

**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 Ethical Review**

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Review of EU Directive 86/609/EEC

Technical Expert Working Group

Final Report from the Ethical Review Sub-Group

Introductory notes

This report presents a summary of the discussions of the Technical Expert Working Group on Ethical Review (TEWGER) at the meetings in Brussels on 1-2 July and 6-7 November, 2003. The text updates the draft report posted on Circa in August. It takes into account the discussion on Circa and the reports of the other three Expert Working Groups. Information from the Commission funded survey of ethics and animal welfare committees across Europe and the similar FELASA survey has also informed the discussion.

Definition of terms

The terms ethical evaluation, ethical review process, ethical review committees and ethics committees are used throughout the “thought starter” document provided by the Commission, sometimes interchangeably and with no definition of what each term means. It is important for all the working groups to have a clear and consistent definition of these terms. The TEWGER uses the following definitions:

- *ethical review process* - a broad concept with the objectives as defined in section 3.2.1 (i) and (ii) below;
- *ethical evaluation* - usually applied to the actual process of reviewing the justification for a particular piece of research, for example an application for a project licence in the UK, or the evaluation of projects submitted under the framework programmes in the EU;
- *ethical review committee* and *ethics committee* - specific mechanisms for carrying out an ethical evaluation or wider ethical review.

Thought starter questions

3.2.1 Ethical review committees

Questions:

- *Should an ethical review committee be established in each user establishment?*
- *Should there be in addition, national (or regional) ethical review committee?*
- *What should be the remit and tasks of a local ethical review committee?*
- *What should be the remit and tasks of a national/regional ethical review committee?*

Background

The TEWGER agreed that ethical review in its broadest sense is a key component of the humane use of animals for experimental and other scientific purposes. Any system of ethical review need to take into account differences in national cultural

views and must be flexible enough to be incorporated into different authorisation and regulatory systems that will be developed to implement the Directive across all member states. Flexibility is also important since it is recognised that ethical review involves value judgements, which will, rightly, change with time and/or with the perspectives, priorities, interests and expertise of those making them, and with the context in which they are made.

The TEWGER agreed that ethical review must embrace a number of aspects and issues, and is relevant to the planning, conduct and review of animal use. Ethical review, therefore, has many components. Review of the justification for animal use through the weighing of harms to animals against the scientific and societal benefits, is only one component. (Note: Some countries use the expression ‘cost-benefit’ but working group members felt this could be confusing in translation and that harm-benefit was more explicit. We suggest this terminology is used by all the working groups.)

The TEWGER was unanimous in the view that ethical review is a ‘process’ rather than a one-off ‘event’ conducted solely by a ‘committee’. The TEWGER believes it is important to focus first on the expected inputs to, and outputs from, the ethical review process as a whole, rather than specifically dealing with ethics committees - which represent only one mechanism (and in truth only one part of a possible mechanism) for implementing an ethical review. With this in mind, we believe that before attempting to answer the thought starter questions posed regarding local and national ‘ethical review committees’, there is a need to define:

- (i) the objectives of ethical review
- (ii) the elements that an ethical review process needs to include to ensure these objectives are achieved.
- (iii) the competencies required for effective ethical review

In doing this the TEWGER considered only the concepts of local and regional/national ethical review processes and set to one side consideration of how such processes could be constructed to fit within the authorisation process since at the time of our discussion this was undefined.

(i) The objectives of ethical review

The objectives of a comprehensive ethical review process are to ensure that:

- all production and use of animals is carefully considered, adequately justified and carried out as humanely as possible with no unnecessary duplication of research/testing;
- the Three Rs of replacement, reduction, and refinement (as defined by Russell and Burch, 1959) are each fully addressed at an early stage in the planning of animal experiments and actively implemented throughout the duration of the research with thoughtful reflection on completion of the work;
- high standards of animal accommodation, husbandry and care are achieved.

(ii) The elements of ethical review

The ethical review process needs to include the following individual activities or elements in order to achieve the objectives outlined above:

- promote the development and uptake of replacement, reduction and refinement alternatives in animal use and ensure the availability of relevant resources and sources of information;
- examine proposals for the use of animals for experimental and other scientific purposes and amendments to these, with reference to the likely harms to the animals, the expected benefits of the work (including the likelihood of success) how these considerations balance; how harms can be minimised and benefits maximised;
- provide a forum for discussion of matters relating to the use of animals including wider policy issues, and consider how people can be kept up to date with relevant ethical advice, legislation and best practice;
- undertake ongoing and retrospective review of projects involving animal use to facilitate continuous progress with the three Rs;
- consider the care and accommodation standards applied to all animals in an establishment, including breeding stock, and the humane killing of protected animals;
- carry out regular reviews of the establishment's managerial systems, procedures and protocols where these bear on the proper use of animals;
- advise on appropriate training of staff involved in animal use and on how their competence can be ensured;
- provide opportunities for transparency, not only about actual animal use, but also with respect to progress in applying the Three Rs, and with regard to the functioning of the ethical review process itself.

Ethical review should be applied to all aspects of animal care and use and take into account and properly balance the legitimate needs of science and industry as well as animal welfare.

Local, regional and national processes

The different elements of ethical review might be tackled in different ways and/or with a different focus at local, regional or national level as indicated below.

The local level

The TEWGER agreed that all of the objectives above need to be pursued at a local level, but some may also be part of a regional or national ethical review process or be part of the authorisation process. For example, ongoing implementation of the Three

Rs clearly needs to be developed at a local establishment level. This could be through a specific focussed Three Rs group which could directly help investigators to apply the Three Rs by working with them to solve problems. However, it is also essential for the national competent authority to have a mechanism to ensure that all of the Three Rs have been adequately addressed before research commences.

Most countries included in both the Commission funded and the FELASA survey have developed, or are developing, local ethical review. This is considered especially valuable because it involves local staff actually involved in the work including those caring for and using the animals, and is based on a working knowledge of local factors such as the facilities and expertise and opinions of local staff. It can, therefore, ensure that everything is in place to conduct studies to a high standard.

The National level

Most of the elements of ethical review above will also need to be addressed at national level. The *focus* at this level however is likely to be on developing consistent standards or on matters of national concern. For example, a national body could provide a forum within which wider policy issues such as the use of primates, transgenic animals, efficiency of regulation or transparency, could be discussed. It could also develop and promote national guidelines (e.g. on husbandry and care, ongoing or retrospective review, severity, harm/benefit and training) which could helpfully inform local ethical review processes. A national body might also be required to deal with appeals or conflicts arising at a local level.

(iii) Competencies and membership

Question: What should be the composition of an ethical review committee at a local level, at national/regional level?

Background

As stated above, a proper ethical review process has many components, and operates at many different levels, developing over time. At a local level it does not relate solely to decisions on individual projects, nor does it constitute a one-off judgement about a project that can be made before work commences. Rather it requires that specific knowledge, skills and attitudes are brought to bear at different stages in the lifetime of a project, and with respect to the general management of all the animal work at the establishment. The TEWGER therefore believes that it is more important to consider the competencies required rather than the “composition”. The same comments apply to regional or national bodies.

Opinion on competencies required

Participants in the ethical review process should have a general awareness of the ethical, animal welfare and scientific issues that are encompassed in ethical review. The process should involve people with the knowledge, skills, motivation, confidence and attitude to identify opportunities for applications of all Three Rs, and between them consider all the different factors that are important in a harm-benefit assessment. The process should also be informed by the views of those with no direct interest in the conduct or findings of the studies i.e. by someone who will not be harmed by, or

benefit from, the outcomes of the process. The specific competencies required include:

- experimental design, including statistics where appropriate;
- veterinary expertise (note article 19(2) as and when revised should make provision for specific expertise in laboratory animal veterinary practice);
- animal husbandry and care, in relation to the species that may be used;
- the Three Rs
- awareness of the areas of scientific use for which animals will be used (note: it would however be unrealistic to expect participants to have knowledge of sufficient depth or breadth of all the individual research areas likely to be covered in ethical review to facilitate a formal peer review of the science, and in many instances the science may already have undergone scientific peer review);
- different perspectives from those outside of the science involving animal procedures, and who are not otherwise involved in animal research .

A “different perspective” is often described as being provided by a ‘lay’ person, although there is much debate over who actually counts as a lay person. In general, ‘lay’ has been defined as describing someone who has no technical knowledge and/or no stake in the work or its output who can therefore provide an independent, novel perspective on the issues. He or she can bring a 'fresh eye' by questioning custom and practice and challenging accepted norms, thus helping to stimulate people to think more widely about the issues.

Current practice in committees dealing with animal research in countries in Europe, Australia, Scandinavia and the USA, shows that people from a wide variety of disciplines are described as lay in this context. This is similar to the situation with medical ethics committees. Sometimes people with expertise in ethics *per se*, such as moral philosophers and theologians, or with expertise in animal welfare are also labelled as 'lay'.

In the UK, which has recently encouraged 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).

It has also been suggested that a lay person is someone who can provide for a measure of public input and help scientists understand how members of the public view their work. This is in turn linked to the transparency of the process, helping to ensure its integrity. However, these latter functions depend on whether the person comes from inside or outside the establishment (see Jennings et al 1999, Smith and Jennings 2003 for a discussion of this issue). TEWGER members disagreed over whether the lay

member should be external. Two said yes, two said there should be both internal and external participants and two wished to retain flexibility.

The group did not discuss the competencies specifically required for a national body other than to recognise that this would critically depend on its function and that a wider variety of perspectives might need to be included to deal with issues of national and international policy and strategy.

Summary opinions on the remit and composition of ethical review processes

The TEWGER agreed that ethical review in its broadest sense is a key component of the humane use of animals for experimental and other scientific purposes. Therefore, there should be a requirement in the Directive for local ethical review processes with the objectives and elements set out in section 3.2.1. (i) and (ii) above. A harm/benefit framework should be part of this.

The expertise and competencies required for an effective ethical review process are as described in 3.2.1(iii)

It was also agreed by a majority within the TEWGER that a national body would also be useful to deal with issues that the local ethical review process could not deal with, or that the member state required to be dealt with at a national level. This would include examination of wider policy issues, the development of national guidelines and conflict resolution.

Any general requirement for ethical review processes within the Directive must fit within the overall framework for the authorisation process proposed by the TEWG Authorisation sub-group and be mindful of the fact that different national frameworks are likely to be put in place to implement the Directive.

Question: How can independence of the committee be guaranteed and conflict of interests avoided?

The TEWGER questioned the context in which the word independence was used in this question, i.e. independent from what or whom?

Opinion

It was agreed that the key point was to ensure that potential conflicts of interests within the ethical review process are recognised and taken into account. One member considered it important that the process should be *seen* to be independent. Thus the participants should be independent from the establishment and nominated by an independent authority designated by each member state after careful consideration of their neutrality and specific competence in the relevant topics. Another view was that the *authorisation* process should be independent. Nevertheless, it was agreed that there should be an *element* of independence in the ethical review process and this could be assisted by the participation of those who would neither benefit from, nor be harmed by, the outcomes of process.

Question: Should the duration of membership be regulated?

Opinion

This question assumes the existence of some form of committee. The duration of membership of, or participation in, any body will depend on factors such as the nature of the process and its function, the role of the participant and the authorisation framework within which it operates. It is an issue of detail for guidance notes rather than for inclusion in the Directive.

3.2.2. The Ethical Review Process

Question: What should be the minimum requirements for information provided for ethical review e.g. species, numbers, and severity, demonstration of Three Rs, humane end-points?

Background

Clarification of this question confirmed that it is about the information required in the *ethical evaluation process* not the *overall* process of ethical review.

Opinion

The TEWGER noted that the Authorisation and Cost/Benefit expert groups were addressing this question and there was no dissent regarding the answer provided by the two groups. The information is therefore not repeated here.

Question: What type of experiments should pass through an ethical review prior to a project authorisation?

Opinion

All experiments/procedures carried out for a scientific purpose on the animals covered by the Directive should pass through an ethical evaluation and be encompassed by an ethical review process

Question: Which experiments should require the opinion of a possible national ethical review committee prior to authorisation?

Discussion

The TEWGER did not reach a consensus on this issue. It was however agreed earlier under 3.2.1 that a national body might deal with issues that the local ethical review process could not deal with, or that the member state required to be dealt with at a national level. This could include examination of wider policy issues relating to the type and purpose of experiment and/or type of species. In this context some member states already have experiments that are dealt with at a national level, for example the

use of non-human primates generally and great apes in particular, procedures of high severity, cosmetics testing and military research.

There was discussion but no consensus as to whether the use of primates should be a matter for review at national level for all member states. Two of the six members of the TEWGER supported this concept. A need for awareness of the public concern and debate around such issues was highlighted as a function for the national body and this emphasised the need for incorporating a wide range of perspectives into national processes of ethical review.

Question: Should the ethical review process have specific guidance on e.g. cloning, xenotransplantation and the use of non-human primates and if so what should be the minimum requirements?

Discussion

This question needs to be taken together with questions relating to the authorisation process and it was argued that this is a matter for the national competent authority. Another view was that, if the Commission considers these issues sufficiently important, it should establish a European body to examine them.

Issues such as those mentioned in the question above may arise either because (a) there are genuine and specific questions about the harms or benefits – for example the advanced cognitive abilities of primates make the harms associated with using them high; or because (b) the issues have been raised in a political forum as a matter of public concern.

It could be argued that in the case of (a) a comprehensive harm benefit analysis on a case by case basis would be sufficient to assess the justification for the experiments, without additional guidance, provided it is accepted that there may be a need to seek advice from a wider range of experts for example in primate behaviour. With regard to (b) the ethical review process would presumably wish to take into account political issues including the prevailing public opinion. Some countries have limited, or banned, the use of some species of primate, wild caught animals or types of experiment. These sorts of decisions are likely to be made at a national Government level and national and local ethical review and authorisation processes would have to abide by them. However, local processes of ethical review are also likely to develop their own policies on the sort of research they are prepared to engage in (this is encompassed within the list of elements of ethical review in 3.2.1.(ii)). Guidance on key factors to take into account in this decision making process would be helpful.

Another point that was briefly discussed is whether as a matter of course particular species of animal require additional justification as is the case in the UK and Italy for primates, cats, dogs and equidae. All of these animals are of particular concern. However, some members of the TEWGER argued that this is not an issue if the Three Rs are properly applied – specifically minimising suffering and using the lowest suitable species.

The TEWGER agreed that it was important that the ethical review process should have access to information and opinion which allows it to be well informed with

good, balanced, contemporary and up to date information and opinion on all of these issues.

Questions: Record keeping

Question: what records should be kept on ethical evaluation?

Opinion

The questions relating to record keeping – the nature of records, public availability, confidentiality and period of keeping - are all matters of detail which depend partly on the outcome of the working group on Authorisation. There are however some important points of principle as follows.

- There will be different types of records depending on the individual functions of the ethical review process and whether it is operating at a local or national level.
- At both local and national level the terms of reference for the process should be recorded together with a description of the way it operates.
- Key outputs should be recorded – in particular the advice given together with the reasoning behind the advice. This will help inform future decision making and allow decisions to be monitored and if necessary defended.
- An ‘audit trail’ to see where value has been added may be useful in monitoring and developing the process.
- At local level, there should be some formal output from the ethical review process for staff and colleagues in the establishment.

Question: what should be made publicly available and at which level?

Opinion

Disclosure of information contributes to transparency and is required in some countries by freedom of information legislation. It should improve public understanding and confidence in the regulatory system. It was therefore agreed that consideration should be given to disclosing as much information as reasonably possible providing it does not compromise intellectual property, commercial confidentiality or the safety of staff. This should be less difficult at a national level than for local establishments. The TEWGER acknowledged that it was unfortunate that in some countries extremist activity meant that there were contraindications to being open because of threats to the safety and security of individuals and establishments.

Question: how can confidentiality be safeguarded?

Opinion

This requires careful consideration and as indicated above the advantages of openness must be balanced against the risk to individuals, business and property. There should be no automatic disclosure of the identity of individuals or institutions carrying out research or of individuals within the ethical review process. All ethical review processes must therefore identify, be mindful of, and safeguard, confidential information.

Question: how long should records be kept?

Opinion

The length of time for which a record is kept depends on the nature of the record and the purpose of keeping it, so there is no simple answer to this question. Some of the reasons for record keeping within the ethical review process are:

- to check that advice provided by the ethical review process is adhered to;
- to see whether it is useful in informing subsequent decisions;
- so that the outcomes of the advice and the project (if this is what the record refers to) can be reviewed.

As a general principle it was agreed that records should be kept for the period the ‘advice’ is current or relevant.

3.2.3. Harmonisation across the EU

Question: How can a harmonised approach by local and national ethical committees be ensured throughout the EU to avoid transfer of experiments from one member state to another?

Background

In discussing this question the working group assumed there would be effective ethical review processes throughout the EU, whether this was at a local, regional, or national level, and whether it involved committees or some other form of ethical review process. It was also pointed out that there were many different reasons that experiments could be transferred between countries and the important question was therefore *how it could be ensured that all experiments were carried out in all countries according to ethical principles.*

Opinion

It was agreed that harmonisation of the *goals and objectives of ethical review* as stated in 3.2.1. are a pre-requisite to meeting the objectives of a free-market, but that it would not be appropriate to try to harmonise the way the ethical review process operated between different member states, and even between different establishments. Individual ethical review processes need to facilitate implementation of the Three Rs and good science within the context in which they operate. These aspects are continuously developing. For effectiveness, diversity of process will be more important than uniformity of mechanisms, providing outputs are harmonised. The ethical review process needs to be sufficiently flexible to allow for this. It is, therefore, important not to strictly prescribe systems, which cannot easily be changed or that are not sufficiently flexible to meet national and local needs. Furthermore, it

is important that local ethical review does not duplicate nor confound national authorising systems.

The TEWGER agreed that it would be desirable to set minimum performance standards and to work towards establishing consistency by helping people to interpret the articles in the Directive (only the European Courts can do this definitively) and set minimum standards.

The Commission could help develop a consistent approach through the following actions:

- (i) Provide easily accessible guidance on what the article/articles in the Directive relating to ethical review are expected to deliver and how they should be interpreted in practice.
- ii) Require the national competent authorities to produce and publish a description of its national framework for the operation of ethical review processes at local, regional and/or national level
- iii) Invoke the standing committee, which exists under the existing Directive as a means of defining and publishing guidance. This could become a standing committee on ethical review processes and supra-national ethical issues, and would be a proactive way of harmonising the Directive.
- iv) Use the National Competent Authority meetings to discuss and disseminate ideas, with the venues rotated around member states to provide the opportunity to demonstrate different activities and/or aspects of good practice. There is no real need for NCA meetings just to provide an information exchange about general implementation issues - at the moment all that is reported is what has changed. These meetings should be about developing best practice, part of which could be identifying useful resources. They could also be used to provide the Commission with information about the impact of other Commission activities (e.g. REACH) on animal use in research and testing.
- v) Organise events such as workshops to define, update or disseminate information on good practice to facilitate effective ethical review processes throughout Europe.
- vi) Facilitate networking between those involved in the ethical review process. There may be a case for a regular, perhaps biennial, EU ethical review process workshop.
- vii) Provide a centralised information resource to facilitate operation of ethical review processes linked to the Directive. However it was noted that, though relatively easy to construct such a resource, there would need to be the resources to maintain it and increasing Commission bureaucracy may not be an option. This could be a role for ECVAM if its role came up for review. Another question raised was whether

documents provided by other bodies would be seen to be endorsed by the Commission if they were listed on a Commission resource and if so did this matter.

- viii) Produce a brief report on ethical issues every three years which would help to develop and promote the Three Rs and explain and publicise how the Directive is implemented. This could be linked to the production of the statistics on animal use (which incidentally need to be concise, clear and meaningful) and it might be timely to review the nature of the information collected and published. This would all increase the transparency of the process.
- ix) An international exchange of ethical review process participants might contribute to furthering training and more generally developing best practice.

Some activities in Points (v) and (vi) above are already being undertaken by the Commission though not under the auspices of Directive 86/609. For example the Science and Society Action Plan states the Commission's intention to promote networking of ethics committees, and there have been meetings to develop the framework of the Action Plan, for example in Bratislava in 2001.

3.2.4. Guidelines to a practical approach to ethical review.

Question: Create some practical guidelines on how to undertake the ethical review process based on best-demonstrated practices. Include a section to cover specific needs e.g. for primates, cloning, etc.

Discussion

The TEWGER did not attempt to do this in the meeting because members had neither the time or resources necessary. However, the following general points were discussed.

There is a lot of material already produced by bodies such as the UK Home Office, CCAC, ANZCCART, PRIM&R, RSPCA Lay members Forum, LASA/FELASA. These could be reviewed to identify some guidelines on general best practice but it would not be a quick and easy task. Furthermore, care would have to be taken to relate proposals to the national culture, legal system and authorisation process.

How should guidance be presented? There is a benefit in including guidance as an Annex to the Directive in that it is distributed more widely and gives weight to the need for member states to provide the resources to implement it. This is particularly important for those member states that do not have a long tradition and culture of ethical review relating to animal experiments. It was considered that the Regulatory Committee Procedure (RCP) would ensure that the guidance could be regularly updated to take into account rapid developments in technical process such as humane endpoints or euthanasia or ethical aspects. However, the converse was also strongly argued by the TEWGER, i.e. that Annexes are perceived by some as normative and

therefore prescriptive, and notwithstanding the RCP, they cannot be rapidly updated to reflect technical progress.

The TEWGER believes that there is a clear need to develop guidance on implementation of the Directive in general and on ethical review in particular. To ensure that guidance on ethical review is both flexible and up to date, it should be produced and disseminated by mechanisms described in points (i) to (ix) above and not by an Annex to the Directive.

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Composition of the Sub-Group Ethical Review:

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Wolf Frühauf	(Austria)
Jon Richmond	(UK)
Kai Pelkonen	(Finland)
Ramunas Zalys	(Lithuania)
Mark Matfield	(EBRA)
Maggy Jennings (rapporteur)	(Eurogroup)
Susanna Louhimies (chair)	(DG Environment)

The Members of the TEWG were expected to act as individuals and not as representatives of the national authority or non-governmental organisation that nominated them.

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02.12.03