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Ethical Review of Animal Experiments - a global perspective

Report commissioned by the World Society for the Protection of Animals, for consideration by the International Whaling Commission

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About the author

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Key Findings and Recommendations

There have been laws on the use of animals for scientific purposes in the United Kingdom and Ireland since 1876, and in countries in North America, Australia/Oceania, Europe and Asia from the 1950s onwards. Within the last decade or so other countries in Africa, Asia and South America have enacted national legislation.

The legislation is supplemented by regulations and/or guidelines. Some countries that do not have national legislation have authoritative guidelines from national bodies, and a number of international bodies (among them the International Council for Laboratory Animal Science and the Organisation for Economic Co-operation and Development) have issued guidance.

All these recognise that scientific use of animals that involves adverse effects (pain, suffering, distress or lasting harm) should be controlled. “Animals” means live vertebrates (with some exceptions in USA and Japan) and in some countries certain invertebrates.

The general stance is that “Animals have an intrinsic value which must be respected… .. animals should always be treated as sentient creatures and their use in procedures should be restricted to areas which may ultimately benefit human or animal health, or the environment.” (EU directive 2010/63).

Of the 52 countries identified as having laws, regulations or national guidelines, 41 clearly expect ethical appraisal of studies before they begin, and others may also do so.

The recognised international tenet of the Three Rs is almost universally used for ethical appraisal. It involves reviewing proposed experiments for scope for Replacement (by non-animal methods), Reduction (in numbers of animals used) and Refinement (of experiments to cause fewest adverse effects). In many countries ethical appraisal also involves a harm-benefit analysis, weighing the adverse effects likely to be experienced by the animals against the expected benefits from the experiments.

Ethical assessment by a group with a range of expertise is the arrangement in all countries with developed systems, though it varies whether that is at national, regional or institutional level, and whether the group is formed by appointed specialists or a committee.

Good monitoring is an important feature of effective systems, and is particularly important for studies conducted outside research facilities.

The commonality of ethical ideas and of the widespread use in national systems of a committee with scientific and veterinary expertise gives a reasonable prospect that international oversight of scientific work on cetaceans within the remit of the International Whaling Commission (IWC) could be set up and deliver, over a period of years, some consistency of outcome and obtain a measure of international confidence.

To that end, the following recommendations, based on the various points made in this report and consideration of the many different systems outlined in the Appendices, are made:

1. An international ethical review panel (IERP) reporting to the Commission should be established. The persons on the panel should between them have scientific, veterinary, and wildlife research expertise, and experience of assessment under different national ethical review systems. The panel should include at least one person with experience of cetacean research and/or capture of cetaceans. Although much of its work could be done by correspondence, the IERP should meet for face-to-face discussion at least once a year.
2. The IERP should produce for the Commission guiding principles for the ethical review of proposals to undertake scientific studies on cetaceans which come above an agreed level of pain suffering distress or lasting harm. These should be based on the International Council for Laboratory Animal Science (ICLAS) principles but adapted to be particularly applicable to wildlife studies in the marine environment.
3. The IERP should research and provide clear criteria for the type and nature of cetacean studies which would qualify for ethical review. These criteria should be shared with the Commission, with a view to requesting all contracting governments to submit to the IERP for review all research proposals which fall within the criteria for ethical review. A guide for the type of information that might be required by the IERP is provided below.
4. When proposals for research qualifying for ethical review are submitted by contracting governments to the Commission, the IERP should assess the proposal against the guiding principles. The assessments should be fed back to the proposers, with invitation to comment. After a period for comment, the assessments, comments and final recommendations of the IERP should be reported to the Commission.
5. A report summarising the results obtained and their significance, and the adverse effects on the animals, indicating for each the severity, duration and numbers affected, should be provided by the researchers to the IERP at the end of each study. The IERP should review this report against the guiding principles and provide comments to the Commission.
6. The Commission should summarise the work and recommendations of the IERP in its annual report.
7. The Commission should consider setting up a system for non-adversarial discussion and inspection of work in progress on a sample of scientific studies considered under the ethical review system. The persons involved could be the same as on the IERP.

Guidance for information to be provided to the IERP to inform ethical reviews

For studies on wild animals in their natural environment which are liable to cause sufficient pain, suffering distress or lasting harm to need regulatory control, the following information is suggested:

1. The objectives of the work, why they are worthwhile, and the expected impact should they be achieved.
2. The likelihood of achieving them:
    - Evidence of good understanding of the background to the proposed work.
    - The track record and expertise of the applicant, or the team, in this type of work.
    - Whether the methods to be used are well established or novel.
    - The difficulties inherent in research in the particular environment.
3. The research strategy for the programme and how it accords with the Three Rs:
    - Why procedures above the pain/distress threshold have to be used instead of, for example, observation or computer modelling.
    - Why the particular experiments are those most likely to give satisfactory results
    - The proposed experimental designs, and reasons for expecting that the minimum number of animals would be used.
    - Why the chosen experimental approach is the one that should cause the least suffering.
4. What animals will be used, and what the effects on them may be:
    - Why the chosen species has the lowest sensitivity.
    - What procedures will be performed.
    - What adverse effects there may be, for how long and to how many animals.
    - Who will assess the level of suffering, and how their ability to do so will be assessed.
    - What steps will be taken to prevent or control the extent of suffering.
    - What will happen to an animal at the end of the experiment.
5. How an animal is to be killed, either if needed for experimental reasons or to alleviate suffering.
6. Where the scientific work is to be carried out and what the expertise of the team in the field will be.
7. What records will be kept and who will monitor the work in progress.

Introduction

Although some ethical concern over the relationship between humans and the animals they control dates back at least to biblical times (Linzey,1987) ethical considerations as to how they should be used in scientific studies came to the fore in the mid 19th century. The ethical principles set out by the physiologist Marshall Hall in 1831 (Box 1) still have resonance today, as do some of the arguments made in the debates, both public and parliamentary, preceding the first recognised legislation in this area, the UK's Cruelty to Animals Act 1876. In the 135 years since that Act many countries across the world have adopted legislation on animal experimentation and although still not universal there are countries in each continent that have done so.

Box 1: Hall's Principles 1831

1. We should never have recourse to experiment, in cases in which observation can afford us the information required.
2. No experiment should be performed without a distinct and definite object, and without the persuasion, after the maturest consideration, that that object will be attained by that experiment, in the form of a real and uncomplicated result.
3. We should not needlessly repeat experiments
4. [an] experiment … should be instituted with the least possible infliction of suffering .. the subject of experiment should be chosen from the lowest order of animals appropriate to our purpose, as the least sentient; whilst every device should be employed, compatible with the success of the experiment, for avoiding the infliction of pain.
5. Every … experiment should be performed under such circumstances as will secure a due observation and attestation of its results, and so obviate, as much as possible, the necessity for its repetition.

Although Europe, North America, Australia and New Zealand have led the way, there is increasing recognition in countries of Asia, Africa and South America that scientific use of animals should be regulated at national level and this should involve ethical judgment. This is not just a shift in moral perception, and perhaps recognition of some truth in the words of Ghandi much quoted by animal welfare organisations that "The greatness of a nation and its moral progress can be judged by the way in which its animals are treated." It is also an appreciation that science that does not keep to certain standards is likely to waste both money and human resources, and that results obtained from animals whose welfare is more than a little compromised are liable to be unreliable, misleading and of limited applicability. The spread of scientific knowledge depends on publication and many journals have a policy of only publishing animal research that meets certain standards of animal care and use. Recent guidelines for publications, such as the Animal Research: Reporting of *In Vivo* Experiments (ARRIVE) guidelines (Kilkenny et al., 2011) highlight the importance of recording adverse effects experienced by the animals during the procedures.

Box 2: Organisation for Economic Co-operation and Development (OECD): Guiding Principles [for safety evaluation]

"All aspects of animal studies should be subject to an ethical review process as defined by animal welfare legislation and the ethical oversight groups of the testing organisation. Where such legislation is not available, it may be necessary for the laboratory to develop its own ethical guidelines and procedures."

"Studies must be designed to minimise any pain, distress or suffering experienced by the animals, consistent with the scientific objective of the study."

A number of international bodies, for example the Organisation for Economic Co-operation and Development (OECD) (Box 2), have seen that there is a need for guidance for countries developing or updating systems of regulation and ethical review, and have published general principles and guidelines (see Appendix 2 for examples). These provide a framework for some degree of consistency of control and outcome. Ethical review before studies are started should help avoid wasting animals on studies unlikely to be productive, and provokes consideration of ways of reducing the number and severity of procedures, which should improve not only the welfare of the animals but also the quality of the results obtained. There are several ways of tagging fish and marine mammals, for example, which differ in the amount they slow down the animal and how they may impact on social, mating and foraging success. Use of a tag which has a marked effect may mean data on range and movement is more applicable to a wounded than a normal animal. Prospective ethical review combined with assessment at the end of studies of the results obtained and the adverse effects experienced by the animals used, allows for continuing improvement in the quality of investigations. It also helps build public confidence in the good conduct of scientific use of animals.

However, there is likely to be a delay of some years before the benefits of ethical review are apparent, and before it is recognised that a study wasted resources or produced unreliable results, so this is not an area in which market competition will operate effectively, and some form of regulation or oversight is necessary.

This report describes the basic ideas behind the regulation of animal experimentation, considers the general features of ethical evaluation and monitoring of regulated work and assesses the different approaches taken by different countries to regulating scientific studies on animals.

Brief history

Over the 135 years since the first UK Act controlling animal experimentation there has been increasing recognition across the world of the need for such control. At least 52 countries now have controls over or guidance for the use of animals in scientific experiments (Box 3).

The 1876 UK Act set up registration of research facilities and a licensing system for researchers, monitored by a national inspectorate, which in the century following became increasingly involved in considering whether the numbers of animals and the degree of severity of studies could be reduced. In the 1950s a number of countries took a similar approach (e.g. Fiji, Solomon Islands). Others have placed emphasis on consideration of proposed studies by ethical committees, in research establishments or as national bodies, with the committees also involved in monitoring and inspection. Australia introduced the animal ethics committee for research establishments in 1978 in a national code of practice. Since 1968 the Canada Council on Animal Care has encouraged institutions to have Animal Care Committees or Animal Research Ethics Boards, and it has

produced a number of internationally respected guidelines. In 1985 the USA's Animal Welfare Act 1966 was amended to require a research facility using animals for scientific purposes to have an institutional animal committee. Although the first function was inspection the committee was also charged with review of the activities in this area. In the US Health Research Extension Act 1985 the institutional committee's role in reviewing scientific use in publicly-funded work was stipulated.

European national laws during the 20th century on animal experimentation included ethical review, with assessors or committees at national, regional or institutional level. A common framework was established in 1986 through two international documents: the Council of Europe Convention ETS 123, to whose standards signatory nations agreed to comply, and Directive 86/609/EEC which mandated minimum ethical standards, almost identical to those of the Convention, for animal experimentation and testing in the 12 European Community (EEC) states. The UK updated its legislation in the Animals (Scientific Procedures) Act 1986, and from 1986 onwards other EEC (and then EU) countries enacted laws or amendments to meet the Directive requirements. Norway, outside the EEC but a signatory of the Convention, took on the standards of the Convention in 1991 (Smith, 1998), subsequently updating regulations. Recently, Norway replaced its Animal Protection Act 1974 with the Animal Welfare Act 2010.

The EEC has become the European Union (EU), with 27 states to which Directive 86/609 applies until 2013. The EU adopted a revised directive with higher standards in 2010 (Directive 2010/63/EU) and member states are in the process of transposing these higher standards into national law by 2013. Iceland, a candidate to join the EU, has regulations under its Animal Protection Act 15/1994 which match the standards of Directive 86/609 and is also in the process of transposing the requirements of Directive 2010/63. Other candidate countries like Croatia and Turkey will similarly need to update their systems to meet the EU requirements.

Over the last two decades, several countries in Africa, Asia and South America have adopted or updated legislation, regulations or guidelines to cover scientific use of animals and include a requirement for ethical consideration. In some of these countries this may only be the limited assessment involved in central licensing, but South Africa's 2004 Guidelines, Brazil's Law No. 11794 of 2008, Peru's Law No. 27265 (2000), Japan's Science Council Guidelines (2006),

Box 3: Countries with controls or guidance on animal experimentation (by continent) include:

Africa – Kenya, South Africa, Tanzania, Uganda

Australia/Oceania – Australia, Fiji, New Zealand, Solomon Islands

Asia – China, India, Israel, Japan, Singapore, South Korea, Taiwan, Thailand

Europe – all 27 EU member states, Croatia, Iceland, Norway, Switzerland, Turkey

North America – Canada, USA

South America – Brazil, Peru

International bodies with guidance on ethical review (see Appendix 2)

ICLAS - International Council for Laboratory Animal Science (30 member countries)

OIE - World Organisation for Animal Health (178 members)

OECD - Organisation for Economic Co-operation and Development (34 members)

Singapore's 2004 Rules, and the 1999 "Ethical Principles" issued by Thailand's National Research Council all expect ethical evaluation of proposals for scientific studies on animals and monitoring of the work.

Ethical review systems

Typically a national system has a regulatory body that licenses or approves research facilities, and/or research proposals, and/or the researchers. How judgments are made on licensing or approval for research is not always clear from the documents, but in at least the 27 EU countries coming under directive 2010/63 and the 14 countries not in the EU which have ethics committee approval or stipulate ethical appraisal of proposals, there is a prospective ethical assessment of proposed studies before they begin. The outcome of this assessment is approval for a period of for example up to five years (which may be with conditions), modification, or refusal of permissions. This appraisal may be conducted at the national level by assessors or a committee, or delegated regionally or to registered, approved institutions and their animal ethics committees or to local assessors. Formal retrospective assessment at the end of the approval period will be expected for some studies in the EU but more usually it occurs when a subsequent request for permissions is evaluated. Monitoring of compliance with permissions and of the conduct of the work is carried out by inspection or scrutiny of records and required reports. As with assessment, this may be conducted from the centre or delegated locally but if the latter there would normally be some oversight of the local operation by the regulatory body.

Principles of Ethical Review

The basic ethical questions may be summarised as:

1. Should animals be used at all for scientific investigation?
2. If yes, should this apply to all animals?
3. If not to all animals, on what basis should particular animals be excluded?
4. Should all scientific work be treated the same?

There is also a question as to whether ethical evaluation should not just encompass the aims of a study and the expected disturbance to the animals involved, but also extend to each action within it (i.e. at what level of detail should a scientific proposal using animals be ethically assessed?).

By passing laws or issuing regulations or guidelines on animal experiments countries effectively answer the first question in the affirmative. The general ethic for scientific use is well summarised in the preamble to the Council of Europe Convention ETS 123 (1986) which provides for the "..... protection of live animals used for experimental and other scientific purposes." It recognises "that man has a moral obligation to respect all animals and to have due consideration for their capacity for suffering and memory" but nevertheless accepts "that man in his quest for knowledge, health and safety has a need to use animals where there is reasonable expectation that the result will be to extend knowledge or be to the overall benefit of man or animal, just as he uses them for food, clothing and as beasts of burden".

This may be explicit in legislation. Thus the recent EU directive (2010/63) states in preliminary paragraph 12 "Animals have an intrinsic value which must be respected… .. animals should always be treated as sentient creatures and their use in procedures should be restricted to areas which may ultimately benefit human or animal health, or the environment." However, in an overarching act on treatment of animals, the legislative intent may be expressed more broadly. For example, in the

Japanese Act, “In light of the fact that animals are living beings, no person shall kill, injure, or inflict cruelty on animals without due cause, and every person shall treat animals properly...”. In Norway “The intention … is to promote good animal welfare and respect for animals”. Tanzania’s Animal Welfare Act is not only “to provide for the humane treatment of animals” but also for “promoting of awareness of the importance of animal welfare”. The South African Medical Research Council Guidelines make the point that “Justification for causing psychological or physical distress, illness or pain to animals should not be based on any explicit or implicit assumption that non-human animals experience these conditions in qualitatively different ways to humans.”

In recognising that animals may be used for scientific studies, countries also realise that this calls for limitations and controls, though the nature of these varies considerably. This is considered in more detail later.

The response to the second ethical question is generally “no” (Tanzania is an exception) and that to the third is to set a threshold of sentience, below which animals are excluded (Box 4). In some cases an upper level of sentience is also considered, above which experimentation on the species is thought unethical, or is permissible only in exceptional circumstances. This is the UK’s position for example on experimenting on great apes, and will be the case for great apes for the 27 EU nations under Directive 2010/63. Work on endangered species may only be allowed in exceptional circumstances. In some countries there is also particular scrutiny of the level of need for a study and of its severity if companion animals or non-human primates are involved.

Box 4: Animals to which regulation of scientific use applies

The range of animals to which legislation on scientific use applies varies considerably. With some exceptions, notably the USA and Japan, the law or practice in all the countries surveyed covers all live vertebrates, sometimes, as in UK law and the recent EU directive, including later stages of development.

In the US, Public Health Service policy, which gives requirements for publicly-funded research, includes all vertebrates but the Animal Welfare Act is restricted to warm-blooded vertebrates, excluding rats, mice and birds. In Japan the Guidelines exclude fish.

In addition to vertebrates some states extend regulation to certain invertebrates. In Tanzania “animal” includes “any invertebrate”. Norway includes decapods and its Animal Welfare Act 2010 adds some cephalopods. The UK regulation extends to one cephalopod, Octopus vulgaris, and the recent EU Directive 2010/63 covers all cephalopods. The Australian Code refers to higher cephalopods, but state law may include others and Queensland’s covers malacostracan crustaceans, citing as examples a number of decapod species. New Zealand law covers cephalopods and decapods.

Some laws (US and Queensland for example) include not just live animals but also dead ones, i.e. those killed for scientific study.

The general answer to the fourth question is “no”. Where there is regulation of the use of animals for scientific purposes there is general international consensus that this should only apply to painful or distressing procedures, and that not all such procedures should be permitted, depending on an ethical evaluation. There are two approaches to considering how scientific use of animals should be ethically evaluated which have widespread support. One is to undertake a “harm-benefit” analysis

(also termed a “cost-benefit” analysis), in which the foreseeable benefit is weighed against the expected severity of the work. The other, which features in almost all the regulation surveyed, is that the Three Rs principles should be applied.

Harm-benefit analysis

This is distinct from the scientific evaluation expected for all scientific work. It allows for the identification of studies with high scientific merit that would involve unacceptable animal suffering or the use of species (like higher primates and some cetaceans) of such high sensitivity that what is proposed is considered unacceptable. It also provokes consideration of whether studies which have scientific validity might have so little potential impact as not to be worth the amount of animal suffering involved, however mild. Even if minimal numbers and lowest severity can be confidently expected, it does not mean the work is worth doing!

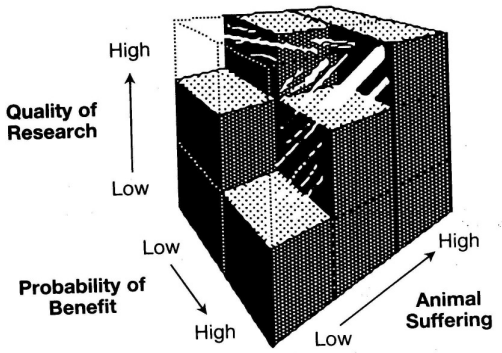
Box 5: Harm-benefit analysis

This weighs the likely adverse effects on the animals concerned against the benefit likely to accrue as a result of the scientific work.

It considers the importance of the objectives of a study, the benefits that come from achieving those objectives, and the likelihood of achieving them, against the adverse effects the animals might experience, taking into account the measures in place to minimise severity.

Harm-benefit analysis is a component of several regimes. The wording in Box 5 is essentially that of the UK’s Animal (Scientific Procedures) Act 1986 section 5 (4), also used in the relevant chapter (7.8) of the World Organisation for Animal Health (OIE) Terrestrial Animal Health Code 2011. One of the International Council for Laboratory Animal Science’s (ICLAS) general principles is that “The expected benefits to humans, animals or the environment of the proposed project involving live animals should be weighed against the likely harms done to the animals” (see Box 8 below). Under EU Directive 2010/63, evaluation of a proposed programme of animal research (“project”) should include “a harm-benefit analysis of the project, to assess whether the harm to the animals in terms of suffering, pain and distress is justified by the expected outcome taking into account ethical considerations, and may ultimately benefit human beings, animals or the environment.” In Tanzania “An animal experiment shall not be carried out ..for a purpose the importance of which does not justify the distress caused to the animal”. In Norway, where animal testing refers to all scientific use, the government’s Specific Guidelines on the Act make clear that the evaluation should consider both the “negative effect the test will have for the animals” and “the usefulness of the test for society”. A harm-benefit analysis would be needed for some types of experiments in Article 15 of Brazil’s Law**.** Under the Australian Code “projects using animals may be performed only after a decision has been made that they are justified, weighing the predicted scientific or educational value of the projects against the potential effects on the welfare of the animals”. Where, as in the USA and Japan, such an analysis is not a legal requirement or expected practice, there may be scope for institutions to set their own requirement. At the University of Minnesota, for example, in scientific projects involving animals “the benefits of animal use must outweigh the ethical cost” (Regulatory Charge of IACUC, 2011).

Figure 1: Bateson's Cube
When a research proposal falls within the opaque part of the cube the experimental work should not be done (from Bateson, 1986).



To assist assessors to undertake a harm-benefit analysis of a proposed study or programme of work, a proposer is typically expected to explain why the likely benefits of the proposed work are considered sufficient to merit the extent of suffering and distress involved. There are also several published approaches to aid this harm-benefit analysis, such as Bateson's cube (see Figure 1) or semi-quantitative evaluations such as that of Porter (Box 6) or (in much greater detail) the scheme given in chapter 7 of *Lives in the Balance* (Smith and Boyd, 1991). An estimate of the harm side of the balance can be obtained by considering the numbers of animals involved and the incidence, extent and duration of the adverse effects that could reasonably be anticipated. The benefits may be more difficult to assess, involving estimates of number of scientific areas likely to be affected, and by how much and with what impact, the number of scientists involved, the numbers of people or animals that might benefit from the better understanding of a disease, injury or parameter that could come from the work, and the seriousness of the condition, and perhaps some estimate similar to the quality assured life years approach used in the medical field.

Box 6: Ethical scoring (from Porter, 1992)

Category	Score range
• Aim	Major reduction in human/animal suffering → basic science
• Outcome	Excellent → very limited
• Species	Little sentience → high sentience
• Pain/Distress/Harm	Very little → severe
• Period of Pain, etc	Seconds → months
• Period of Experiment	<1% lifespan → 100%
• Numbers	<5 → 1000s
• Quality of care	Excellent → poor

The Three R's

The Three Rs concept of replacement, reduction and refinement was put forward by Russell and Burch (1959), and has been developed since. It conveys similar ideas to Hall's principles but in a way that is easier to appreciate and it has now become the main basis for ethical evaluation across the world.

Box 7: The Three Rs

Replacement - using non-sentient material that replaces use of animals in experiments or tests,

Reduction – using the minimum number of animals for the scientific objectives

Refinement – avoiding, alleviating or minimising potential pain, distress and other adverse effects.

EU Directive 2010/63, for example, explicitly invokes the Three Rs by name in Article 4, and in Australia and Canada, where legislation in this area is devolved to the state or territory and province respectively, there are overarching national guidelines which include sections on the Three Rs, give detailed guidance on how to implement them, and expect them to be applied to scientific studies on animals. In the US, publicly-funded research is obliged to accord with Public Health Service policy which expects conformity with the Institute for Laboratory Animal Research Guide, and this includes the Three Rs among the key concepts. The OECD issued a guidance document in 2000 whose purpose was "to apply the principles of the Three Rs to the use of animals in regulatory toxicity tests". The OIE Terrestrial Code 2011 endorses the Three Rs as "the internationally accepted tenet".

Usually in legislation or regulations the approach is just apparent from the text. For example, Japan's Act on Welfare and Management of Animals 1973 was amended in 2006 to include Three Rs wording " .. consideration shall be given to .. alternative methods to that of the use of animals .. and reducing the number of animals ... a method that minimises the pain and distress to the animal as much as possible shall be used" (Article 41 (1) (2)). In the UK's Act, section 5 (5) specifies that a licence for a programme of work shall only be granted if " .. the purpose .. cannot be achieved satisfactorily by any other reasonably practicable method not entailing the use of protected animals; and .. the regulated procedures to be used are those which use the minimum number of animals, .. cause the least pain, suffering, distress or lasting harm, and are most likely to produce satisfactory results". In the Norwegian Act s13 states that "Approvals .. cannot be given if the intention can be achieved without the use of animals, or if the animals may be subjected to unnecessary stress or strains. The number of animals used shall be restricted to the number necessary, and the animals should be subjected to least possible strain." There is similar wording in the Tanzanian Animal Welfare Act. Brazil's Law No. 11794 calls for minimum numbers and minimal suffering (Article 14 s4). The US Animal Welfare Act includes much on refinement, mandating standards that require "practices in experimental procedures to ensure that animal pain and distress are minimised" (S2143 3(a)), but also includes minimising numbers and a requirement "that the principal investigator considers alternatives to any procedure likely to produce pain to or distress in an experimental animal" (S2143 3(a) (B)).

To decide the scope for application of each of the Three Rs in a study or programme of work, it is necessary to have clear aims and objectives formulated. Although broad aims may be appropriate for a long-term programme, a study should normally have one or more well-defined objectives, and each should lead to a definable outcome. It should be evident when the objective has been achieved and when it has not been, or is unattainable. Recognising this, several regimes require the purpose or objective of the work to be clearly stated in any proposal (see Appendices).

Replacement

Russell and Burch (1959), in formulating the Three Rs concept, considered replacement as any scientific method using non-sentient material that replaces use of animals in experiments or tests. "Non-sentient" is usually taken to include creatures whose nervous systems are insufficiently developed for them to experience pain and "animals" usually taken as "living vertebrates" - so use of insects instead of mice would be a replacement. However in a number of countries some invertebrates (cephalopods like octopus and squid, for example) fall within the definition of "animal" in the regulatory documents, so their use would not be considered replacement.

Replacement can be considered at two levels:

- Complete replacement, where the method does not require any animal derived material, e.g., the Ames test which uses bacteria for screening for mutagens.
- Incomplete replacement, in which the method requires biological material obtained from living or killed animals or uses embryonic stages or invertebrates. An example would be using orientated brain slices instead of the whole animal for studies on the visual system.

As with these examples, most replacements are very procedure or objective specific, so to be sure there is no replacement available each section of a work plan needs a clear objective, i.e. what the research is hoping to achieve. Also, if animals are needed to meet a particular objective there may be scope to consider a comparable objective for which animals may not be needed.

There are also general replacement possibilities to consider.

- Computer models, physico-chemical characteristics can be used to predict mechanism of action or toxicity. If sufficient *in vivo* data is available simulation models can be used to explore possible interactions between components of a body system, effects of substances, distributions of wildlife populations and so on.
- Human volunteers, human tissue or tissue fractions, though not relevant for wildlife studies and much animal work these possibilities may be particularly important to consider for non-human primate investigations.

Reduction

The numbers of animals involved in experiments can be minimised

- By design:
  - Of the programme.
  - Of each experiment.
- By minimising variability (by inducing minimal stress, for example).
- By collaboration to reduce numbers of experiments – and by full publication.
- By maximising use of tissue.
- By re-using animals.

To achieve reduction, experiments should normally have suitable controls, be designed to avoid or estimate possible bias, and have adequate and independent replicates, and the planning should include consideration of how variability will be minimised (e.g. by technical standardisation, using animals as their own controls, reducing stress effects). However, this may not be appropriate for preliminary studies for data-gathering, in which statistical analysis is not envisaged and which would not lead to conclusions, but provide information for subsequent experiments that would.

Collaboration may avoid needless repetition of experiments (or false trails!) by different groups, and help maximise use of any tissue taken from the animals or data collected.

Reducing numbers in a programme of several experiments may involve making good use of early experiments to improve the design of later ones. It may also be appropriate to stage the programme around some specified review points at which improvements in methods could be discussed, the numbers needed reappraised in the light of experience, or the need for further experiments reconsidered.

Refinement

This could be considered as not only lessening the severity of procedures but also enhancing animal well-being to obtain reliable scientific measures. Housing conditions, husbandry and care, and health status, as well as being liable to affect animals adversely, can all impact on the scientific measures. In the case of wildlife studies these considerations translate to care not to inadvertently injure the animal, affect the animal's environment or put it at a social, mating or foraging disadvantage.

Refinement should be part of the design of a programme of work and the individual experiments. Generally a refined programme would be expected to start with lesser severity experiments, and to use the data obtained to limit the number or severity of later studies. For each experiment refinement involves prior assessment of the severity of the procedures, taking into account intensity and duration of any suffering and the numbers of animals affected, and considering whether less or non-invasive methods would suffice. For example, whether photographing an individual's marking or body characteristics could be used instead of tagging in studies on the movement of wild animals within a home range. Refining also involves observing adequately and recognising adverse effects, and having strategies to avoid or alleviate them. In wildlife studies this may mean considering beforehand how to deal with unexpected adverse effects, and how if necessary an affected animal can be swiftly and humanely killed. In marine studies there should be consideration of how the difficulties of working at sea will be coped with, and some commitment to avoiding working in poor weather conditions which may compromise researchers' control over the welfare outcome for the animal. It is also important to consider what humane cut-off points (in terms of recognisable clinical signs) are to be implemented, when and by whom, how the training and competence of personnel working on a project will be assured, and the likelihood of technical success. With some more sophisticated techniques, such as radio-telemetry, the value of lesser disturbance during data collection and obtaining more data from the same animal has to be balanced against the cost and harm of instrumentation.

Ethical Evaluation

General considerations

Ethical evaluation would be expected to be continuing, and to include:

1. Prospective evaluation before permissions are given.
2. Ongoing evaluation during the conduct of the work.
3. Retrospective evaluation after the end of each experimental set, and the whole programme.

As the ICLAS general principles put it "There should be a mechanism to ensure initial and ongoing review of the work and to use the results of the work to inform future scientific, welfare and ethical reviews".

ICLAS has developed a useful set of principles for ethical review, which are given in full in Box 8.

Box 8: International Council for Laboratory Animal Science: principles for ethical review

- Whenever possible, methods employed to achieve scientific objectives should avoid the use of animals.
- Where animal use is unavoidable, the proposed project should have been demonstrated to have merit, in terms of its potential to advance scientific knowledge and/or benefit human or animal health (scientific merit), to protect/benefit humans, animals and/or the environment with respect to new products/devices or to toxic substances (regulatory testing) or to teach animal based principles and procedures (pedagogical merit).
- The expected benefits to humans, animals or the environment of the proposed project involving live animals should be weighed against the likely harms done to the animals, and opportunities should be sought to maximize benefits and minimize harms.
- The species/strain and numbers of animals to be used should be scientifically justified to use the most appropriate animal model and the optimal number of animals, neither too many nor too few. The experimental design should be optimized according to the type of study undertaken.
- Studies should be designed to refine procedures undertaken on animals to the greatest extent possible, and the care, housing, transport and restraint of animals should also be optimized.
- Pain or distress likely to be experienced by the animals must be prevented, or minimized to the greatest extent possible, with veterinary advice for the use of appropriate anesthesia, analgesia and/or other measures as applicable to the type of animal and study.
- Those who use or care for animals must be skilled and competent to do so, both for their own safety and for the health and welfare of the animals (see the following section on Education and training of animal users in science).
- The earliest possible endpoint for the animals should be used consistent with the scientific objectives of the study.
- A method of euthanasia that is appropriate for the species, life stage and type of work should be described and chosen.
- There should be a mechanism to ensure initial and ongoing review of the work and to use the results of the work to inform future scientific, welfare and ethical reviews.

From *International harmonization of guidance on the ethical review of proposals for the use of animals and on the education and training of animal users in science* (2010)

The approach, the questions to consider and the personnel concerned differ somewhat for each stage of ethical review. Prospective evaluation involves value judgements on the work proposed, the people intending to do it, and the place or places where it will be carried out. Normally sufficient information should be available to allow a reasonable "harm-benefit analysis" before permissions are granted, even if that is not formally required by the regulatory system.

In many countries the information needed for prospective evaluation is specified. For example, the Australian Code, the Canadian CCAC Guidelines on ethical review, the Japanese Guidelines (box 9), and the US regulations all give a listing of what should be in a proposal. The UK specifies in law the nature of what should be assessed, as does the EU's Directive 2010/63.

For the UK and other EU countries the assessment includes a harm-benefit analysis, so information pertinent to this is needed. Most of the guidelines however only specify what is needed for a Three Rs appraisal. They also may not highlight that adverse effects need to be summed for all the animals involved and for the full time period, or cover some extra considerations for work in the wild, including the marine environment.

Based on the several systems surveyed and a need for a harm-benefit analysis, suggestions for what would be useful for evaluating a proposal for work in the wild are:

1. The objectives of the work, why they are worthwhile, and the expected impact should they be achieved.
2. The likelihood of achieving the objectives:
    - Evidence of good understanding of the background to the proposed work.
    - The track record and expertise of the applicant, or the team, in this type of work.
    - Whether the methods to be used are well established or novel.
    - The difficulties inherent in research in the particular environment.

Box 9: From Japanese Science Council Guidelines

Items requiring consideration when drafting an animal experiment protocol

- The objective and necessity of the animal experiment
- Whether or not the animal experiment is unnecessary repetition
- Whether an *in vitro* experiment could be conducted or the animal could be replaced by a phylogenetically lower species (use of alternative methods)
- Whether a change could be made to a less invasive animal experimentation method.
- The species of laboratory animals used and the genetic and microbiologic quality
- The number of laboratory animals used
- Educational and training experience of the researcher(s) and animal technicians.
- Reasons why special cages and rearing environment are required
- The anticipated disorders, symptoms and severity of pain resulting from experimental procedures
- Measures to alleviate pain when it is anticipated that the laboratory animal will suffer severe pain
- The use of sedatives, analgesics and anesthetics
- Terminal treatment of laboratory animals (method of euthanasia, etc.)

3. The research strategy for the programme and how it accords with the Three Rs:
    - Why procedures above the pain/distress threshold have to be used instead of, for example, observation or computer modelling.
    - Why the particular experiments are those most likely to give satisfactory results.
    - The proposed experimental designs, and reasons for expecting that the minimum number of animals would be used.
    - Why the chosen experimental approach is the one that should cause the least suffering.
4. What animals will be used, and what the effects on them may be:
    - Why the chosen species has the lowest sensitivity.
    - What procedures will be performed.
    - What adverse effects there may be, for how long and to how many animals.
    - Who will assess the level of suffering, and how their ability to do so will be assessed.
    - What steps will be taken to prevent or control the extent of suffering.
    - What will happen to an animal at the end of the experiment.
5. How an animal is to be killed, either if needed for experimental reasons or to alleviate suffering.
6. Where the scientific work is to be carried out and what the expertise of the team in the field will be.
7. What records will be kept and who will monitor the work in progress.

Ongoing evaluation needs review of the objectives, and whether they should be revised, of the impact of any changes to what might be achieved, and of whether advances in science or techniques affect the proposed work, including whether there are new alternative methods/models available that would involve less suffering. It should consider whether ways of refining the experimental procedures to cause less suffering have been identified, the nature and extent of the suffering being experienced by the experimental animals, and the effectiveness of strategies to minimise that suffering, such as humane end-points. The people best placed to carry out this evaluation are the researchers themselves, with input from animal care staff and veterinarians.

Retrospective evaluation might be expected to assess whether the expected advances were obtained and if not why not (for example were they unrealistic, were there technical problems, or was the approach abandoned as unlikely to merit further use of animals). It could also include review of the strategy to publicise the results. Based on the nature and extent of the suffering actually experienced by the experimental animals, and the effectiveness of strategies to minimise that suffering, such as humane end-points, it should re-evaluate the cost-benefit analysis to inform future judgements. This is a task for the person who made the original proposal or directed the work, for the assessor or committee or panel approving it, for the institution under whose head the work was carried out and for the funding agency supporting it.

Prospective evaluation may go further than just an ethical assessment of a proposal, assessing conformity to legislation and perhaps also resource allocation. It may also take account of the extent to which it will be supplemented by ongoing and retrospective evaluation. With reliable ongoing assessment, monitoring and means for corrective action, it may not be necessary to have all the information available for prospective assessment. Permissions for example could be made conditional if there are systems in place to ensure the conditions are met. It is reasonable to accept some flexibility which allows researchers to adapt what they do, so that without needing to seek

revised permissions, they can reduce the invasiveness of a procedure in the light of experience, provided there is confidence that a condition requiring that they do so will be conscientiously complied with. However flexibility has to be coupled with good monitoring and realistic sanctions.

Monitoring and inspection

The importance of monitoring was highlighted by the Federation of Laboratory Animal Science Associations (FELASA) Report of the Working Group on Ethical Evaluation (2005) which stated “For effectiveness and credibility, it is vital that all ethical review processes have means of ensuring that their decisions actually are implemented, and their recommendations given due weight, in practice. The power to stop animal studies, when, for example authorisations are exceeded or unexpected adverse events occur that prejudice their justification, should be built into the process.” Good monitoring and inspection are essential for this. The prospective evaluation decisions presume adequate monitoring and inspection, and without it prospective evaluation and approval may educate but not be respected in practice.

Monitoring can be considered at several levels. There is personal monitoring of the scientific work by the researchers themselves, the scientific supervisors or study directors, the animal care staff, and the advisory or attending veterinarians. At the level of the institution the ethical review panel can monitor through scrutiny of reports or records and by visits, by key personnel or the committee as a whole, to animal units or to inspect work in progress. Similarly the institution can monitor its ethical review system by requiring reports, reviewing minutes of meetings, and by a senior manager attending some of the discussions.

An important level is external monitoring and inspection. The regulatory body can require reports from the institution, and audit documents and records of the internal monitoring. It could also audit the scientific progress and the uptake of Three Rs. It can have inspectors, or a review panel, visit establishments to check how the procedures are conducted, to inspect the animal units/housing, to observe the condition of the animals, and to scrutinise the records and documents. By finding no or few problems visits can indirectly give assurance of the competence and quality of researchers, care staff and veterinarians. A minimum visiting frequency might be expected, but with flexibility to take account of size of the place, the type of work carried out, and the extent to which there is a local culture of care.

Even brief visits can do much to bolster public and political confidence in the operation of the regulatory system. An experienced eye can quickly note the behaviour, posture, coat, and presence or absence of injuries in animals under experiment or held as stock or for breeding, and see any deficiencies in their housing or environment. Procedures taking place can be observed, and socialisation or training programmes discussed. A sample of records of source, use and disposal of the animals can be scrutinised, as can procedure records, with notes of any losses or adverse effects seen. An expert, thorough and well-structured inspection that finds little at fault both reassures the institution and researchers and provides objective verification for the regulatory body. External inspection can also educate the local personnel, by providing information on improved approaches, or on problems and adverse effects encountered elsewhere and not published (though not confidential), and by stimulating discussion on ethical matters. It is likely to achieve best results by not being adversarial, by taking an attitude of confirming compliance rather than seeking fault, but dealing with any irregularities firmly and fairly, and by encouraging good practice, good science and a culture of care.

Operational Issues

Ideally a system for ethical review and monitoring would meet public and political expectations with minimum bureaucracy, and without being too intrusive, or harming scientific competitiveness. In practice a balance has to be struck. This section considers some of issues that need to be addressed.

Arrangements for assessing proposed work

Assessment might be at national, regional or institutional level, and at each of these by a committee or assessor or set of assessors, with a range of expertise. Biomedical scientific understanding, veterinary knowledge and animal care experience are important elements in that range of expertise.

The advantages of performing assessment at national level are that nationwide standards are more easily imposed; the small group of persons involved become good at the task and inform and help each other; it can more readily raise standards in response to advances in knowledge than local institutional assessment; it would be expected to have better consistency; and it can be responsive to political imperatives. It is likely to be more efficient overall by involving fewer people than many local assessments, but that also risks only a narrow range of views and backgrounds informing the assessment decisions, and leaves them open to being too readily swayed by politics. The decision-making may be more objective with a freedom from local influences, but it is also distanced from where the work is carried out and may not appreciate local conditions. Another consideration is that placing ethical evaluation with the institution also places most of the responsibility and of the cost there.

The advantages of having assessment performed by an individual rather than a committee are that it is efficient in resource, can take place continuously, independent of meeting dates, can be speedy and responsive to individual cases, and should give better consistency over time than a committee with changing personnel. An individual focussed on ethical evaluations should develop expertise and specialist knowledge, and has more stimulus to devote time to doing so than a committee whose members have other occupations. The appropriate scientific, veterinary and animal care expertise may not readily be found in one person, but this can be effectively offset by having a set of assessors with differing backgrounds that communicate well, or providing the assessor with a good range of contacts available for advice. However committee assessment allows the involvement of persons not involved in animal research and able to take the view of the public at large, and reduces the risk of judgement being affected by a single person’s opinion or ethics.

The local culture or anticipated amount of work may dictate the level at which assessment can be efficiently carried out, and whether a single assessor with an appropriate range of knowledge or a committee is involved. Thus Norway with a small population but a lot of scientific work in the field has a central assessing committee. In practice, systems have been adopted which to some extent offset the potential problems of a particular approach. The UK has a set of national assessors (“inspectors”), with medical and veterinary backgrounds and scientific expertise, but this is supplemented by an ethical review process at the establishment. The US relies on evaluation by institutional committees, but also has a national inspectorate which monitors how the committees operate, and there is a requirement for institutions to report to the regulatory body. Japan relies on institution Directors advised by institutional committees but running a voluntary system, with oversight at the prefecture level.

Monitoring arrangements

The advantages and disadvantages discussed for the different approaches to assessment apply similarly to monitoring and inspection. One additional consideration is the concern that if both assessment and monitoring are left to the institution, there is potential for abuse or neglect and wide variation from national norms. External scrutiny of some kind, by external review as indicated in the Australian Code and the Japanese Ministry Guidelines, state inspection as occurs in the US, or involvement of a respected and influential non-regulatory national (like Canada's CCAC) or international body (such as the accrediting body Association for Assessment and Accreditation of Laboratory Animal Care (AALAC)), helps to reduce the risk of this.

Work outside recognised establishments

Clearly the general ethical considerations are the same irrespective of the place where the scientific work is carried out. In nearly all the countries considered, the system expects the research facility to bear a measure of responsibility for the scientific work on its premises, but there is also recognition that studies may have to take place outside the establishment, and that the institution's responsibility extends to work outside undertaken by those for which it has management responsibility.

However, the ability to exert control and monitor activities is different off-site. In a research or testing facility there may be considered to be five roles related to the animals, with differing responsibilities. There is the person doing the procedures who should minimise adverse effects on the animals of the procedures, the person planning and supervising the study and responsible for the good conduct of the science, an institutional manager in charge of the facility which provides housing and care and responsible for its standards and smooth operation, a veterinary surgeon providing professional advice and expertise and a person looking after the day-to-day care of the animals. The expertise needed and relationship to the animals is different in each role, and ideally there would be a different person in each. For work in the wild three of these roles (manager, care provider and veterinarian) would normally be absent, placing more responsibility on the researchers themselves, so keeping of good records and inspection of these and the conduct of the work on site is particularly important.

There are also particular difficulties for studies in the wild. It may be harder to reduce numbers by efficient design and to refine procedures. For example, there is liable to be bias in what is captured or observed. Capture methods carry risk of injuring the animal, and capture is likely to cause stress and other adverse effects - as may the presence of an observer. The after-effects of a procedure may be difficult to judge or offset. An animal released after procedures may be at a social, mating or foraging disadvantage and the risk and extent of this may be unknown. Killing the animal as a way of limiting suffering may not be an option.

In addition there are practical difficulties in monitoring by inspection. Seeing the work in progress depends on knowing where and when it is taking place. Inspection involves locating the site and timing a visit to coincide with regulated activity, and, for wildlife investigations, and some farm studies, this may change from day to day. If an inspector joins the research team, as is necessary for many visits to remote or controlled locations or for much marine work, he/she may have difficulty remaining objective, particularly if this entails many days of living with the team.

Conclusions

The recognition that there is an ethical dimension to the scientific use of animals has led to regulatory approaches in all but a few of the most economically developed nations and is now spreading to those at a lesser stage of economic development. There are many differences in types of animals covered and in the elements and operation of different national systems that include some form of ethical appraisal. However there are several commonalities. Prior appraisal of proposals for scientific use of animals against the principles of replacement, reduction and refinement is one, and weighing the potential benefits against the likely adverse effects is another (with significant exceptions of USA and Japan). This gives a basis for some degree of consistency of outcome from the various national systems. In these, the use of some form of ethics committee, and the involvement of scientific and veterinary expertise is widespread, as is an element of external monitoring. Several inter-governmental organisations have successfully integrated principles and practice of ethical review into policies and guidelines for animal research. There is therefore a reasonable prospect that international oversight with resonance with these approaches could gain the support and respect needed to be effective.

Difficulties for international oversight are: the considerable variations between national ethical review systems where they are in place; the problems of gaining acceptable consistency of evaluation; and the influence of the culture on ethical evaluations made and the operation of systems for appraisal and monitoring. However, these are also the reasons why a means of reaching some consistency in outcome is necessary for there to be international confidence in the operation of agreements in this area. As mentioned many times above, it is also important to have good monitoring.

Bearing these points in mind and with consideration of the various other points made in this report and of the features of the many different systems outlined in the Appendices, the following are recommendations that would allow for international oversight of scientific work on cetaceans within the remit of the International Whaling Commission (IWC), with a good prospect of moving over a period of years to some measure of conformity:

1. An international ethical review panel (IERP) reporting to the Commission should be established. The persons on the panel should between them have scientific, veterinary, and wildlife research expertise, and experience of assessment under different national ethical review systems. The panel should include at least one person with experience of cetacean research and/or capture of cetaceans. Although much of its work could be done by correspondence, the IERP should meet for face-to-face discussion at least once a year.
2. The IERP should produce for the Commission guiding principles for the ethical review of proposals to undertake scientific studies on cetaceans which come above an agreed level of pain suffering distress or lasting harm. These should be based on the ICLAS principles but adapted to be particularly applicable to wildlife studies in the marine environment.
3. The IERP should research and provide clear criteria for the type and nature of cetacean studies which would qualify for ethical review. These criteria should be shared with the Commission, with a view to requesting all contracting governments to submit to the IERP for review all research proposals which fall within the criteria for ethical appraisal.

4. When proposals for research qualifying for ethical review are submitted by contracting governments to the Commission, the IERP should assess the proposal against the guiding principles. The assessments should be fed back to the proposers, with invitation to comment. After a period for comment, the assessments, comments and final recommendations of the IERP should be reported to the Commission.
5. A report summarising the results obtained and their significance, and the adverse effects on the animals, indicating for each the severity, duration and numbers affected, should be provided by the researchers to the IERP at the end of each study. The IERP should review this report against the guiding principles and provide comments to the Commission.
6. The Commission should summarise the work and recommendations of the IERP in its annual report.
7. The Commission should consider setting up a system for non-adversarial discussion and inspection of work in progress on a sample of scientific studies considered under the ethical review system. The persons involved could be the same as on the IERP.

References

Australia: Queensland (2009). Animal Care and Protection Act 2001 as in force on 1 December 2009. Accessed at http://www.legislation.qld.gov.au/LEGISLTN/CURRENT/A/AnimalCaPrA01.pdf on 2 August 2011

Australian Government National Health and Medical Research Council (2004) *Australian code of practice for the care and use of animals for scientific purposes, 7th Edition*. Accessed at http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/ea16.pdf on 23 August 2009

Bateson, P. (1986). When to experiment on animals. *New Scientist* 109, 30-32.

Brazil Law N.º 11.794 (2008). Accessed at http://www.leidireto.com.br/lei-11794.html. on 11 August 2011

Canada: Province of Alberta (2008). Animal Protection Act 2000: Animal Protection Regulation 203/2005. With amendments up to and including Alberta Regulation 210/2008. Accessed at http://www.qp.alberta.ca/574.cfm?page=2005_203.cfm&leg_type=Regs&isbncln=9780779737260 on 11 August 2011

Canadian Council on Animal Care (1993) *Guide to the Care and Use of Experimental Animals, Vol. 1, 2nd ed*. Accessed at http://www.ccac.ca/Documents/Standards/Guidelines/Experimental_Animals_Vol1.pdf on 7 March 2011

Canadian Council on Animal Care (1997). *Guidelines on: animal use protocol review*. Accessed at http://ccac.ca/Documents/Standards/Guidelines/Protocol_Review.pdf on 11 August 2011

Canadian Council on Animal Care (2003) *Guidelines on: the care and use of wildlife*. Accessed at http://ccac.ca/Documents/Standards/Guidelines/Wildlife.pdf on 11 August 2011

Council for International Organisations of Medical Sciences (1985). *International Guiding Principles for Biomedical Research Involving Animals*. Accessed at http://cioms.ch/publications/guidelines/1985_texts_of_guidelines.htm on 18 December 2011

Council of Europe (2005) Convention ETS123 (1986) - European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes, as amended. Accessed at http://conventions.coe.int/Treaty/en/Treaties/html/123.htm on 3 March 2011

Federation of European Laboratory Animal Science Associations (2005). *Principles and Practice In Ethical Review of Animal Experiments Across Europe*. Accessed at http://www.felasa.eu/media/uploads/Principles-practice-ethical-review_full%20report%20.pdf on 3 March 2011

Hall M (1831) Of the Principles of Investigation in Physiology**.** Reprinted in *Circulation (*1973) 48, 651-654.

Institute for Laboratory Animal Research (2011). *Guide for the Care and Use of Laboratory Animals, Eighth Edition.* Washington: National Academies Press.

International Council for Laboratory Animal Science (21010). *International harmonisation of guidance on the ethical review of proposals for the use of animals, and on the education and training of animal users in science*. Accessed at http://www.iclas.org/Document/Ethical%20review%20-%20training%20article%20for%20Laboratory%20Animals%20-%20Official%20DOC%20Juin%202010.pdf on 9 December 2011.

Japan: Ministry of the Environment (2009). Act on Welfare and Management of Animals (Act 105, 1, 1973, as amended under act 68, 2005; translated 2009). Accessed at http://www.env.go.jp/en/laws/nature/act_wm_animals.pdf on March 2011.

Japan: Ministry of Education, Culture, Sports, Science and Technology (2006). *Notice No. 71: Fundamental Guidelines for Proper Conduct of Animal Experiment*. Accessed at http://www.hokudai.ac.jp/sangaku/suishin/d/kihon_houshin_e.pdf on 10 August 2011.

Kilkenny, C., Browne, W.J., Cuthill, I.C., Emerson, M.and Altman D. G. (2010). Improving bioscience research reporting: the ARRIVE guidelines for reporting animal research. *J Pharmacol Pharmacother 1*, 94-99.

Linzey, A. (1987). *Christianity and the Rights of Animals*. London: SPCK

Marques, R. G., Morales, M. M. and Petroianu,A. (2009) Brazilian law for scientific use of animals. *Acta Cir. Bras. 24*, 69-74.

National Research Council of Thailand (2006). Ethical Principles and Guidelines for the Use of Animals for Scientific Purposes. Accessed at http://www.aaalac.org/resources/Ethical_Principles_and_Guidelines_for_the_Use_of_Animals_for_Scientific_purposes.pdf on 5 December 2011

Norway: Ministry of Agriculture and Food (2010). Animal Welfare Act 2010. Accessed at http://www.regjeringen.no/en/doc/laws/Acts/animal-welfare-act.html?id=571188 on 10 March 2011

Norway: Ministry of Agriculture and Food (2010). Forskrift om forsøk med dyr (Regulations on Animal Experimentation 1996 as amended). Accessed at http://www.lovdata.no/for/sf/ld/xd-19960115-0023.html on 10 March 2011

Norway: Ministry of Agriculture and Food (2009). *Specific guidelines regarding the Animal Welfare Act*. Accessed at http://www.regjeringen.no/en/dep/lmd/aktuelt/nyheter/2009/mai-09/new-animal-welfare-act-/specific-guidelines-regarding-the-animal.html?id=562555 on 11 August 2011

Official Journal of the European Union (2010). Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 On the Protection of Animals Used For Scientific Purposes**.** Accessed at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:276:0033:0079:EN:PDF on 3 March 2011

Organisation for Economic Co-operation and Development (2002),*Guidance Document on the Recognition, Assessment and Use of Clinical Signs as Human Endpoints for Experimental Animals Used in Safety Evaluation*, OECD Series on Testing and Assessment, No. 19, OECD Publishing. Accessed at http://www.oecd-ilibrary.org/docserver/download/fulltext/9750191e.pdf?expires=1327278300&id=id&accname=guest&checksum=F0DA8124F40FE4E1E6C8D50B731F32B5 on 5 December 2011.

Peru (2000) Law No. 27265. Ley de Protección a los Animales Domésticos ya los Animales Silvestres Mantenidos en Cautiverio. Accessed at http://www.glin.gov/view.action?glinID=70024 on 8 Dec 2011.

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

Russell, W.M.S. and Burch, R.L.(1959). *The Principles of Humane Experimental Technique.* London: Methuen.

Science Council of Japan **(**2006). *Guidelines for Proper Conduct of Animal Experiments*. Accessed at http://www.scj.go.jp/ja/info/kohyo/pdf/kohyo-20-k16-2e.pdf on 14 March 2011
Smith, A. (1998) *The regulation of animal experimentation in Norway: An introduction*. Oslo: Norwegian School of Veterinary Science. Accessed at http://oslovet.norecopa.no/booklet/Booklet.pdf on 10 August 2011

Singapore: Agri-Food and Veterinary Authority (2007) Animals And Birds Act (Chapter 7, Section 80) Animals And Birds (Care And Use Of Animals For Scientific Purposes) Rules, as revised. Accessed at http://statutes.agc.gov.sg/aol/search/display/view.w3p;page=0;query=CompId%3Aa74f77c4-35ac-4e32-8713-ccdd294d6951;rec=0;resUrl=http%3A%2F%2Fstatutes.agc.gov.sg%2Faol%2Fbrowse%2FrelatedSLResults.w3p%3Bletter%3DA%3BpNum%3D1%3Bparent%3Df0719c63-6c52-4222-b991-3804d749ea36%3Btype%3DactsAll on 8 December 2011

Smith, A. (1998) *The regulation of animal experimentation in Norway: An introduction*. Oslo: Norwegian School of Veterinary Science. Accessed at http://oslovet.norecopa.no/booklet/Booklet.pdf on 10 August 2011.

Smith, J. A. and Boyd, K. M. (1991). *Lives in the Balance*. Oxford: Oxford University Press.

South Africa Medical Research Council (2004). *Guidelines on Ethics for Medical Research, Book 3: Use of Animals in Research and Training*. Accessed at http://www.sahealthinfo.org/ethics/book3.htm on 30 November 2011

Tanzania: Animal Welfare Act (2008). Accessed at: http://www.fao.org/fileadmin/user_upload/animalwelfare/tanzania.pdf on 10 August 2011

United Kingdom Home Office (1998). Animals (Scientific Procedures) Act 1986 as amended. Accessed at http://www.legislation.gov.uk/ukpga/1986/14/data.pdf on 2 March 2011

United States Department of Agriculture (2009). Animal Welfare Act 1966, as amended. Public Law 89-544 (7 U.S.C. 2131 et seq.). Accessed at http://www.gpo.gov/fdsys/pkg/USCODE-2009-title7/html/USCODE-2009-title7-chap54.htm on 22 March 2011

United States Department of Agriculture (2009). Code of Federal Regulations (CFR) Title 9, Chapter I, Sub Chapter A, Parts 1 , 2 and 3, 1–1–09 Edition. Accessed at: http://www.gpo.gov/fdsys/pkg/CFR-2009-title9-vol1/pdf/CFR-2009-title9-vol1-chapI-subchapA.pdf on 2 March 2011

United States: Office of Laboratory Animal Welfare (2004). Health Research Extension Act 1985 Public Law 99-158, Sec.495. Accessed at: http://grants.nih.gov/grants/olaw/references/hrea1985.htm on 2 March 2011

United States Office of Laboratory Animal Welfare (2002). Public Health Service Policy on Humane Care and Use of Laboratory Animals. Accessed at: http://grants.nih.gov/grants/olaw/references/phspol.htm on 10 August 2011

University of Minnesota (2011). Regulatory Charge & Governing Principles of IACUC**.** Accessed at http://cflegacy.research.umn.edu/iacuc/about/charge.cfm on 5 December 2011

World Organisation for Animal Health (2011) *OIE Terrestial Animal Health Code, Vol II, Chap 7.8: Use of Animals in Research and Education*. Accessed at http://www.oie.int/index.php?id=169&L=0&htmfile=chapitre_1.7.8.htm on 5 December 2011

APPENDIX 1
Ethical Review – National Systems

Australia

Australia provides an example of a mandatory Code of Practice, regionally applied. Regulation of the scientific use of animals is devolved to State or Territory legislation. Queensland's Animal Care and Protection Act 2001 (ACAP) is taken as an example of this so "state" below refers to Queensland.

The national code is the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes 2004. It stipulates that institutions involved in animal experimentation should have Animal Ethics Committees (AECs), details how an AEC should operate and specifies the information needed for proposal assessment. There is a separate section on wildlife studies.

Animals covered:

Live non-human vertebrates and cephalopods such as octopus and squid in the Code. Extended in ACAP to malacostracan crustaceans such as crabs lobsters crayfish and prawns, and to later stages of development, and animals killed for a scientific purpose.

Regulatory system:

- State registration of scientists using or directing the use of animals, (or of educational institutions) by the chief executive, if satisfied that the applicant and animal ethics committee(s) proposed in the application are likely to comply with the Australian Code.
- Proposal assessment and local monitoring under the Australian Code.
- State requirement that a person using an animal for scientific purposes complies with the Australian Code and penalties for non-compliance.
- External monitoring under the Australian Code.
- Scope for state external monitoring.

Ethical review system: Institutional Animal Ethics Committees

Expertise involved – Scientific, veterinary, welfarist independent of the institution, and independent lay person. Animal care expertise desirable.

Ethical review

- Prior assessment of justification (including harm-benefit analysis), application of Three Rs, and the proposal information by AEC.
- Ongoing monitoring by AEC.

Proposal information:

- Potential benefits of the work.
- Why animals have to be used.
- How the numbers used will be minimised.
- What the impact will be on the animals – including step-by-step listing of procedures, adverse effects that may occur and refinements proposed.

- How the animals will be monitored and any problems dealt with.
- Justification for the work including a harm-benefit analysis.

Internal monitoring

- Day-to-day monitoring by researcher.
- Inspection of work in progress and facilities by AEC.
- Examination of annual AEC report by the institution.

External monitoring

- Triennial external review of the institutional operation (including, for example, scrutiny of paperwork, inspection, attendance at AEC meeting) expected under the Australian Code.
- State-level scrutiny of annual written report from person registered.
- Option for a state monitoring program in which authorised officers monitor compliance with the Australian Code, and promote standards of animal care.

Brazil

Brazil enacted a national law regulating the scientific use of animals, Lei No.11794, in 2008. The operation of this is described in Marques et al. (2009).

Animals covered:

Live vertebrates

Regulatory system:

- National Council for Control of Animal Experimentation (CONCEA) accredits institutions involved in experiments or teaching using live animals, and sets national standards.
- Accredited institutions have to maintain an Animal Use Ethics Committee (CEUA), which must assess proposals, register researchers, record procedures and ensure compliance to the law and national standards in the use and housing of the animals.

Ethical review system: Institutional Animal Use Ethics Committees.

Expertise involved:

- CONCEA has representatives of ministries covering science, the environment, education, health and agriculture, of university rectors, and of various scientific bodies, and two from animal protection societies.
- CEUAs have scientific and veterinary personnel, and a representative of animal protection societies.

Ethical review:

- Some harm-benefit analysis by CONCEA in setting limitations for more severe experiments.
- Prior assessment of application of Three Rs by CEUA.
- Ongoing monitoring by CEUA.

Proposal information: Not specified

Internal monitoring:

- Day-to-day monitoring by researcher.
- Monitoring by CEUA.

External monitoring

- Review by CONCEA of list of researchers and procedures and other information provided by CEUAs, and information from other sources.

Japan

Japan's Act on Welfare and Management of Animals 1973 included in Article 41 stipulations regarding animals for scientific use. This was updated with Three Rs wording in 2006. The Ministry of Education, Culture, Sports, Science and Technology then issued *Notice No. 71: Fundamental Guidelines for Proper Conduct of Animal Experiment* 2006 and the Ministry of Health, Labour and Welfare issued *Basic policies for the conduct of animal experimentation*. These provide general standards and the regulatory framework. At the behest of these Ministries, the Science Council produced *Guidelines for Proper Conduct of Animal Experiments 2006*. Research institutions can use them to compile their own specifications for animal experimentation. In the words of the Guidelines "Each institution should formulate voluntary in-house regulations for proper scientific conduct of animal experiments based on these Guidelines."

Animals covered: Mammals, birds and reptiles.

Regulatory system:

- Approval of protocols by Institution Director after evaluation by Institutional Animal Care and Use Committee.
- Reporting to Director of conduct and outcome by researchers.
- Institutional disciplinary measures.

Ethical review system: Institutional Animal Care and Use Committee

Expertise involved: " researchers conducting animal experiments, laboratory animal specialists and other persons of knowledge and experience".

Ethical review

- Prior assessment of proposed application of Three Rs, and the proposal information by IACUC.
- Ongoing monitoring by IACUC.

Proposal information:

- Research objective.
- Detailed experimental procedure to be used on the laboratory animals.
- Term of animal experiment.
- Type of animal experiment.
- Laboratory animal species, strain, sex, age, etc, and number of animals used.
- Location where the animal experiment is to be performed.
- Rearing methods.

- Reasons why an animal experiment is necessary.
- Severity of pain the animals may suffer due to each of the procedures.
- Pain alleviation methods.
- Euthanasia procedures.

Internal monitoring

- Day-to-day monitoring by researcher.
- Inspection of work in progress and facilities by IACUC.
- Self-inspection and evaluation by the institution director.

External monitoring

- Inspection and evaluation by an independent third party.
- Some public monitoring of disclosed information.

Norway

Norway signed the Council of Europe Convention ETS 123 in 1986, and developed regulations under the Animal Protection Act 1974 to meet its standards. The Ministry of Agriculture issued Regulations on Animal Experimentation in 1996, with subsequent amendments up to 2010. A new Animal Welfare Act became law in 2010 and revision of the regulations to meet the standards in EU Directive 2010/63 is in progress.

A significant amount of the research is field studies: these have a separate section in the present regulations and are only approved for up to two years.

Animals covered:

Living mammals, birds, reptiles, amphibians, fish, including embryonic and fetal stages of development, and decapods. Also, under the 2010 Act, cephalopods.

Regulatory system:

- Approval of institution by the Norwegian Animal Research Authority (NARA).
- Appointment by NARA of a competent person in each institution.
- Approval of researchers and research projects by NARA or the competent person (field studies have to be approved by NARA).
- Monitoring by NARA and local competent persons.

Ethical review system: Norwegian Animal Research Authority; institutional competent person.

Expertise involved:

In NARA - veterinary, medical, legal, laboratory animal specialist, biologist, representative of Norway's animal welfare organisations, laboratory animal technician, and others. For competent persons – scientific with animal experimentation experience.

Ethical review

- Prior assessment of proposed work both with a harm-benefit analysis and regarding application of Three Rs.
- Ongoing monitoring by competent person.

Proposal information:

- The purpose, type of experiment, scope, including the species and numbers, duration and, for field studies, the location.

Internal monitoring

- Monitoring by researcher.
- Day-to-day supervision by competent person.

External monitoring

- Inspection by NARA of research facilities and specific animal experiments.
- Scrutiny by NARA of all proposals approved locally by competent persons.
- Inspection by state animal welfare committee members and official veterinarians from The Norwegian Food Safety Authority.

Tanzania

Tanzania passed an Animal Welfare Act in 2008. This includes sections on animal experiments.

Animals covered:

Non-human vertebrates and invertebrates.

Regulatory system:

- Standards set in regulations issued by the Minister.
- Permit for research from the Director responsible for animal welfare.
- Prohibition of experiments for which there is a replacement or a lower severity alternative, and of experiments for a purpose which does not justify the distress caused.
- Requirement for permit holder to ensure minimum severity.
- Requirement for permit holder to keep records and make these available to the Director.

Ethical review system: The Director, advised by an Animal Welfare Council.

Expertise involved:

- The composition of the Animal Welfare Council is unknown. A permit holder is obliged to have a veterinarian available.

Ethical review:

- Prior assessment, before issue of permit, of adverse effects and conformity with the prescribed ethical rules and standards (including the prohibitions given above).

Proposal information:

- Not specified.

Internal monitoring:

- Day-to-day monitoring by researcher.

External monitoring:

- Scrutiny by Director of records provided by permit-holder.

United Kingdom

In 1986 the Animals (Scientific Procedures) Act replaced the two-level regulatory system of the 1876 Cruelty to Animals Act, under which premises were registered and individual researchers licensed, with a three level system including licences for scientific projects. All authorities are issued with conditions that require ongoing monitoring by the person granted the authority. A condition on establishments is maintenance of an Ethical Review Process (ERP). The regulatory authority also issues Guidance and Codes of Practice.

Animals covered:

Live non-human vertebrates and Octopus vulgaris.

Regulatory system

- Certificate for the establishment held by a senior member of the institution.
- Project licence for each scientific project, held by the scientist responsible, and limited to 5 years.
- Personal licence for each researcher performing procedures on animals.
- Assessment and advice on approval of these by national inspectorate.
- Monitoring of compliance with permissions and conditions on all these authorities (including proper operation of ERP) by national inspectorate.

Ethical review system:

National set of assessors (the inspectorate), establishment ERP. Scope for referral to external experts and to the national Animal Procedures Committee (APC).

Expertise involved

- Medical or veterinary specified in law for the inspectors with additional scientific expected.
- Scientific (project and personal licensees), veterinary and animal care specified in Guidance for establishment's ERP.
- Named advisory veterinarian and named animal care person required for each establishment.
- National advisory APC has medical, veterinary, scientific, animal care, legal, lay and animal welfare organisation personnel.

Ethical review:

- Prior assessment, before issue of each type of authority, by inspector (with advice from colleagues).
- Prior assessment of conformity of project proposals with local requirements by ERP.
- Ongoing assessment by establishment personnel and visiting inspectors.
- Retrospective review when succeeding project assessed.

Proposal information:

- Background and skills of the applicant and research team.
- Scientific background to the proposed work.
- Project objectives, plan of work and experimental protocols, including adverse effects.

- Sufficient information for a harm-benefit analysis to be carried out and to demonstrate that the Three Rs principles will be followed.
- Information on the need for work outside the establishment and for use of special species, including non-human primates.

Internal monitoring

- Day-to-day monitoring by researchers and animal care staff.
- Visits by veterinarian.
- Visits by ERP members.
- Reporting as required by establishment certificate holder or ERP.

External monitoring

- Inspection and discussion of scientific matters by national inspector.
- Attendance by inspector at ERP meetings.
- Sporadic visits by APC and by government ministers.

United States

The situation in the US is complicated by the existence of two frameworks. The Animal Welfare Act 1966 (AWA) covers broader use of animals than just scientific, is the responsibility of the Ministry of Agriculture, and is supplemented by regulations. The Health Research Extension Act 1985 (HREA) is more focused and covers publicly-funded research. Activities under it are overseen by the Office of Laboratory Animal Welfare, which publishes a Public Health Service (PHS) Policy and expects conformity with the Institute of Laboratory Animal Resources Guide for the Care and Use of Laboratory Animals. The common element of both frameworks is requirement for an institutional committee, differently named in the different laws but routinely called the Institutional Care and Use Committee (IACUC).

Animals covered:

- Live and dead warm-blooded animals excluding mice, rats and birds (AWA);
- Live vertebrates (PHS Policy)

Regulatory system:

- Registration of research facilities (with triennial update); responsible Institutional Official.
- Approval of proposals by IACUC.
- Inspection by IACUC.
- Monitoring of IACUC by inspectorate (but not for publicly funded work outside AWA remit).
- Reporting by IACUC to institution.
- Central reporting by inspectors and IACUC.

Ethical review system: Institutional Care and Use Committee

Expertise involved:

- Veterinary and scientific, community representative; lay (ILAR Guide).
- Institutions must have an attending veterinarian.
- External experts may be consulted.

Ethical review:

- Prior assessment of research protocols by IACUC.
- 6 monthly review by IACUC.
- Ongoing monitoring by researchers.

Proposal information:

- Species and numbers proposed.
- Rationale for using animals and appropriateness of the species and numbers proposed.
- Full description of proposed use and procedures to be used.
- Adverse effects that may be encountered (ILAR Guide).
- Measures to be taken to minimise suffering.
- Euthanasia methods.

Internal monitoring:

- Monitoring by researchers and animal care staff.
- Visits by veterinarian.
- Inspection by IACUC.
- Reports to institution.

External monitoring:

- Inspection and audit of reports by national inspector.
- Attendance by inspector at IACUC meetings.
- Scrutiny of inspector and institution reports by national authority.
- Scrutiny of reports by responsible authority (publicly-funded work).

APPENDIX 2
Ethical Review – International Bodies

International Council for Laboratory Animal Science (ICLAS)

ICLAS is an international scientific organisation dedicated to advancing human and animal health by promoting the ethical care and use of laboratory animals in research worldwide. Argentina, Austria, Belgium, Canada, China, Costa Rica, Cuba, Cyprus, Denmark, Finland, Germany, Hong Kong, Hungary, India, Iran, Ireland, Israel, Italy, Japan, Netherlands, Norway, Poland, South Africa, Spain, Sweden, Thailand, the United Kingdom, the United States, Mexico, and Tunisia are all members of ICLAS as are several national and international laboratory animal science or scientific bodies.

Among its aims are

- To promote worldwide harmonisation in the care and use of laboratory animals;
- To promote the humane use of animals in research through recognition of ethical principles and scientific responsibilities; and
- To promote the 3Rs tenets of Russell and Burch.

ICLAS does not conduct ethical review itself but promotes harmonisation of different countries' approaches. The ICLAS document "International harmonisation of guidance on the ethical review of proposals for the use of animals, and on the education and training of animal users in science" of 2010 includes principles that countries developing or updating ethical review systems could use as guidance. These are:

- Whenever possible, methods employed to achieve scientific objectives should avoid the use of animals.
- Where animal use is unavoidable, the proposed project should have been demonstrated to have merit, in terms of its potential to advance scientific knowledge and/or benefit human or animal health (scientific merit), to protect/benefit humans, animals and/or the environment with respect to new products/devices or to toxic substances (regulatory testing) or to teach animal based principles and procedures (pedagogical merit).
- The expected benefits to humans, animals or the environment of the proposed project involving live animals should be weighed against the likely harms done to the animals, and opportunities should be sought to maximise benefits and minimise harms.
- The species/strain and numbers of animals to be used should be scientifically justified to use the most appropriate animal model and the optimal number of animals, neither too many nor too few. The experimental design should be optimised according to the type of study undertaken.
- Studies should be designed to refine procedures undertaken on animals to the greatest extent possible, and the care, housing, transport and restraint of animals should also be optimised. Pain or distress likely to be experienced by the animals must be prevented, or minimised to the greatest extent possible, with veterinary advice for the use of appropriate anesthesia, analgesia and/or other measures as applicable to the type of animal and study.
- Those who use or care for animals must be skilled and competent to do so …..
- The earliest possible endpoint for the animals should be used consistent with the scientific objectives of the study.

- A method of euthanasia that is appropriate for the species, life stage and type of work should be described and chosen.
- There should be a mechanism to ensure initial and ongoing review of the work and to use the results of the work to inform future scientific, welfare and ethical reviews.

These principles incorporate both harm-benefit analysis and application of the Three Rs, and expect that prospective evaluation should be supplemented by ongoing and retrospective. ICLAS recognises that there are various systems that can accord with these principles and does not give recommendations on how the ethical review should be carried out.

Organisation for Economic Co-operation and Development (OECD)

As its website proclaims, OECD's "34 Member countries and the OECD Secretariat work together to develop and co-ordinate chemical and pesticide related activities on an international basis."

The OECD is not itself involved in ethical review but it produces OECD *Guidelines for the Testing of Chemicals*. These are internationally agreed testing methods for identifying and characterising potential hazards of chemicals that are accepted by governments and regulatory agencies across the world.

It has also produced a *Guidance Document on the Recognition, Assessment, and Use of Clinical Signs as Humane Endpoints for Experimental Animals Used in Safety Evaluation*, the purpose of which is to apply the principles of the Three Rs to the use of animals in regulatory toxicity tests.

That document includes the following guiding principles:

- There is strong scientific evidence that pain and distress are present in animals in comparable situations as they occur in humans
- Severe pain, suffering, or death are to be avoided as endpoints.
- Studies must be designed to minimise any pain, distress or suffering experienced by the animals, consistent with the scientific objective of the study.
- The earliest possible endpoints that are indicators of distress, severe pain, or impending death that should be used as indications for humanely killing the animals should be determined prior to the animals' reaching a moribund state.
- Studies should be terminated prior to their anticipated termination time if the objectives of the study have been satisfied, or if it is obvious that they will not be achieved.
- Studies should build on existing knowledge about the substance to be tested. ….
- The successful application of humane endpoints is dependent on the involvement of all members of the study team who should be adequately trained and aware of their individual roles and responsibilities, e.g.,
    - the Study Director or designated responsible person (design, protocol development, study monitoring, interpretation of results).
    - the veterinarian (advice on interpretation of clinical signs)
    - the animal caretaker/technician (observation, action, husbandry, care)
    - an ethical review committee or a prescribed ethical review process.
- Study Directors, and the other responsible individuals should be free to exercise professional judgement in the design and conduct of the experiments.

- All aspects of animal studies should be subject to an ethical review process as defined by animal welfare legislation and the ethical oversight groups of the testing organisation. Where such legislation is not available, it may be necessary for the laboratory to develop its own ethical guidelines and procedures.
- Conditions under which interventions should be made to alleviate pain and distress by humane killing, and the individuals who are adequately trained and authorised to kill the animals, should be defined in the protocol ...

It also calls for the assembly of background information that will help define the objectives of the test, avoid duplication, aid selection of the most appropriate species and the best design for the protocol, and help to identify potential clinical signs and to estimate the timing and duration of their occurrences. It points out the value of preliminary or pilot studies and the importance of appropriate training of personnel.

World Organisation for Animal Health (OIE)

By international agreement of 28 states, the Office International des Epizooties, concerned with the prevalence and spread of epizootic disease in agricultural animals, was created in1924. Now 178 countries are members of OIE, which in 2003 became the World Organisation for Animal Health (OIE), reflecting its development into wider concerns on animal health and welfare. Its objectives include " to promote animal welfare through a science-based approach".

Chapter 7.8 of the OIE 2011 Terrestial Animal Health Code is on the "Use Of Animals In Research And Education". It details an oversight framework to be implemented by a Competent Authority, usually involving a system of authorisation (such as licensing or registering of institutions, scientists, and/or projects) and monitoring of compliance at the national, regional and/or institutional level. It should include ethical review of animal use, undertaken by regional, national or local ethical review bodies or committees, and ensure the impartiality and independence of the personnel involved. There should be scientific, veterinary and lay participation in the process, with other participation considered, particularly from animal care staff and statisticians, ethicists and other experts.

Three elements are envisaged – project proposal review, facility inspection and ethical evaluation. Project proposal review should precede the start of the work and include appraisal of any previous project's conduct and outcome, and any approval given should be for a set time period. As relevant, a proposal should include:

1. the scientific or educational aims, including consideration of the relevance of the experiment to human or animal health or welfare, the environment, or the advancement of biological knowledge;
2. an informative, non-technical (lay) summary which may be made publicly available;
3. the experimental design, including justification for choice of species, source and number of animals, including any proposed reuse;
4. the experimental procedures;
5. methods of handling and restraint and consideration of refinements such as animal training and operant conditioning;
6. the methods to avoid or minimise pain, discomfort, distress, suffering or lasting impairment;

7. application of humane endpoints and the final disposition of animals, including methods of euthanasia;
8. consideration of the general health, husbandry and care of the species proposed to be used, including environmental enrichment and any special housing requirements;
9. ethical considerations such as the application of the Three Rs and a harm/benefit analysis;
10. an indication of any special health and safety risks;
11. resources/infrastructure necessary to support the proposed work, e.g. facilities, equipment, staff trained and found competent to perform the procedures described in the proposed project.

Some form of post-approval monitoring, independent of the researchers should be considered. Informal noting by veterinary or animal care staff in the course of their duties and external inspection are given as ways of achieving this.

European Union

Unlike the other international documents considered, acceptance of whose standards is voluntary, EU Directives are binding on the EU member states. Directives regarding the scientific use of animals provide a framework of minimal requirements that allows flexibility for different national systems for ethical appraisal, with the expectation that the outcomes would be reasonably comparable. This is not confined to general principles but sets required components of the process of ethical review and monitoring. The general arrangement is shown in the box.

EU Directive 2010/63 regulatory framework - simplified

Member States designate Competent Authority/ies which are
advised by a National Committee and
authorise and register Breeders, Suppliers and Users and
authorise Projects for work at a User Place
for a scientific Purpose
on Particular animals (live vertebrates and cephalopods)
which may cause Pain, suffering, distress or lasting harm
[all 3 are needed to come within the regulation]
.. on the basis of an ethical evaluation
.. with monitoring by inspectors
[and local animal welfare bodies]
and with effective, proportionate and dissuasive penalties

Article 38 gives requirements for **Project evaluation**

1. The project evaluation shall be performed with a degree of detail appropriate for the type of project and shall verify that the project meets the following criteria:

(a) the project is justified from a scientific or educational point of view or required by law;

(b) the purposes of the project justify the use of animals; and

(c) the project is designed so as to enable procedures to be carried out in the most humane and environmentally sensitive manner possible.

2. The project evaluation shall consist in particular of the following:

(a) an evaluation of the objectives of the project, the predicted scientific benefits or educational value;

(b) an assessment of the compliance of the project with the requirement of replacement, reduction and refinement;

(c) an assessment and assignment of the classification of the severity of procedures;

(d) a harm-benefit analysis of the project, to assess whether the harm to the animals in terms of suffering, pain and distress is justified by the expected outcome taking into account ethical considerations, and may ultimately benefit human beings, animals or the environment;

Project approval is limited to five years, and retrospective review may be specified.

Establishments are required to have a designated veterinarian, and an animal welfare body that includes animal care staff and undertakes some day-to-day monitoring.

Inspection by the Competent Authority is required and at a frequency related to the nature of the work, the animals involved and the track record of the place, with a set minimum. There is also scope for some oversight by the European Commission, i.e. at EU level.

The EU mandatory requirements thus include an ethical evaluation incorporating both harm-benefit analysis and consideration of application of the Three Rs, and external and internal monitoring.