

Principles and practice in ethical review of animal experiments across Europe: summary of the report of a FELASA working group on ethical evaluation of animal experiments

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Summary

This paper summarizes a more detailed report produced by the Federation of European Laboratory Animal Science Associations (FELASA 2005), which describes and explores a set of principles for the conduct of ethical review of laboratory animal use. It presents a synopsis of results from a questionnaire that elicited information on how each of 20 countries represented in FELASA currently approaches such ethical review. This information suggests that, although local practices differ, there is an emerging consensus on the key elements that any ethical review process should involve. Drawing on the questionnaire findings, this summary also includes a brief discussion to support and amplify a series of recommendations, covering the objectives of ethical review; legal requirements; the scope of work reviewed and the 'level' at which review is approached; general principles for the organization of ethical review processes; the factors considered in the review; needs for ongoing review after initial authorization; participants in the review process; wider impacts of the review process; and strategies that can help to ensure quality and consistency of review outcomes. For further information and examples of current practice, as well as more detailed discussion to support the recommendations, readers are urged to refer to the complete report, available at http://www.lal.org.uk/pdf/files/FELASA_ethics_FULL_Report.pdf or via: <http://www.felasa.eu/recommendations.htm>.

Keywords Ethical evaluation; ethics committee; ethical review process; animal experiments; Europe

At present, relevant European rules (EU Directive 86/609 (Council of the European Communities 1986) and Council of Europe Convention 123 (Council of Europe 1986)) contain no specific requirement for prior ethical review of proposed animal studies.¹

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.

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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 subgroups, 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 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 organized and carried out in the different FELASA member countries, using a detailed questionnaire completed by carefully chosen representative(s) of each country – that is, people with an intimate, practical understanding of ethical review in that country, as recommended by the FELASA Board. The questions are listed in an Appendix to the full report.

In this way, the Working Group gained 'snapshots' of experiences of ethical review from the following 20 FELASA member countries: Austria, Belgium, Czech Republic, Denmark, Estonia, Finland,

France, Germany, Greece, Ireland, Italy, Latvia, Lithuania, The Netherlands, Norway, Poland, Spain, Sweden, Switzerland and the 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 laboratory animal science organizations, and wherever possible double-checked against other published accounts.

This information and comment, together with reviews of relevant published and online literature, enabled the Working Group to consider the advantages and disadvantages of a range of different approaches to ethical review, identify common elements and principles, and then to draw up FELASA's recommendations for the conduct of effective ethical review in practice, which have been agreed upon by the FELASA Board.

This paper summarizes key points from the survey, lists in bold (#1 – #30) the emerging principles for effective ethical review recommended by FELASA, and presents a brief bibliography. The full report (FELASA 2005) contains more extensive examples of current practice in ethical review across Europe and an in-depth discussion in support of the recommendations. It can be found at http://www.lal.org.uk/pdf/files/FELASA_ethics_FULL_Report.pdf and via: <http://www.felasa.org/recommendations.htm>.

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

Defining 'ethical review': objectives of the process

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:

1: Ethical review should aim to ensure that, at all stages in scientific work involving animals, 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 ongoing, critical evaluation. This should involve consideration of:

- (i) **the possibility that the objectives might be achieved by alternative means, not involving the use of animals;**
- (ii) **the balance of the predicted (or actual) benefits of the work over the harms caused to the animals involved;**
- (iii) **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 maximized; and**
- (iv) **whether and how far animal suffering is minimized and animal welfare enhanced, by implementation of the Three Rs (replacement, reduction and refinement), optimization 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 not only need to subject particular scientific uses of animals to ethical review, but also 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 animal work, communication, and the training, experience and resulting competence of personnel. Importantly, they will also need adequate resources, including time, and both national and institutional support.

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.

Respondents from Italy, Spain and Ireland report that their countries 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, 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 signed charters committing them to set up ethics committees for animal experimentation.

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

- (i) all relevant animal studies (see below) are, in fact, subjected 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 decisions arising from the review are implemented in practice.

Beyond this, care should be taken to ensure that the law does not unnecessarily prescribe or restrict the way in which the ethical review process can discharge its duties. The practical organization 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 that make best use of locally available resources and support.

2: As is largely already the case, 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 organized 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 are implemented, and their recommendations given due weight, in practice. The power to stop animal studies, when, for example, authorizations are exceeded or unexpected adverse events occur that prejudice their justification (see # 1), 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

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 report that at a minimum this accords with the definitions in EU Directive 86/609.² Beyond this, there are a number of national variations in how a 'scientific use of animals' is defined for purposes of regulation and/or ethical review. For example:

Some countries extend the definition of 'animal' to include vertebrate embryos and fetuses and/or invertebrate species.

*Some also extend the definition of a 'regulated procedure' to include 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); and/or scientific uses of protected animals that do not cause pain, suffering, distress or lasting harms, e.g. some behavioural, dietary and field studies.*

Interpretation of 'regulated purposes', as defined in EU Directive 86/609 and Council of Europe Convention 123, varies between countries in that:

- some include purposes that are covered in the European Convention but not the EU Directive, e.g. the use of protected animals in regulated procedures for education and training purposes and forensic enquiries; and/or
- some countries explicitly exclude from ethical review the use of protected animals in regulated procedures carried out for safety or efficacy tests that are required under local or international legislation.

Our full report presents the reasoning behind the following recommendations concerning the scope of laboratory animal use subject to ethical review:

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 authorization, 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.

5: 'Initial' ethical review should be carried out when authorization to use animals is requested; and mechanisms should also be in place to ensure that there is 'ongoing' 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 authorization 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 minimized 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 (from birth to death) and the scientific value of studies in which they are used.

Level of detail in ethical review

The 'level' at which initial ethical review should be approached will be difficult to prescribe. At present, practice in this regard also 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 authorization – e.g. 5 years maximum – after which, if the project is not yet complete, further application for authorization 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 harms – where examples of 'technical acts' would include gavage, injection, laparotomy, withholding of food/water.

8: It is FELASA's view that in general initial ethical review should be at the project level. 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 five-year *maximum*, would not preclude a more limited duration – which might vary between countries according to local requirements and context.

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.

Principles for the organization of ethical review

Confidence in ethical judgements 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 & Boyd 1991).

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;
- recognizing 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 ongoing review and re-evaluation; and
- being *seen* to do these things.

As will be generally accepted, it is also important that the overall organization 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.

Table 1 summarizes the general organization 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 methods – 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.

One-person review processes, compared with wider involvement in ethical review

As Table 1 shows, in three respondent FELASA countries, mandated review is

carried out by one person – in all circumstances for two of the countries and in industry for the third (though there may be voluntary local ethics committees in some institutions).

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.

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.

Table 1 shows that this is already the case in some institutions.

National, regional and/or local (institutional) review

Table 1 shows that in five of the 20 FELASA countries surveyed – falling to four in 2006, because of a change in the law in Finland – local (institutional) review is mandatory, by virtue of statute or other binding requirement.

In the remaining 15 countries (rising to 16 countries in 2006), there is no mandatory, national 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 nine of the other countries ethical review processes are voluntarily established in some institutions.

Table 1 General organization 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 authorization 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 (22); institutional committee in each industrial firm ¹
Germany	Review by Institutional Animal Welfare Officer (a veterinarian, medical doctor or zoologist), then by Regional Animal Welfare 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

Table 1 (continued)

Country	Mandatory processes*	Voluntary processes
The Netherlands	<p>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 that do not have their own</p>	
Norway	<p>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</p> <p>Regional committees (18) set up by the National Ethics Committee on Animal Experimentation (NEC/AE), which oversees their work as an appeal authority</p>	Institutional committees in some facilities
Poland	<p>Regional committees (18) set up by the National Ethics Committee on Animal Experimentation (NEC/AE), which oversees their work as an appeal authority</p>	
Spain	<p>Regional committees in <i>Catalonia, Andalusia and Aragon</i>; institutional committees in <i>all research centres in Catalonia and Aragon</i>. <i>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></p>	Institutional committees in most other research centres in the remaining regions
Sweden	<p>Regional committees (7)</p>	
Switzerland	<p>Regional committees (10), which advise the Cantonal Authority whether or not experiments should be authorized; plus a National committee to advise the cantons in controversial cases and more general matters. The Federal Veterinary Office has the right to appeal</p>	Institutional committees in some facilities
UK	<p>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 are 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</p>	

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

†Although not legally required, the organizations involved signing a binding commitment to submit work to these processes for ethical review

Table 1 also shows that all four of the countries in which local, institutional review remains mandatory after 2006 also have other national processes (national committees and/or inspectorates) that may 'oversee' the local review and/or act as final arbiter in decisions whether or not to authorize the work.

Regional or national review has the clear advantage of 'distance' from the personnel and work at hand and hence brings a measure of independence and impartiality 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. This approach can also provide *support and advice* for researchers preparing and submitting applications for more formal approval and performing ongoing ethical evaluation. Furthermore, involving local participants in ethical review will add to the awareness-raising effect of the review process within institutions.

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 overarching process within each country (or region) that can act as an 'independent' monitor of the performance of the local processes, and set standards; and as a body 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 may be contested – see, for example, Nuffield Council on Bioethics (2005) for further discussion of ethical positions), a 'justification' for the use of animals will usually 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. Such an ethical weighing is often referred to as a cost-benefit analysis. However, so as to 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:

- 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,
- 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 minimize 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 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), and a harm-benefit assessment is *not* a requirement of pan-European law.

Despite the lack of a Europe-wide legislative requirement, most respondents to the FELASA survey report that their ethical review processes carry out harm-benefit assessments. However, a small but significant number 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 five of the countries surveyed does not appear to include a requirement to perform such an ethical weighing of benefits against harms, focusing only on the harms and how these can be minimized.

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.

Carrying out harm-benefit assessment in practice

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 & Boyd 1991).

Respondents from nine 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. Eighteen (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 that 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 (for further comment, see the following section).

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 & Boyd 1991, APC 2003).

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 harms in scientific projects involving the use of animals. Such lists should be used as aide-mémoires, 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.

Many such lists are in current use, often locally developed or adapted from published lists and other guidance. A range of examples of practical guidance currently in widespread use is presented in the references and bibliography at the end of this paper.

Drawing on a number of such published schemes, a list of key, general factors that are important in ethical evaluation of scientific projects involving animals are 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. Our full report (FELASA 2005) includes further discussion of approaches to harm-benefit assessment in practice (including the use of harm/severity classification schemes), making reference in particular to the useful, extended analysis contained in a recent report from the UK's Animal Procedures Committee (APC 2003).

Initial review: information to be provided by applicants

Eighteen (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 undated and 2004) and UK (Home Office 2005a).

Respondents from six of the 20 FELASA countries surveyed say that, at the time of writing, their countries definitely do *not* require researchers to 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 website (Home Office 2005b) in a move towards greater openness and in order to comply with the UK's Freedom of Information Act 2000.

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. This should include information relevant to the questions in Table 2. 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 is 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 they are labelled 'lay' or not), and optionally for public information purposes.

19: Applications to the ethical review process should be named (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.

Ongoing ethical review, after initial authorization

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

Elsewhere, ongoing review may be achieved via the work of a national inspectorate and/or the work of local Animal Welfare Officers (or their equivalent) and/or ongoing interest of local ethical review processes.

Respondents from five 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 (Swiss Veterinary Office 1994) – though in some countries, local ethical review processes design and use their own forms.

Where individual experiments are subject to formal ethical review, ongoing review is, in a sense, built into the system, since

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 ongoing 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 ongoing 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 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, 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?)
- optimization 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 while 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 endpoints
 - better use of anaesthesia and analgesia and/or provision of other special care

*As defined above

This table draws on a number of published schemes for assessment, including: Animal Procedures Committee (APC, 2003); Canadian Council on Animal Care (1997); Delpire *et al.* (1999); Home Office (1998); Mellor and Reid (1994); Prentice *et al.* (1990); Smith and Boyd (1991); Smith and Jennings (2003); Swiss Federal Veterinary Office (undated)

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 ongoing ethical evaluation (see also # 5), 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 & Howard 2005) has recently published, as a discussion document, some guidelines on retrospective review.

20: Effective ongoing review should be incorporated into the ethical review process, via:

- (i) **ongoing 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 reconsideration 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;**
 - **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

A table in our full report illustrates how respondents to our questionnaire report that participation in ethical review processes varies between FELASA member countries (FELASA 2005). The findings are summarized below and give rise to the following overall recommendation:

21: Ethical review processes need to 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 regularized membership:

- (i) 11 report that veterinarians are routinely involved; four that veterinarians are not *always* involved, and two that veterinarians, although mandatory participants in ethical review, are there only 'in attendance', to give advice, and cannot 'vote';
- (ii) six report that animal care staff are routinely involved in ethical review;
- (iii) eight report that other animal welfare specialists are consistently involved in ethical review, usually in addition to veterinarians 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 wellbeing of the animals in the project under review and can be considered to act as the animals' advocates in the review process.

22: All ethical review processes should include specific competence in animal welfare relevant to the species and techniques 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 regularized 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:

23: Scientific expertise is also of vital importance in ethical review, and should 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 serves to emphasize that ethical review involves, and is not separate from, the scientific community.

Other expertise

Only two respondents report that their country's ethical review processes always/routinely involve statisticians or alternatives experts in ethical review. Other specific competencies that are frequently represented in review processes include legal and ethics expertise.

It is clear that 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. Therefore, researchers should always have access to relevant statistical, experimental strategy 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 also acknowledged, however, that it can be 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.

'Lay' and/or external perspectives

Respondents from three out of 20 FELASA countries report that 'lay' people are consistently involved in ethical review (i.e. involved in *all* ethical review processes within that country). Note, however, that at least 10 other countries involve lay people in some, but not all, ethical review processes.

Such people can 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 emphasize 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 is unique to lay participants, but indicate the kinds of benefits that lay perspectives might bring (Smith & Jennings 2003; see also Dresser 1999).

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.

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.

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 email. 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 authorize 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.

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

Other perspectives

It is valuable for national authorization 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 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.

'Training' for participants

Respondents from three 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, two of these three respondents also report that uptake is usually low.

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 organized; and further that they:

- 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. There will be need for adequate resources to support any such initiatives.

27: 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'

As noted, ethical review can also bring important educational benefits, which extend beyond review of particular research proposals and can also 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.

However, only one respondent to our questionnaire reports that their ethical review processes at present are required to promote such educational/awareness-raising activities within their own institutions.

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. 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 ongoing 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.

Again, it is clear that if these aims are to be met, ethical review processes will need to be properly resourced.

Designing ethical review to meet national and local needs

29: The overall organization of ethical review must meet both national and local needs and enable 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.

In designing an ethical review process, it is also important to ensure that bureaucracy is kept to the minimum necessary to achieve the review objectives effectively; and 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.

Quality and consistency of the outcomes of ethical review

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. 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.

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.

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 (COST Action B24 <http://biomedicum.ut.ee/costb24/>). The Action includes a working group on ethical evaluation and cost-benefit analysis, which (like other working groups within the programme) will draw on the support of the FELASA ‘network’ of laboratory animal science organizations across Europe.

Notes

- 1 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 authorized 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).
- 2 With the exception of Switzerland and Norway, all countries represented in FELASA are members of the European Union. As already noted, at the time of writing, EU Directive 86/609 is undergoing revision. This includes reconsideration of which

animals are covered by the legislation, and which scientific uses of such animals require specific authorization.

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