 'Animals' as defined in footnote 2. This Table draws on a number of published schemes for assessment, including: Animal Procedures Committee (2003); Canadian Council on Animal Care (1997); Delpire *et al.* (1999); Home Office (1998); Mellor & Reid (1994); Prentice *et al.* (1990); Smith & Boyd (1991) Smith & Jennings (2003); Swiss Federal Veterinary Office (2005b).

(i) Potential benefits

Evaluating the potential benefits of scientific projects involving animals, be they in terms of gains in scientific knowledge or more practical applications, is perhaps the most difficult part of the 'ethical weighing' – because, for example, it is in the nature of an experiment that the outcome of the work is not (fully) known, and the benefits may only be fully realised some while after the study has taken place.

The role that ethical review processes should play in evaluating potential benefits, including who has the competence to judge the factors listed under this heading in Table 2, is particularly controversial. Some people argue that evaluation of issues to do with scientific merit and potential benefits should be left to those within the particular field of work (such as during scientific peer review when funding is applied for), because, they suggest, only those with intimate knowledge of the particular field of work have the competence to evaluate these factors. However, not all proposed projects will be subjected to such scientific peer review, and often ethical review will be required *before* funding applications are made, because funding bodies require evidence that the work is ethically acceptable (a Catch-22 situation).

Moreover, it can be argued, compared with funding body review, ethical review looks at potential benefits from a different perspective – that is *in relation to* detailed consideration of the harms likely to be caused to the animals.

Clearly, in considering potential benefits it will be important to take into account the source of funding and whether the proposed work has been subject to competitive peer review to secure those funds. Nevertheless, for purposes of harm-benefit assessment, researchers also ought to be able to convince participants in the ethical review process (usually including the people who will be caring for the animals) of the value of their work (e.g. how the results will add to existing scientific knowledge and how they might be used; what potential applications, if any, might be envisaged at this stage), so that the likely harms to animals can be considered in this light. See Animal Procedures Committee (2003) for more detailed discussion; also Mann and Prentice (2004) for debate about the pros and cons of review of 'scientific merit' by US IACUCs.

(ii) Likelihood that the potential benefits will be achieved in practice

Whatever the potential benefits of a project, it is clearly vital that the proposed methods are scientifically valid, well designed and carefully conducted, so that there is a reasonable expectation that the potential benefits will be achieved in practice. A study that is of doubtful scientific validity should not be carried out, no matter how mild the harms to the animals. Participants in the ethical review process will therefore also want to consider, and ask questions about, factors that can influence the likelihood that the potential benefits will be realised in practice. Examples of questions that could be asked are set out in Table 2. See also the extended discussion of assessment of scientific validity, including lists of factors for consideration, in Animal Procedures Committee (2003).

(iii) Harms to animals and application of the Three Rs

In considering and assessing the likely harms to the animals, a 'holistic' approach should be adopted, so that the ethical review process is alert to all the different adverse effects (psychological as well as physical) that might be experienced by the individual animals involved, all the different factors that can potentially cause harms (including wider factors, such as husbandry and care, as well as the procedures themselves), and the likely duration of those harms. A key part of this assessment will be to ask whether and how the harms have been (or could be) reduced and/or avoided altogether, by application of the Three Rs. This will include consideration of (i) whether it necessary to use protected animals *at all*; (ii) if the use of protected animals cannot be avoided, whether the use of animals can be (further)

refined in any way, so as to cause less suffering; and (iii) what steps will be taken to try to ensure that the numbers of animals involved are optimal for achieving the aims of the work. See Table 2.

(iv) Categorising the severity of harms to animals

In some countries, national and/or local ethical review processes not only assess the severity of the likely harms to the animals, but also attempt to *categorise* that severity according to a numerical or descriptive classification scale.

Examples of the use of severity classification schemes given in responses to our questionnaire are listed in the box below. For further examples, see the classifications described by the Canadian Council on Animal Care (1991), and in the New Zealand animal use statistics (New Zealand Ministry of Agriculture and Forestry 2004).

In the Netherlands, information on the degree of discomfort experienced by the animals has to be reported after experiments have been performed. A summary of these data is published in Dutch annual statistics on animal experiments (see VWA, 2003), according to whether the suffering experienced by the animals was: 'minor', 'minor/moderate', 'moderate', 'moderate/severe', 'severe', or 'very severe'. At meetings of Animal Welfare Officers information is exchanged and discussed to promote consensus of opinion on how to apply the categories.

Poland has a 'scale of invasiveness' of animal experiments, which is used to assist in the harm-benefit assessment, in that 'stronger biomedical justification' is required for higher levels of invasiveness; and only the lowest level of invasiveness is permissible for education and training.

In Switzerland, applications for licences to carry out animals experiments must include estimates of the maximum degree of severity (stress category) that experiments will impose on the animals, classified as: 'no stress'; 'mild stress'; 'moderate stress'; or 'severe stress'. When the experiments are completed, licence holders must report estimates of the severity of the actual adverse effects on the individual animals for publication in annual statistics. Detailed guidance, with many examples, is provided to assist in these assessments (see Swiss Veterinary Office, 2005a, 1994 and undated, for details).

In the Federal Republic of Germany an application for a licence to perform animal experiments has to include an estimation of the possible severity of harm, pain and suffering. The applications ask for the type of experiment, whether the experiment includes an anaesthesia, whether the experiment has repeated treatments, and for the severity of harm, pain and suffering, scaling from 'none', to 'mild', 'moderate' or 'severe'. Finally the duration of this harm, pain and suffering has to be given as 'less than 1 day', '1 to 7 days', '7 to 30 days' and 'more than 30 days' (Hackbarth and Lückert 2002).

Likewise, in the UK, the anticipated severity of the harms to animals is classified according to a descriptive scale of 'mild', 'moderate' and 'substantial' (plus 'unclassified' for procedures performed solely under terminal anaesthesia). Using this nomenclature, a severity 'limit' is determined for each protocol in which animals are used, thus setting an upper limit to the harms that can be caused to animals in the protocol; and an overall severity 'band' is assigned to the project as a whole (see Home Office 2000, pp.32-33 for further information).

Although, as we have said, ethical judgement cannot be reduced to a set of quantitative scores, categorising severity can be valuable in: encouraging and assisting scientists and animal care staff in thinking about the harms likely to be caused to the animals; facilitating communication between them; and setting 'rules-of-thumb' upper limits for the harms that can be caused in particular procedures and in pursuit of particular scientific goals. However, it is important to recognise that these labels are merely convenient short-hand descriptions and therefore, in both reviewing and managing studies in practice, also to refer to more detailed narrative descriptions of harms and methods of reducing, avoiding or alleviating them.

Whenever a severity classification scheme is used, and for whatever purpose, it is important that there is adequate description of the adverse effects that are encompassed by each label and sufficient worked examples to illustrate how the scheme is to be applied in practice, and hence to help to ensure that all those who use the scheme are 'speaking the same language'. There is a need for guidance covering all the main classes of protected animals (i.e. all five vertebrate classes, and any invertebrates covered by the legislation), and a wide range of different types of procedure and adverse effect. For purposes of harm-benefit assessment, severity labels that refer to the 'average' animal's experience should be avoided: each animal should 'count as one', in that milder harms in one animal should not be taken to reduce or otherwise mitigate more substantial harms in another. See reports of focus group discussions on the application of severity classification in practice, Boyd Group/RSPCA, 2004.

A number of publications offer assistance in grading severity – including the report of a FELASA Working Group on Pain and Distress, and publications cited therein (Baumans *et al.* 1994); the classification scheme used by the Swiss Federal Veterinary Office (undated), which includes numerous examples; Mellor and Reid's 'domain-based' classification, which draws on the (farm animal welfare) concept of the Five Freedoms (1994); and the detailed discussion provided by Morton and Hau (2002), which, amongst other things, includes lists of clinical signs useful in establishing humane end-points and examples of severity 'score sheets'.

(v) Arriving at a judgement: weighing harms and benefits

A major part of the 'ethical weighing' process will need to involve attempts to maximise likely benefits and, as far as possible, minimise harms. This should be a dynamic, on-going process. Beyond this, there will also be need for judgements about whether it is acceptable to cause the predicted harms in light of the expected (and later actual) benefits of the work concerned.

Although 'decision models' such as Bateson's cube (Bateson 1986; see also discussion in Smith and Boyd 1991, Chapter 7 and the report of a Nordic Forum for ethical evaluation of animal experiments – Voipio *et al.* 2004; and 2005, in press) can help in thinking through such decisions, there can be no straightforward 'algorithm' for ethical weighing, nor any other quantitative approach that can remove the need for sensitive ethical judgement. As already noted, being responsive to a variety of perspectives, bringing a range of relevant expertise to bear, asking appropriate, searching questions and requiring appropriate responses can all help in working towards a judgement and, in the words of Donnelly (1990), 'go a long way towards promoting ethical science'.

Because contestable judgement is inevitably involved, it is important that the weighing should be open to further re-evaluation and challenge over time, in light of experience. That is, as already noted, ethical review should be an on-going process. See pp. 21-22 for further discussion and recommendations on continuing review.

(vi) 'Ethical limits'

In addition to considering ethical justification in terms of the balance of likely benefit over harm, ethical review processes (nationally, regionally and/or more locally, e.g. within institutions) can, indeed sometimes do, set their own 'ethical limits' – deciding that some scientific uses of animals are *always* unacceptable, and cannot be justified in terms of weighing harms and benefits. For example, most FELASA countries regard the use of Great apes in research and testing (other than in non-harmful veterinary or ecological research for the animals' own benefit) as unacceptable.

Initial review: information to be provided by applicants

Application forms and/or criteria which applications must cover

18 (out of 20) respondents to our questionnaire report either that the information that applicants must provide is set out in law, and/or that special application forms are available. The latter are either nationally agreed or drawn up by local review processes. Examples of national application forms available in English include those from Switzerland (Swiss Federal Veterinary Office 2005a and b) and UK (Home Office 2005).

In the Netherlands, each committee has its own form, which must comply with national guidelines that require the following information to be given:

- Goal and relevance of the experiment
- Competence and experience of researcher and care personnel
- Argument as to why alternatives have been rejected
- Argument to support the chosen animal model
- Origin of the animals used and destination after experiment
- Housing and care conditions before, during and after the experiment
- Experimental conditions (nature of the conditions, frequency and duration)
- Anticipated amount of discomfort
- Anaesthesia, analgesia or other methods of reduction of discomfort
- Re-use
- Humane end-points (when and how)

In some countries, applicants are not only asked to describe the harms to animals and benefits likely to result from the study (including their efforts to implement the Three Rs) but to provide a statement addressing how they have weighed the harms and benefits, one against the other. Although it is recognised that providing such a statement can be difficult, this requirement is intended to encourage applicants to take personal responsibility for the ethical acceptability of their work, and not to defer judgements about the ethical weighing to others, such as participants in the ethical review process. In Switzerland, for example, applicants are asked to provide an "assessment of the importance of the knowledge which may be obtained or of the expected result *in relation to* [our italics] the pain, suffering, injury or anxiety which may be inflicted on the animals."

Whenever scientific proposals to use animals are reviewed, it is vital that applicants provide adequate information and argument on which to base the ethical review. Furthermore, since the application process itself can be an important prompt to encourage and assist applicants in thinking about ethical aspects of their proposed use of animals, it will usually be helpful to have special application forms that are designed to promote appropriate thought.

For comparison, see the list of information required for ethical review of proposals in Australia, which includes explanations of 'why the information is required' (Australian Government NHMR Council, 2004)

The ethical review process will be enhanced when applicants are required to describe their own harm-benefit assessments.

Lay ('non-technical') summaries of applications

Respondents from 6 of the 20 FELASA countries surveyed say that, at the time of writing, their countries definitely do *not* require researchers prepare 'lay' (non-technical) summaries of their applications to the ethical review process. In other countries such summaries are sometimes or always required.

None of the respondents to our questionnaire report that there are particular guidelines on how to prepare such summaries for the purposes of ethical review. In the UK, however, the Home Office provides guidelines for the production of project licence abstracts, which are made publicly available on the Home Office web-site in a move towards greater openness and in order to comply with the UK's Freedom of Information Act 2000 (Home Office, 2005).

The information provided should be accessible and meaningful to all participants in the ethical review process. Experience suggests that non-technical summaries can be valuable for *all* participants in the ethical review (whether these participants are labelled 'lay' or not), and optionally for public information purposes.

See Nerlich (1997) and ensuing correspondence from Mellor (1997) and Williams *et al.* (1997) for an interesting discussion of the value of lay descriptions of animal experiments. Also Smith and Jennings (2003, Appendix B) for a suggested format for lay summaries, based on observations of people who attended a forum for lay members of ethical review processes.

'Named' applications

It has been emphasised that the *personnel* and *facilities* involved in scientific projects using animals can have important impacts on the harms and benefits of those projects and therefore on the ethical weighing involved in their justification.

Applications to the ethical review process should be named (i.e. not anonymous), so that issues relating to who will carry out the work and where it will be carried out can be identified and considered in the review.

On-going ethical review, after initial authorisation

Where ethical review is carried out at the experiment level, on-going review is, in a sense, built into the system, since the review is carried out each time a new experiment is proposed. However, where initial review is carried out on longer-term projects, which might involve diverse experiments, there is a need for processes that can ensure that there is on-going ethical evaluation, in order to facilitate appropriate responses to (i) issues arising as individual experiments are planned; (ii) the actual harms and benefits that arise; and (iii) advances in practice in animal use and in science during the life of the project – as well as (iv) to help to ensure that the decisions and recommendations of ethical review processes are actually implemented in practice.

The LASA Ethics and Training Group (Jennings and Howard, 2005) has recently published, as a discussion document, some guidelines on retrospective review.

9 out of 20 respondents to the FELASA questionnaire report that their countries have formal mechanisms for interim review of studies in progress.

Elsewhere on-going review is achieved via the work of a national inspectorate (Denmark and UK) and/or the work of local Animal Welfare Officers (or their equivalent) and/or on-going interest of local ethical review processes.

In the Netherlands, on-going review is the norm, because most ethics committees review single experiments, rather than entire projects, and there is therefore ongoing review of projects when sequential experiments are reviewed. Committees regularly ask about the connection between the separate experiments.

Respondents from 5 out of 20 countries report that they carry out some form of retrospective review when projects have been completed.

It appears that only one country (Switzerland) has special nationally agreed forms to facilitate interim and retrospective review (see Swiss Veterinary Office 1994) – though in some countries, local ethical review processes design and use their own forms.

Effective on-going review should be incorporated into the ethical review process, via:

- (i) on-going monitoring and evaluation by everyone involved, including locally competent people, such as animal care staff, veterinary staff, animal welfare officers (and similar) and/or inspectors, in dialogue with researchers themselves; and**
- (ii) more formal process(es), such as:**
 - **formal interim review of projects (e.g. halfway through) to provide an opportunity for re-consideration of ethical issues arising in the work, including re-evaluation of the harm-benefit assessment in light of the actual harms and benefits arising, identification of possibilities for better implementation of the Three Rs, and any needs for training or expert advice; and**
 - **retrospective review when studies are completed, in order to help inform future ethical evaluations and learn from experience.**

Participants in ethical review: expertise and perspective

Table 3 (overleaf) illustrates how respondents to our questionnaire report that participation in ethical review processes varies between the 17 FELASA member countries in which, respondents report, the types of participant in ethical review processes are set out in law or are otherwise 'regularised'. Table 3 is an attempt to summarise the consistent participants in ethical review in each country: a 'Yes' (Y) in the Table implies that the expertise and perspective represented by a particular kind of person (e.g. veterinarian, lay person) is always involved in review by that particular process.

Country	Review Process	Required/regular membership							
		Scientist using animals	Vet	Animal care staff	Other animal welfare expert	Scientist not using animals	Animal welfare/protection society member	Lay person	Other members
Austria	Academia - National Comm.	Y	Y		Y		Y		
	Industry - Gov. inspector		Y						
Belgium	Local (institutional) committees	Y	Y or	Y or	Y				The Government inspector is an obligatory member; other mandatory members are the Director of the Institution and the laboratory technician carrying out the experiment. There must also be an 'independent member' – this could be someone from any of the last three categories listed
Czech. Rep	Local (institutional) committees	Y	Y		Y				
Denmark	National committee	Y (4) [†]					Y (4)	Y [∞]	Government representatives (2)
Estonia	National committee	Y (2)	‡		Y (1)		Y (2)		Government representatives (3) (veterinary civil servant and lawyer from Ministry of Agriculture; civil servant from Ministry of Environment)
Finland	Local (institutional) committees, <i>national committee from 2006</i>	Y		Y					Committees may also include vets, animal welfare specialists and animal protection representatives
France	Government inspectors		Y*						Researchers or Health Ministry experts
	Local (institutional) committees	Y*	Y*	Y*				Y*	
	Regional committees	Y*	Y*	Y*				Y*	
Germany	Regional committees	Y#				Y#	Y		Statistician. People in veterinary medicine, medicine or another branch of science. Plus the institutional Animal Welfare Officer, as an adviser (not voting).
Greece	Government inspectors		Y						
Latvia	National committee	Y (5)	Y (1)	Y (1)	Y (1)	Y (2)	Y (1)	Y (2)	
Lithuania	National committee	Y	Y		Y	Y	Y		Representative of State Food and Veterinary Service
Netherlands	Local (institutional) committees	Y	Y _φ		Y	Y			Alternatives experts; ethics specialists. Rarely, lay people
Norway	Local 'competent person'								Person approved by National Committee
	National committee	Y	Y	Y	Y				Legal expert
Poland	Regional committees	Y	Y			Y	Y		University veterinarians normally in attendance
Sweden	Regional committees	Y (6)					Y (2)	Y (5)	
Switzerland	Regional committees	Y					Y		All members must be experts in their fields; and must be independent of the authorising authority.
UK	Government inspectors								Veterinary or medically qualified
	Local (institutional) committees	Y	Y	Y					Many also have scientists not involved in animal use, lay people, animal welfare specialists and some have animal welfare organisation representatives and others
	National committee	Y	Y			Y	Y	Y	See note ♦

Notes: † Three scientists from academia, one from industry

∞ i.e. the Chairman, who is a High Court judge

‡ Animal welfare expert, one animal protection society member and one govt rep are all vets

* Although not mandatory, all public research organisations must conform to this model

Scientists must be involved, but it is not specified whether these are animal users or not

φ Competent person: could be a vet or other FELASA Category D (occasionally) C trained person – in attendance, not voting

♦ 2/3 must be medics or vets or have qualifications or experience in a biological subject. One must be a lawyer. At least half must not have held a licence within past six years. Animal welfare interests must be adequately represented.

Table 3: Membership of mandatory ethical review processes (to be read in conjunction with information in Table 1)

Ethical review processes must involve a wide enough range of expertise and perspective to facilitate comprehensive and detailed review of the factors that are relevant in the ethical evaluations. However, this does not (indeed cannot) mean that participants will be able to provide 'all the answers', but should mean that they have sufficient relevant understanding and insight to ask pertinent questions and know where to go for further expert advice. Some competencies will be needed at all times in ethical review; other relevant expertise and perspective should be called upon when required.

Veterinary and animal care expertise

Of 17 respondents from countries and regions that have ethical review processes with regularised membership:

- (i) 11 report that veterinarians are routinely involved; 4 that veterinarians are not always involved, and 2 that vets, although mandatory participants in ethical review, are there only 'in attendance', to give advice, and cannot 'vote';
- (ii) 6 report that animal care staff are routinely involved in ethical review;
- (iii) 8 report that other animal welfare specialists are consistently involved in ethical review, usually in addition to vets and/or animal care staff.

The ethical review process needs to be designed to give participants with veterinary and animal care expertise a clear 'voice' that is really listened to and acted upon. Wherever possible such participants should represent the staff who will share responsibility for the well-being of the animals in the project under review and can be considered to act as the animals' advocates in the review process.

All ethical review processes should include specific competence in animal welfare relevant to the species in question. Moreover, it is vital that veterinarians and animal care staff are directly involved in ethical review of animal research. These people should not be merely 'in attendance', but should be full, and key, participants.

Biomedical scientists who may or may not be involved in animal experiments

All 17 respondents from countries and regions that have ethical review processes with regularised membership report that these processes always include biomedical scientists.

Clearly, no one scientist can be 'expert' in all the different fields of work and animal procedures that are likely to come to the attention of an ethical review process; and often the scientific aspects will already have been subject to scientific peer review (e.g. during applications for funding). Nevertheless:

Scientific expertise is also of vital importance in ethical review - to assist, for example, in evaluating the scientific justification for, and ethical conduct of, procedures on animals, asking pertinent questions that can help to guide thinking, and helping to provide advice to researchers. Moreover, participation of practising scientists helps to emphasise that ethical review involves, and is not separate from, the scientific community.

Other expertise

Only 2 respondents report that their country's ethical review processes always/routinely involve statisticians or alternatives experts in ethical review: in Germany, a statistician and in the Netherlands, an alternatives expert, is a mandatory participant in the ethical review process. Other specific competencies that are frequently represented in review processes include legal and ethics expertise.

As already noted, there are needs for mechanisms to ensure the validity of experimental design, and conscientious efforts to search for alternatives, every time an animal experiment or other test is planned. Ideally, therefore, researchers should always have access to relevant statistical and information advisory services (which might be shared between institutions), which can also be called upon by the ethical review process when required. It is acknowledged, however, that it can be very difficult to find people with suitable expertise who are willing and able to offer such advice, and that this can be costly. Likewise, both researchers and ethical review processes should have access to sources of information on the Three Rs (e.g. electronic databases) and expertise to help in searching them.

Whilst specific expertise in other areas, such as law and ethics is also valuable, it is also clear that good ethical judgement is not limited to those who are specifically trained in these or other related disciplines. The involvement of lawyers and ethicists might bring similar benefits to those brought by wider 'lay' participation (see below). Moreover, the inclusion of a specialist in (bio)ethics can be valuable in providing a broader ethical perspective within the review process.

Lay and/or external perspectives

Respondents from 3 out of the 20 FELASA countries surveyed report that 'lay' people are consistently involved in ethical review (i.e. involved in *all* ethical review processes within that country – note that the entries for France in Table 3 do not refer to all establishments within the country).

Note, however, that the involvement of lay participants varies *within* some countries, between committees: at least 10 other countries involve lay people in some, but not all, ethical review processes. Sweden is particularly interesting in this regard, in that the regional committees must have at least 5 lay people, plus 2 representatives of animal protection organisations, who are also regarded as lay.

These 'lay' people come from a wide range of backgrounds. They include: administrative staff, including managers in areas unrelated to animal use, employees from human resources or communication, human scientists, sociologists, legal experts, academics from the arts or social sciences, lawyers, librarians, and safety officers.

In countries that have mandatory local ethical review processes, 3 (out of 5) respondents (from Belgium, Czech Republic, and Netherlands) report that these must involve people from outside the institution concerned.

Inclusion of uninvolved, 'lay' perspectives (i.e. people who are not involved in animal research and testing and have no technical expertise related to the scientific use of animals) and preferably external perspectives can add value to the ethical review process. Such participation is recommended.

Such people can, for example, provide an independent, novel perspective on the issues, supply a measure of public representation, help to ensure the integrity of the process of review, and above all might emphasise to participants that the public at large has an interest in the process of ethical evaluation of laboratory animal use. Of course, none of these roles are unique to lay participants, but indicate the kinds of benefits that lay perspectives might bring (Smith and Jennings 2003; see also Dresser 1999).

In the UK, which has relatively recently allowed for the involvement of lay people in ethical review, a Government report on the effectiveness of local ethical review processes expresses enthusiasm about the role of lay participants, concluding that:

"Lay members of ERPs have asked questions from a different perspective. They have constructively challenged existing assumptions and practices, with the result that improvements have been made with respect to licence applications and animal care and use" (Home Office 2001).

When lay people are included in an ethical committee with such intentions, it could be argued that in time they might lose their detachment from the issues at hand. It may therefore be wise to limit lay participants' terms of service within ethical review processes, bringing in 'new faces' from time to time. Similarly, in order to keep the approach 'fresh' it might also be desirable to rotate other participants from time to time.

Involvement of researchers whose work is under review

In none of the countries surveyed by FELASA do researchers whose work is under review *always* participate in meetings, and in most it seems that they are present only rarely, when the ethical review process has identified needs for additional information or there are some special issues to discuss. By contrast, in the UK, researchers are frequently present when their work is subjected to local ethical review, and/or engage in dialogue with the review process, at least in the early stages.

Ultimately, responsibility for what is done to animals in the name of science rests with the researchers involved: they therefore need to recognise their essential role in ethical review, and to see themselves as part of the process, rather than regarding ethical review committees or processes as something special and separate (something 'out there', that 'merely sits in judgement' on their work) – see Animal Procedures Committee (2003) for further discussion.

Ethical review should be carried out in dialogue with the researchers involved, recognising the researchers' responsibility for what happens to the animals in practice.

In order to facilitate dialogue, it is important for researchers whose work is under review to be involved in the review process, either in person or by e mail, for example. Such dialogue is needed to achieve the 'educational benefits' of ethical review, outlined below. However, this need not mean that the researchers are present during actual deliberations leading to a decision whether or not to authorise the project: it is important to strike a balance between enabling a beneficial dialogue and ensuring that the independence of the committee or other process, and its members, is not compromised.

Other perspectives

It is valuable for national authorisation and/or inspection bodies (where they exist) to take an interest in how ethical review is performed 'on the ground' (e.g. in order to assess the quality

of the advice that they are offered) and therefore periodically to attend meetings or otherwise review the impact of the local processes.

Similarly, it can be valuable for senior institutional management to be involved in local ethical review, in order, for example, to provide visible management support for the process, to understand where any difficulties lie and how they might be overcome, and to facilitate practical responses to such difficulties from within the institution (e.g. changes in management structure, provision of resources).

'Training' for participants

Respondents from 3 FELASA countries report that participants in their ethical review processes have the opportunity to receive some form of special training or education (over and above the normal professional qualifications and updates that participants would be expected to have in relation to their particular field of work). However, 2 of these also report that uptake is usually low.

It should be ensured that participants in ethical review processes understand their role in the process, the reasons for requiring ethical review, and how their own ethical review process is organised; and, further:

- **appreciate the wider legal context in which the review process operates;**
- **are aware of the general ethical principles involved; and**
- **feel able to ask relevant and suitably challenging questions when necessary.**

These goals might be achieved by some form of 'training', but perhaps more effectively, by provision of suitable resources to support participants in ethical review processes, as well as opportunities to exchange ideas and experiences and debate issues of common concern.

FELASA would be well placed to collate and disseminate resources and promote dialogue to support and assist participants in ethical review across Europe.

Role of ethical review in promoting a wider 'culture of care'

Ethical review can also bring important educational benefits, which extend beyond review of particular research proposals and which can help to ensure that everyone involved in the scientific use of animals is:

- aware of the relevant legislative requirements and ethical implications of their work;
- appraised of relevant developments in laboratory animal science and the application of the Three Rs and is motivated to adopt current best practice;
- encouraged to reflect and learn from experience; and
- has access to, and knows where to find, resources and advice on all these matters.

It might be argued that if these educational roles are properly fulfilled, ultimately an effective ethical review process could 'put itself out of business'. However, only one respondent to our questionnaire reports that their ethical review processes at present are required to promote such educational/awareness-raising activities.

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.

Effective ethical review processes can advance and facilitate such educational outcomes by, for example:

- **providing, in themselves, a 'forum for discussion' of issues arising in laboratory animal use;**
- **supplying on-going advice and resources to support researchers;**
- **promoting awareness-raising activities, such as seminars on contentious or difficult issues in animal use; and**
- **being open, by explaining their work both to people both within and without the institutions concerned.**

Designing ethical review to meet national and local needs

It is important that the overall organisation of ethical review meets both national and local needs and enables the process to operate effectively within the various wider legal and political structures of each country. As our analysis shows, the general principles outlined above can be implemented in a variety of different but effective ways, integrating the work of 'committees' with other processes and mechanisms.

We also note that, to command confidence, the benefits of ethical review should be seen to outweigh the time and effort put into the process. Therefore, in designing an ethical review process, it is important to ensure that bureaucracy is kept to the minimum necessary to achieve the review objectives effectively. Furthermore, that review processes monitor and assess their own performance and are responsive to suggestions for changes in practice that could make the process more effective and expedient.

Some examples of potentially effective approaches are illustrated by means of the flow chart in Appendix 2. Note that the following elements are incorporated, following from the principles outlined in our report:

- ***local review***, to take into account the local context in which the animals will be used and to consider wider local issues that have a bearing on the use of animals;
- ***means of providing support and advice to the researchers involved;***
- ***opportunities for discussion*** that can bring different perspectives to bear on the issues involved;
- ***means of ensuring and checking that the advice and decisions of the ethical review process are actually implemented in practice;***
- ***an over-arching body or other mechanism to oversee the process as a whole:*** to provide advice and set standards; and also to act as final arbiter, either routinely, or in difficult cases.

Quality and consistency of the outcomes of ethical review

Much of the foregoing discussion focuses on the *process* of ethical review. However, what really matters, above all else, is the quality of the *outcomes* of ethical review.

The benefits of ethical review usually seem clear to those involved, but it is difficult to provide objective (or quantitative) assessment of the value of the outcomes of review in practice (Jennings and Miller 2000). Analysis of the modifications made to proposals as a result of ethical review has been attempted in some studies, most recently in an interesting survey in Sweden, by Hagelin, Hau and Carlsson (2003), who also review other attempts to assess such outcomes. Retrospective studies such as these are valuable in providing illustrations of the refinements in practice that ethical review promotes and, perhaps, could also be used to show how these can benefit the science itself. The latter is important in helping to convince

researchers that such review is worth the time and effort it requires. There are, however, few studies of this kind available.

In addition to potentially 'measurable' outcomes, such as refinement of scientific procedures, ethical review should also have wider educational benefits – promoting awareness of possibilities for implementing the Three Rs and on-going critical evaluation of other ethical aspects of the studies, for example – which are even more difficult to measure.

Careful design of the process of ethical review, and diligence in its application can go a long way in promoting value and consistency of outcomes (to the benefit of both animals and science), but not the whole way. Clearly, it is in the nature of ethical evaluation that different ethical review processes will, on occasion, come to different decisions (see Plous and Herzog 2001 for a relevant quantitative study). However, if different processes, between or within countries, are operating to significantly different 'standards' in that, for example, they diverge significantly in their concepts of what comprises 'good practice' or a 'humane endpoint', or in how well they are informed about advances in possibilities for applying the Three Rs, then the value and credibility of the review process will be compromised.

It is vitally important that efforts are made to develop common ethical goals and outputs as well as common processes of ethical review – both within and between countries – and, as part of this, to ensure that all involved are aware of developments in laboratory animal science and advances in application of the Three Rs.

This will require the opening of channels of communication between a wide range of ethical review processes, in order to compare existing guidelines and how they are applied, and begin to work towards consensus on common goals and outputs. Within Europe, a major aim of a current EU-funded COST (European Co-operation in the field of Scientific and Technical Research) Action on "Laboratory Animal Science Welfare" is to begin to generate and inform such dialogue. The Action includes a working group on ethical evaluation and cost-benefit analysis, and will draw on the support of the FELASA 'network' of laboratory animal science organisations across Europe.

Acknowledgement

We should like to thank all those who responded to our questionnaire.

References

- AALAS (2002). *Working with the IACUC: Writing an animal protocol*. AALAS: Memphis TN. Available to order, via: <http://www.aalas.org/Bookstore/misc/bookstore.pdf>
- Animal Procedures Committee (2003). *Review of cost-benefit assessment in the use of animals in research*. Home Office, Communication Directorate: London. www.apc.gov.uk
- ARENA (Applied Research Ethics National Association) and OLAW (Office of Laboratory Animal Welfare), NIH (2002). *Institutional animal care and use committee guidebook*. Second edition. OLAW, NIH: Bethesda, MD. <ftp://ftp.grants.nih.gov/IACUC/GuideBook.pdf>
- Australian Government National Health and Medical Research Council (2004). *Australian code of practice for the care and use of animals in scientific procedures*. Australian Government. <http://www7.health.gov.au/nhmrc/publications/synopses/ea16syn.htm>
- Bateson, P. (1986). When to experiment on animals. *New Scientist* **109** (1496), 30-32.
- Baumans, V., Brain, P.F., Brugere, H., Clausing, P., Jeneskog, T. and Perretta, G. (1994). Report of the Federation of European Laboratory Animal Science Association Working Group on pain and distress in laboratory rodents and lagomorphs. *Laboratory Animals* **28**, 97-112.
- Boisvert, D.P and Porter, D.G. (1995). Ethical scoring systems. pp.637-641, in: Report of the 1995 World Congress on Alternatives, Alternative Methods in Toxicology and Life Sciences Series **11** (eds A.M. Goldberg and L.F.M. van Zutphen).
- Boyd Group/RSPCA (2004). *Categorising the severity of scientific procedures on animals: summary and reports from three round-table discussions*. Published by the RSPCA Research Animals Department. www.boyd-group.demon.co.uk
- Canadian Council on Animal Care (1997) *CCAC guidelines on animal use protocol review*. CCAC: Ottawa. www.ccac.ca/en/CCAC_Programs/Guidelines_Policies/GDLINES/PROTOCOL/PROTGDE.HTM
- Canadian Council on Animal Care (1991) *Categories of Invasiveness in Animal Experiments* CCAC: Ottawa. www.ccac.ca/en/CCAC_Programs/Guidelines_Policies/POLICIES/CATEG.HTM
- Delpire, V.C., Mephram, T.B. and Balls, M. (1999). A proposal for a new ethical scheme covering the use of transgenic laboratory animals in the European Union. *ATLA* **26**, 21-43.
- Donnelly, S. (1990). Animals in science: the justification issue. pp.8-13, In: *Animals, science and ethics* (eds S. Donnelley and K. Nolan), The Hastings Center: NY.
- Dresser, R. (1999). Community representatives and nonscientists on the IACUC. What difference should it make? *ILAR Journal* **40**, 29-33.
- Hackbarth, H. and Lückert, A. (2002). *Tierschutzrecht*. Verlag Jehle Rehm: München/Berlin
- Hagelin, J., Hau, J. and Carlsson, H-E. (2003). The refining influence of ethics committees on animal experimentation in Sweden. *Laboratory Animals* **37**, 10-18.
- Higgs, R. (1997). Entry on *Ethical debates, methods of*, pp.87-88, in: Boyd, K.M., Higgs, R., Pinching, A.J. eds. *A New Dictionary of Medical Ethics*. BMJ Publishing Group: London.

Home Office (1998). The cost/benefit assessment, *Chapter 2 Annexes 1-3 in Appendix F to the Report of the Animal Procedures Committee for 1997*. TSO: London.
www.apc.gov.uk/reference/ar97.pdf

Home Office (2000). *Guidance on the operation of the Animals (Scientific Procedures) Act 1986*. HC 321. TSO: London. www.official-documents.co.uk/document/hoc/321/321.htm

Home Office (2001). *Animals (Scientific Procedures) Inspectorate review of the 'ethical review process' in establishments designated under the Animals (Scientific Procedures) Act 1986*. November 2001. <http://www.homeoffice.gov.uk/docs/erpreview.html>

Home Office (2005). *Animals (Scientific Procedures) Act 1986, Application for a project licence*. Revised version January 2005 http://www.homeoffice.gov.uk/docs4/PPL_Form.doc. Includes hyper-links to detailed notes on completing the application, including notes on producing an Abstract (http://www.homeoffice.gov.uk/docs4/PPL_Form.doc#Abstract)

Jennings, M. and Miller, J. (2000). Harmonising IACUC practices. pp. 1705-11, In: *Progress in reduction, refinement and replacement of animal experimentation*. (Balls, M., van Zeller, A.M., Halder, M.E. eds). Elsevier Science BV: The Netherlands

Jennings, M. and Howard, B. (2005). *Guidance notes on Retrospective Review: A discussion document prepared by the LASA Ethics and Training Group*. LASA: Tamworth.
http://www.lasa.co.uk/position_papers/publications.asp

Mann, M.D. and Prentice, E.D. (2004). Should IACUCs review scientific merit of animal research projects? *Lab Animal* **33**,1.
<http://www.labanimal.com/laban/journal/v33/n1/full/laban0104-26.html>

Mellor, D.J and Reid, C.S.W. (1994). Concepts of animal well-being and predicting the impact of procedures on experimental animals. pp.3-18, In: *Improving the Well-Being of Animals in Research Environments* (eds. R.M Baker, G. Jenkin and D.J Mellor). ANZCCART: Adelaide and Wellington.

Mellor, D. (1997). Lay descriptions in ethics applications. *ANZCCART News* **10 (3)**, 7-8.

Morton D.B. and Hau J. (2002). Welfare assessment and humane endpoints. pp. 457-486 in: *CRC Handbook of Laboratory Animal Science Volume 1: Essential principles and practices* (2nd edition). Eds Jann Hau and Gerald L Van Hoosier, Jr.. CRC Press.

Nerlich, G. (1997). The point of lay descriptions. *ANZCCART News* **10 (2)**, 7.

New Zealand Ministry of Agriculture and Forestry (2004). *Animal use statistics*. MAF: Wellington. <http://www.biosecurity.govt.nz/animal-welfare/naeac/animal-use-statistics.htm>

New Zealand National Animal Ethics Advisory Committee (2002). *Good practice guide for the use of animals in research, testing and teaching*. MAF: Wellington.
<http://www.biosecurity.govt.nz/animal-welfare/naeac/papers/guide-for-animals-use.pdf>

Nuffield Council on Bioethics (2005). *The ethics of research involving animals*. Nuffield Council on Bioethics: London. Available at: www.nuffieldbioethics.org

Plous, S. and Herzog, H. (2001). Reliability of protocol reviews for animal research. *Science* **239**, 608-609.

Porter, D.G (1992). Ethical scores for animal experiments. *Nature* **356**, 101-102

Prentice, E.D., Crouse, D.A. and Rings, R.W. (1990). Approaches to increasing the ethical consistency of prior review of animal research. *Investigative Radiology* **25**, 271-274.

Smith, J.A. and Boyd, K.M. eds. (1991). *Lives in the Balance: The Ethics of Using Animals in Biomedical Research*. Oxford University Press: Oxford.

Smith, J.A. and Jennings, M. (2003). *A resource book for lay members of local ethical review processes*. Available from: Research Animals Department, Wilberforce Way, Southwater, Horsham, West Sussex RH13 7WN, UK

Stafleu, F.R., Tramper, R., Vorstenbosch, J. and Jones, J.A. (1999). The ethical acceptability of animal experiments: a proposal for a system to support decision-making. *Laboratory Animals* **33**, 295-303.

Swiss Federal Veterinary Office (2005a). *Explanatory notes on licence application and notification of animal experiments*. Version 1.1.05
<http://www.bvet.admin.ch/tierschutz/00237/00832/index.html?lang=en>

Swiss Federal Veterinary Office (2005b). *Form A: Application for the execution of animal experiments*. Version 1.1.05
<http://www.bvet.admin.ch/tierschutz/00237/00832/index.html?lang=en>

Swiss Federal Veterinary Office (1994). *Explanatory notes on interim and final reports of animal experiments*. <http://www.bvet.admin.ch/tierschutz/00237/00832/index.html?lang=en>

Swiss Federal Veterinary Office (undated). *Classification of animal experiments according to grades of severity prior to the experiment (stress categories)*.

TEWG (2003a). Technical Expert Working Group for the revision of Directive 86/609/EEC on the protection of animals used for experimental and other scientific purposes *Final report, sub-group on ethical review*.
http://europa.eu.int/comm/environment/chemicals/lab_animals/pdf/finalreportethicalreviewprocess.pdf

TEWG (2003b). Technical Expert Working Group for the revision of Directive 86/609/EEC on the protection of animals used for experimental and other scientific purposes *Final report, sub-group on scope*.
http://europa.eu.int/comm/environment/chemicals/lab_animals/pdf/finalreportscope.pdf

Voipio, H-M., Kaliste, E., Hirsjärvi, P., Nevalainen, T. and M. Ritskes-Hoitinga (2004). Nordic-European workshop on ethical evaluation of animal experiments. Workshop report on the cost-benefit principle in Hanasaari, Helsinki, Finland 7-9 November 2003. *Scandinavian Journal of Laboratory Animal Science* **31**, 251-26

Voipio, H-M., Kaliste, E., Hirsjärvi, P., Ritskes-Hoitinga, M. and Nevalainen, T. (2005, in press). Nordic forum for ethical evaluation of animal experiments. *Proceedings of the 9th FELASA Symposium*.

VWA (2003) *Zo Doende 2003 (Statistics of animal experimentation in the Netherlands)*. VWA: Den Haag. http://www.vwa.nl/download/rapporten/Dierproeven/zodoende_2003.pdf

Williams, K., Finlay-Jones, Sims, N. and Close, E. (1997). Light on the subject of lay descriptions. *ANZCCART News* **10 (3)**, 8.

Appendix 1

Questions asked of representatives of FELASA member countries

1. Is ethical review of scientific work involving animals a legal requirement in your country or region? YES NO

If NO, please continue to complete the questionnaire where relevant.

If YES, which law(s) apply and what do they require?

2. Is all scientific work involving animals subject to ethical review? YES NO

If YES, how is 'animal' defined?

If NO, which kinds of scientific work involving animals are selected for review?

At what 'level' is the ethical review carried out? e.g. at project, study protocol or other level?

3. Who carries out the ethical review(s)?

- 3.1 Please tick all the people and processes involved:

- Government inspectors
- A national ethics committee
- Regional ethics committees (how many nationwide:)
- Institutional ethics committees
- Other – please state:

- 3.2 If local ethics committees are involved, are these established in every institution in which animals are used? YES NO

If NO, where are they found?

- 3.3 If more than one process is involved (e.g. Government inspection and local committee review) what is the relationship between the different processes?

- 3.4 Who is involved in the review process(es)?:

(i) How many people are involved in each committee or other process? How many people are mandatory (by law)?

(ii) Who are the people involved? Please tick all that apply, for each process ticked in 3.1:

- | | |
|--|---|
| <input type="checkbox"/> Scientists who use animals | (mandatory? <input type="checkbox"/> YES <input type="checkbox"/> NO) |
| <input type="checkbox"/> Veterinarians | (mandatory? <input type="checkbox"/> YES <input type="checkbox"/> NO) |
| <input type="checkbox"/> Animal care staff | (mandatory? <input type="checkbox"/> YES <input type="checkbox"/> NO) |
| <input type="checkbox"/> Other animal welfare specialists | (mandatory? <input type="checkbox"/> YES <input type="checkbox"/> NO) |
| <input type="checkbox"/> Members of animal protection organisations | (mandatory? <input type="checkbox"/> YES <input type="checkbox"/> NO) |
| <input type="checkbox"/> Scientists who are not involved in animal use | (mandatory? <input type="checkbox"/> YES <input type="checkbox"/> NO) |
| <input type="checkbox"/> Lay people | (mandatory? <input type="checkbox"/> YES <input type="checkbox"/> NO) |

- Statisticians** (mandatory? YES NO)
- Alternatives experts** (mandatory? YES NO)
- Other – please state:**

- (iii) If 'lay' people are involved, what kinds of background do they have and how are they selected?
- (iv) For institutional processes, are only people from within the institution involved, or are there external people as well?

3.5 Do members of the ethical review process(es) receive any special training?

YES NO

If YES, what does this entail?

3.6 Are there any collaborations with other committees or other processes?

YES NO

If YES, please explain:

4. **What does this ethical review involve?** If more than one process is involved (as indicated above), please describe the aspects considered by each of the processes.

4.1 What information has to be provided by researchers about their project/protocol?

Are there special forms for researchers to complete? YES NO

If YES, please would you attach a copy/copies, or give a web site address:

4.2 Do you require 'lay' (non-technical) summaries of projects/protocols? YES NO

Do you have any special guidelines on preparing such summaries? YES NO

If YES, please would you append a copy, or give a web site address

4.3 What aspects of studies are examined in the ethical review?

Are there particular guidelines for carrying out the review and/or lists of factors / checklists that have to be considered? YES NO

If YES, please would you attach a copy/copies, or give a web site address.

If NO, please describe the aspects that are covered, by ticking all that apply:

- aim and necessity of study**
- experimental design**
- scientific validity of using animals**
- likely benefits of the studies**
- the need for animal experiments**
- severity of the harms caused to the animals**
- application of the Three Rs and the priority given to them**
- harm('cost')/benefit analysis: whether the harms to the animals are justified by the hoped-for scientific benefit**
- Other – please state:**

5. Do the people involved in the ethical review process(es) visit the animal facilities and/or view animals being used in experiments? YES NO

If YES, is this a legal requirement?

6. Are the decisions made on a written basis or do the members of the review process meet?

If the members meet, are the researchers involved invited to a part of these meetings?

7. Are the decisions of the ethical review processes/committees mandatory or advisory?

8. How long does the ethical review usually take for a project or protocol?

9. Is there ethical review after initial permission for the work is granted?

- 9.1 Is there on-going review? YES NO

If YES, how is this achieved?

- 9.2 Is there retrospective review after the project or protocol is completed? YES NO

If YES, how is this used to inform future judgements?

- 9.3 If there is on-going or retrospective review, please describe below the factors that are considered:

Are there special forms for researchers to complete? YES NO

If YES, please would you attach a copy/copies, or provide a web address

- 9.4 Is there an inspection system, to check that the project is carried out as planned and according to the permissions given? YES NO

If YES, please describe what this entails:

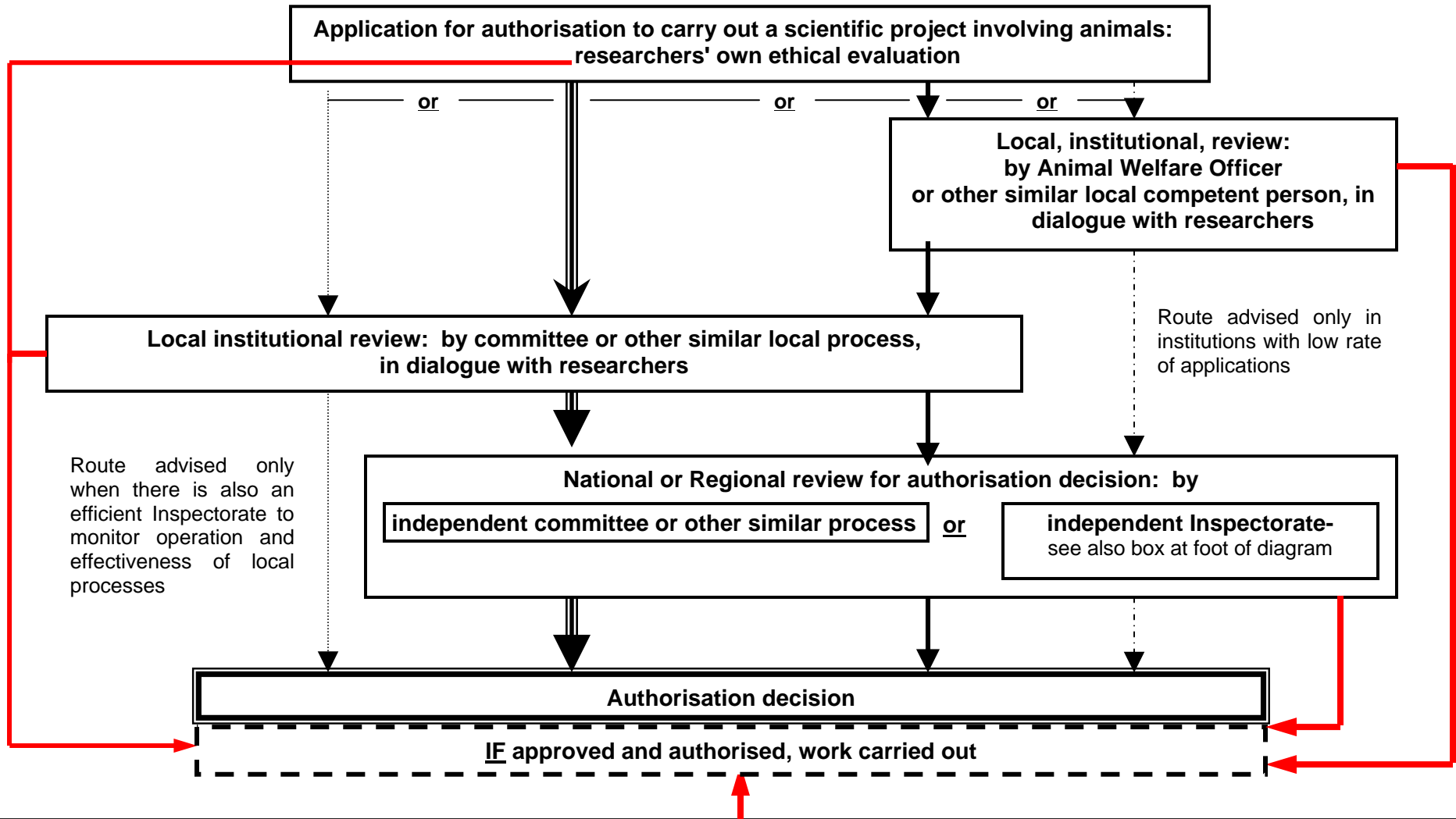
10. Are the ethical review procedures used the same for all scientific work involving animals - or are some uses subject to special review (e.g. use of non-human primates; transgenic animals; other)? If some work is subjected to special review, which kinds of studies, and what does the special review involve?

11. Do you have, or use, any particular resources to help the work of your ethical review process and/or the scientists wishing to submit a project/protocol? For example, books, scientific papers, data bases, web pages. If so, please would you provide details for us:

12. Is there any other information about your country's system(s) of ethical review that you think we should know about? (For example, do your ethics committees, or other ethical review processes, have roles or functions that you have not yet described in this questionnaire?)

In particular, please indicate any areas of difficulty in your ethical review system and ideas on how these might be addressed, as well as examples of particularly successful or innovative approaches that you feel should be shared with others

Appendix 2: Examples of strategies for the organisation of ethical review that can meet the general principles outlined in this report. *Follow black arrows of similar style to see different 'routes' for review. Red arrows show some routes for on-going monitoring and ethical review of work in progress.*



Independent Inspectorate or other over-arching process: to check that work is carried out only as authorised and impose sanctions if not. Note: may also be involved in ethical review as shown above; if not another role should be to monitor effectiveness of other elements of the review.