Nordic-European Workshop on Ethical Evaluation of Animal Experiments

Workshop Report on the Cost-Benefit Principle in Hanasaari, Helsinki, Finland 7-9 November 2003

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Summary

Ethical evaluation of animal experiments is gaining an increasingly important role in the general review process of animal experiments. In order to discuss various aspects of ethical evaluation, a workshop was organised in Helsinki. Forty participants representing the scientific community, animal welfare organisations and regulators from Nordic and Baltic countries and The Netherlands took part. The workshop was organised by the Cooperation Group for Laboratory Animal Sciences within the Finnish Ministry of Education. Costs refer to the cost or harm to animals when they are used in experiments, and include aspects such as pain, suffering and distress. Benefits are defined as the benefits gained by humans or other target groups resulting from animal studies, *e.g.* therapies for human diseases, and/or increased knowledge from basic scientific studies. Use of animals is considered ethically justifiable if the benefits outweigh the costs. "Cost modifiers" or "means" can be used to decrease the costs for the animals, *e.g.* an improved or refined technique that is less distressing to the animal. This will translate to better ethical acceptability. The use of scoring systems for ethical assessment was not supported by the participants since these systems can lead to a false impression of objectivity. A classification of costs versus benefits into three degrees (low, medium and high) was considered the most suitable analysis method. Furthermore, some example protocols were evaluated by the workshop participants; the result revealed a large variation in scoring the degree of costs, the importance of the benefits, and the possibilities of modifying the means. Clearly, further and continuing interaction between all of the interest parties is necessary for the creation of precision tools for ethical assessment of animal studies necessity.

Introduction and background

Ethical evaluation of animal experiments is becoming increasingly important, and is likely to be included in the revised EU Directive. The European Science Foundation's policy document on laboratory animals (2001) emphasizes that animal experiments must be assessed by an independent review board and that this review should be based on a cost/benefit analysis. Even though the current EU law does not require ethical evaluation, many countries have already started this as a voluntary process or included it in their national legislation. As a result, quite variable processes and standards for ethical review are seen throughout Europe: hence the decision by the Cooperation Group for Laboratory Animal Sciences in the Finnish Ministry of Education to organise a Nordic-Baltic workshop on this topic. Altogether 40 invited participants from the Nordic and Baltic countries – Denmark, Estonia, Finland, Iceland, Latvia,

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Lithuania, Norway, Sweden – and The Netherlands took part. The participants represented the scientific community (including laboratory animal science), regulators and animal welfare organisations. Many of the participants were members of ethics committees in their own countries. The main aim was to compare the situation in each and to review methods for ethical evaluation. The ethical review aims at ethically sustainable, scientifically sound research with the highest possible transparency.

Regulations and legal requirements in the various countries

EU regulations are changing - how about the ethical evaluation?

The European Union (EU) have issued legal guidelines for the protection of laboratory animals used in research *(EU Directive 86/609, 1986; European Convention ETS123, 1986)* but as yet these do not include ethical evaluation. Some EU countries have already included the ethical review process in their national legislation, which requires protocols for animal studies to be subjected to an independent ethical review process before they can be performed; and some that are not yet EU members have developed similar legislation.

Currently, the European Convention is being revised. The first part of the revision addresses the housing and care of laboratory animals (Appendix A). In 1997, the Council of Europe, discussing Convention ETS 123, decided on a resolution to modify accommodation and care *(Council of Europe, 1997)*: in the light of the current knowledge, housing and care of laboratory animals had to be improved, in order to meet species-specific needs. The EU Directive will soon be revised accordingly. In their report on the Directive 86/609, the Committee on the Environmental, Public Health and Consumer Policy (A5-0387/2002) stated: *"..considers that to obtain a licence to perform experiments on animals, the applicant must be able clearly to substantiate and justify the purpose of the experiment in terms of the criterion that the experiments will be of benefit to animals or humans. In addition, a licence may be issued only where the applicant can show that the desired outcome can only be achieved by using live animals and that there are no alternative testing methods. Before a licence is issued, an ethical and animal-welfare assessment must be carried out, setting limits to the level of stress to which the animals may be subjected. Even if it can be shown that certain experiments may be of benefit to animals or humans, they should not be authorised if the stress on the animals used in the experiment exceeds the maximum level."* This implies that a consistent way to evaluate the purpose of an individual animal experiment is needed, as well as an evaluation of the possible harm that the experiment may cause to the animals, *i.e.* a cost-benefit analysis.

Basic elements of the ethics committees in participant countries

Each of the participating countries in the workshop has variable national legislative requirements concerning the ethical evaluation of animal experiments (Table 1). The committees may be local, regional and/or national, and the members of these committees can include scientists, laboratory animal specialists, ethicists, animal technicians, lawyers, civil servants representing governmental bodies and/or representatives of animal protection organisations. The function of the ethics committees is to ensure that an ethical review is done, before the animal experiment can be performed, in order to guarantee that animal welfare is safeguarded at an optimum level.

Some of the elements which ethical committees will evaluate are:

- is this experiment really necessary and of value?
- has an in-depth literature review been performed, in order to avoid unnecessary duplication?
- have alternatives been considered?
- are the animals subjected to no more suffering than is absolutely necessary?

Table 1. Ethics committees in Nordic countries, Baltic countries and The Netherlands
ETS123: European convention, Council of Europe 1986
Directive 86/609: European Union 1986
National requirements: does national legislation require ethical evaluation?

Country	**Legislation**			**Type of committees**	**Members in committees**	**Number of animals used in 2002**		**Maximum time of licence**	**Cost-benefit analysis**
	ETS123	Directive 86/609	National	Local, Regional or National		Mammals	Fish and amphibians		
Denmark	Yes	Yes	To a certain degree	- 4 voluntary institutional committees in pharmaceutical industry - 1 National committee	Local: variable National: 10: - Scientists, - Animal welfare organisations, - 1 judge (chairman) - 1 veterinarian (secretary, national inspector)	334 901	36 171	5 years	Local: no formal guidelines National: cost-benefit analysis to a certain degree (very high cost never allowed; if no substantial benefit, animal use not allowed)
Estonia	Will be ratified (EU)	Yes Current animal welfare legislation is harmonised to this directive	Yes	National according to the current legislation (earlier local)	8 altogether: - Scientists - Person familiar with animal houses (veterinarian) - Animal welfare organisation -Lawyer - Person from the Ministry of Agriculture	unknown	unknown	Not described in the current legislation	New national committee is starting – the principles are unknown. Hopefully the principles of cost-benefit analysis will be applied.
Finland	Yes	Yes	Yes	Local	- Scientists - Animal technicians - Animal welfare organisations	142 480	502 400	3 years	Yes in general, no formal guidelines or practice
Iceland	No	Yes Current animal welfare legislation is based on the directive	Yes	National	National: 3 - Scientist, - Chief veterinarian (chairman) - Ethologist	3 500	2 500	4 years	Yes, no formal system. According to regulations.

Latvia	Yes	Yes	Yes	National	- Scientists - Animal technicians - Animal welfare organisations - Laymen	3 200	No	3 years	Yes in general, no formal guidelines or practise
Lithuania	No	No	Yes	National	- Scientists - Animal welfare organisation - Officers from the State Food and Veterinary Department - Member of Lith-LASA - Animal technicians	200	1300	1 year	Yes
Norway	Yes	Yes	Yes	National	- Scientists - Lawyers - Animal technicians - Animal welfare organisations	49 191	1 432 881	4 years	Yes, no formal system
Sweden	Yes	Yes	Yes	Regional	- 6 scientists (incl animal technicians) - 6 laymen (= county politicians + <= 2 representatives for animal welfare organisations) - Judge as chairman - Individual substitutes	329 000	152 000	3 years	Yes, that is general guideline
The Netherlands	Yes	Yes	Yes	Institutional	- Scientist - Ethicist - Advisers (no vote) - Animal technicians	687 554	36471	One year	According to the law, yes

- are the planned technical procedures appropriate and performed by skilled personnel?
- can techniques be refined?
- have humane endpoints been considered?
- is the number of animals appropriate, *i.e.* has a statistical calculation been done?

These points are discussed in all ethics committees, but as yet there are no consistent ways to do so or to come to an appropriate ethical conclusion, even though methods have been proposed *(Bateson, 1986; Porter, 1992; Stafleu et al. 1999)*.

The ethical evaluation of animal experiments: costs against benefits

The starting point in the ethical review process is to consider the costs versus the benefits while noting that the European Convention states that humans have a moral obligation to respect animals. We suggest three principles: para (i) As to: animal experiments should only be performed when they are absolutely necessary and be aimed at achieving a clear benefit in terms of reduced suffering and improved life quality in man and/or animals *(Smith & Boyd, 1991)*. The benefits of an experiment are easily demonstrated when the results are directly applicable, such as the development of a new life-saving drug, but may, especially in basic research, be indirect or uncertain. Nevertheless basic reaearch can lead to new scientific knowledge or new practical applications even if often only first appreciated in the long-term, major discoveries often being made "by accident" (serendipity). Hence, although the knowledge obtained by basic research may not be directly applicable now, it may have considerable value in the future.

(ii) Secondly as to "costs": plainly animal suffering must be minimized, and an experiment which involves excessive pain or suffering, should not be carried out. The harm caused to the animals, such as pain, illness, suffering, distress, is generally considered the "costs" of the experiment *(Smith & Boyd, 1991; Orlans, 1997)*. But the costs may also be considered in a broader context for society as a whole, *e.g.* what is the cost if some new drug is not developed, with the consequence that the survival time of patients is shortened, or that they are subjected to less effective treatments. In the workshop in Helsinki, the term costs was used in the more limited context, *i.e.* referring to the costs to the animals.

(iii) The third principle represents the validity of the animal studies. Experimental methods must be sound and relevant for the objective of the experiment, *i.e.* must have scientific validity *(Smith & Boyd, 1991)*. This consists of factors like proper experimental design and statistics, the use of the most suitable species and the correct number of animals, proper methodology, and, crucially, optimisation of the welfare of animals, since the results of animal experiments are affected by their welfare. Overly stressed animals will not yield reliable results. Animal welfare is ensured with proper housing conditions, effective pain relief and refined experimental techniques, thereby reducing the burden, or "cost", borne by the animals *(Jennings, 1998)*.

When costs and benefits of an individual experiment have been defined, a judgement must be made whether or not it can be considered ethically acceptable. Generally, the benefits of the experiment should override the costs *(Smith & Boyd, 1991)*. However, the weighing of different factors is complex and may be strongly affected by personal values: hence, the importance of commonly defined and accepted values in the scientific community. In recent years, various scoring systems for ethical evaluation of animal experiments have been presented *(Bateson, 1986; Smith & Boyd, 1991; Porter 1992; Stafleu et al., 1999)*, but are not yet fully accepted.

The output from the forum

The work of the forum was based on lectures, group work (items 2,3,4 below) and plenary discussions (items 2-6). The overall aim was to come to a consensus on how to carry out the ethical evaluation of animal experiments.

The following themes were highlighted and discussed:

1. What are the current procedures in various European countries?
2. How to find the correct balance between the benefits and the costs?
3. Which elements belong to benefits and which to costs?
4. Relative weight of cost and benefit elements?
5. How to apply the cost-benefit principle?
6. Is it possible to reach consensus on the outcome after ethical evaluation?

What are the current procedures in various European countries?
This has been addressed in Table 1.

How to find the correct balance the benefits and the costs?
Participants agreed with much of what was identified under **3**. above: *i.e.* that the costs are easier to identify and define than the benefits. This is because the benefits have various themes and are related to society's values. Thus there are those derived from applied medical research which are easier to explain, defend and approve, compared with the possible benefits resulting from the uncertain outcome of basic research where as there is no clear immediate (medical) benefit. So, how should we weigh these benefits? And it was concluded that because either type of research can lead to major (unexpected) breakthroughs in the longer term, a value in itself , the corresponding benefits should receive the same weight .
However scientists should formulate the benefits of animal studies better, as an essential part of an ethical evaluation and to demonstrate to the general public why a certain study is expected to be of value. The participation of "lay people" in ethics committees was therefore considered valuable, as they are considered to represent "public opinion" and, with time and experience, could add value to the discussions. However they should not of course be involved in evaluating the scientific value of the studies, as this falls outside their competence.

Three levels of benefits were distinguished by the participants:
1. the direct benefit of a study;
2. long-term expectations;
3. studies being part of a larger picture: pieces of a puzzle.

When trying to balance costs versus benefits, it is difficult to rate these two very different entities versus one another. Also the time scale complicates the comparison: the costs to animals are essentially immediate, whereas the benefits can be uncertain and may appear (much) later. Models using mathematical calculations were not supported by the workshop participants, as they give a false impression of objective accuracy. Estimates based on 3 degrees of severity (slight/low, moderate, severe/high) for costs and benefits (see *e.g.* model by Bateson 1986) were preferred. When rating the benefits of animal studies, the quality of the research and of the research group must be included, as these are clearly related to the probability of success. Good quality research groups also make sure that the results are published in international peer-reviewed journals, so that the information is made available to everyone. It was considered unethical that negative results are not published, as this can lead to unnecessary duplication of the use of animals. Ethics committees could strongly encourage and educate scientists to publish these findings and request editorial boards of scientific journals to adopt ethical review policies which would include the publication of "negative results". In the case where local ethics committees perform the ethical review, there is a risk that the various committees apply variable standards in the evaluation process. This poses the risk that researchers start "shopping around" in order to find the committee that will evaluate most "favourably". Regional or national committees can partly prevent this risk, though, there is also the risk that scientists will start "shopping around" in other countries. Therefore, there is a clear need for communication and harmonisation in the ethical review decision-making process.

The benefits and costs defined during the workshop are listed in Table 2.

Table 2. The lists of benefits and costs

Benefits	**Costs**
Benefits for humans	***Costs for the animals***
New drugs/therapies	Pain, distress and discomfort differing in duration, frequency and severity
Better health, survival and well-being	Species: animal development level
Increased quality of life	Numbers of animals: too small or too many
Safety/toxicology	Transportation
Increased knowledge	Housing in cages and limited freedom
Learning/experiencing – educational benefits	Animals cannot perform the behaviour they want to perform
Benefits for animals	Mistakes are made, in order to increase knowledge and develop methods
New drugs/therapies	Not publishing negative results (increases numbers unnecessarily)
Better health, survival and well-being	Health care
Increased quality of life	Quality of staff
Increased knowledge	Death
Benefits for ecology	
Preservation of wildlife	
Increased knowledge (of use in captivity as well)	
Improved environment	
Benefits for economy	
Improved production possibilities	
Preserved wildlife as a food source (hunting)	
Providing jobs / welfare of society	
Saving indirect costs of health care	
Basic science	
Increased knowledge	
New/improved methodologies	

Which elements belong to benefits and which to costs?
Statistics are an essential element to be incorporated into the ethical evaluation, to guarantee that the correct *numbers of animals* are used. Using too few animals to prove a result is significantly different, ethically unacceptable (unless it is a pilot study) as is using too many animals. Even though numbers are important, the *suffering per individual* should be given even more emphasis: where the same result can be obtained with an increased number of animals, but with less suffering per individual, this is the preferred option over using fewer animals with a higher degree of suffering for each individual.
By using standard protocols it becomes possible to minimise costs for the animals, and at the same time to improve the benefits of research. On the basis of legal requirements *e.g.* for toxicity studies, many experiments are performed in a standardised manner. However, those (many) studies in industry and universities related to discovery may not be so controlled, which could increase the costs for those animals.
Day-to-day care of the animals is the sole responsibility of the veterinarian/animal welfare officer (AWO) who has to make sure that anaesthesia, analgesia, surgery, euthanasia etc. are performed strictly to the rules. Veterinarians, however, often have an advisory role in ethics committees (Sweden, Holland), which is valuable as they can provide many answers regarding the costs borne by the animals. They can also give advice before applications are submitted to the ethics committees, which will help to improve applications and aid communication between researcher and veterinarian. This will also make it easier for he/she to keep an eye on the project while it is being performed. Conversely the ethics committees can provide important back-up for the veterinarian in certain cases. It is essential that the ethics committees are regarded as bodies that collaborate with scientists, not control them (as that may increase non-compliance). The working methods should be made transparent, *e.g.* question lists used by the ethics committees must be published. An important role of ethics committees is also to educate scientists, as they are the ones designing the experiments, and the dialogue between ethics committees and scientists is essential to achieve this goal.

Long or short lists of benefits and costs?
Long checklists for benefits ensure more factors are considered, which helps in seeing the overall picture, and also makes the applicant aware of all possible benefits of a certain experiment. The disadvantage is the increased chance of different views between individual committee members and a lengthy debate. Short checklists have the advantage that decision making becomes easier, and helps to focus on the main points but there is a risk that no comprehensive overview is reached, increasing the chances for incorrect conclusions.
Long checklists for costs are advisable, because then all possibilities of welfare compromises will be considered. It is important that such lists are made available to the applicants, so that they will systematically consider these points and address the use of the 3R's during the planning stage. It will also improve transparency and the quality of experiments and can provide a basis for constructive dialogue between the scientists and the ethical committees. The disadvantage of long lists is poor compliance, as they will make the process more complicated and more theoretical for the researchers. However, as the costs are defineable, long checklists of costs are considered more a necessity than the use of long lists of benefits, which will be (partly) hypothetical.
Some practical guidance was provided. It was concluded that long lists of costs are appropriate where costs and benefits are both high. Where the benefits are low and costs are high, the result of the ethical evaluation is rejection and so using a long checklist for costs is then pointless. When the benefit is high and the cost low, experiments are ethically acceptable, and then a short checklist on the costs will suffice to guarantee that unnecessary suffering is avoided.

Relative weight of cost and benefit elements?

When weighing the costs versus benefits, a relative value is given to these various elements. Weighing/scoring systems that address this topic have already been developed by Porter (1992), in which all elements receive the same weight and Stafleu et al (1999), where the various elements are given different weights. As both systems are based on a mathematical calculation, they were not considered by the participants to be appropriate for reaching an ethical decision because they give a false impression of accuracy and also imply, wrongly, that the values are additive. The two-dimensional model by Bateson *(1986)* is a relatively simple and clear decision model, and a modified version was considered to be the preferred evaluation method. On the X-axis, the costs are graded as mild, medium, and severe, and the Y-axis gives the benefits to science and society divided into the categories low, moderate and high (Figure 1). Where the costs to the animals are severe and the expected benefits small, the ethical evaluation of the experiment will lead to rejection. Severe costs but only medium-score benefits have a high chance of rejection; similarly for medium costs and small benefits. Costs expected to be severe but benefits high, should lead to a discussion on the possibilities of reducing the costs; and similarly for medium costs and moderate benefits.

The difficulties in the weighing process are that costs and benefits are scored subjectively. The benefits are more influenced by subjective evaluation than the costs, which can be based on more objective criteria. The subjective evaluation of the benefits will also differ from study to study, even though the goal remains the same *e.g.* human safety. The safety of a vaccine versus that of a new colouring substance are weighed differently, even though both examples illustrate animal experiments that are being carried out to prevent harm to humans.

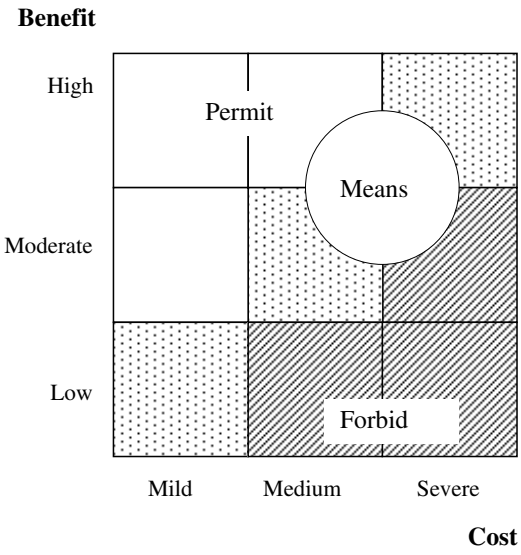

Figure 1. A simple model for cost-benefit analysis modified from the model of Bateson (1986). The means (cost modifiers) section has been added to the original model.

Means as cost modifiers

The chances of experiments being ethically acceptable can be improved, when the costs can be reduced. For that reason, the term “means” or “cost modifiers” was added as an important element of the ethical evaluation (Figure 1).

In practice, the acceptability of the experiment is assessed first (cost versus benefit analysis), before the means are considered. Especially, when the costs exceed the benefits, there is a need to try to lower the costs by using some means, but even where the benefits are higher than the costs, it is an ethical responsibility to make sure the costs are minimised.

Benefit

When evaluating the benefit, there is a breakdown into two major elements:

1. Aim of the benefit of the single experiment/ project
2. Benefit of the total process

The aim can be an immediate benefit, *i.e.* the result

of the study being performed, but it can also be a hypothetical benefit, as the outcome of the study is often uncertain, which is inherent in the conduct of science. Also a surprise benefit can occur, *i.e.* a benefit not expected from the current experiment. It is obvious that surprise benefits cannot be evaluated beforehand, but a chance of obtaining such a benefit may become a part of the evaluation of the benefit score.

Questions need to be asked about the aim of the benefits, in order to come to a score:

1. How well is the aim defined?
2. What is the probability of reaching this aim?
3. What is the quality of the research and the research group?

Assessing the benefit of the total process requires a broad perspective including enquiries about possible cost modifiers: *e.g.* have alternative approaches been considered, is the staff properly educated, trained and experienced, does the experimental design confer a high probability of success, are the facilities of a high standard, is welfare being safeguarded, *etc*; and the evaluation should include benefit at various levels at the individual experiment, research project, or research programme levels – at the individual experiment, research project, or research programme levels.

As already agreed under **4**, both applied and basic research can and should be equally rated. A systematic review of literature databases on past projects could be helpful in providing support for this thesis.

How to apply the cost-benefit principle?

Instead of a basic cost-benefit analysis, it was felt necessary to extend this to a cost-benefit-means analysis. Costs refer to the costs to the animals in the experiment, and benefits for to the benefits for science and society. Means are defined as "cost modifiers" or "cost minimisers". Figure 2 elaborates. Examples of cost modifiers can be the use of

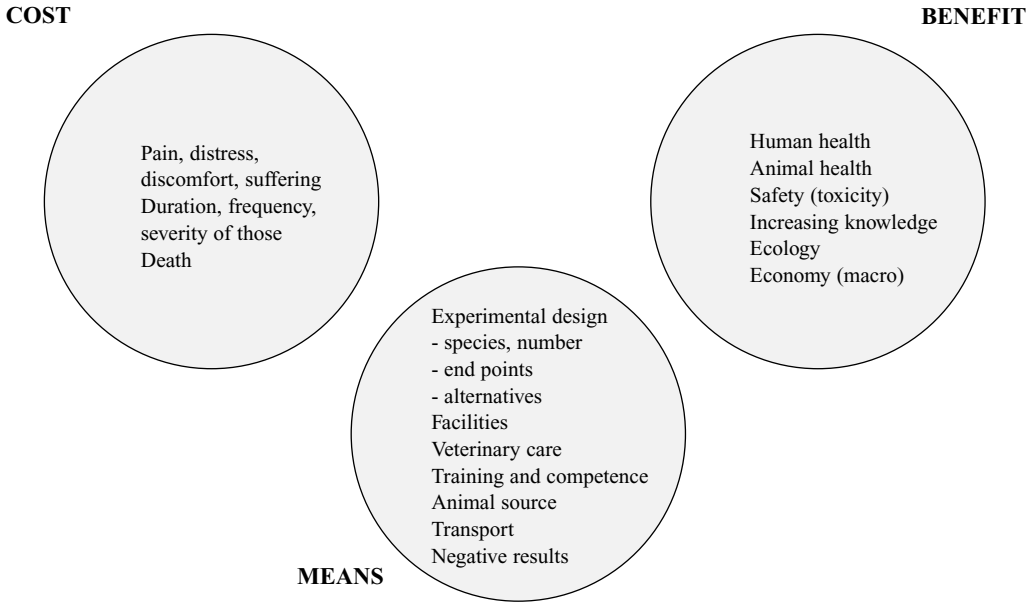

Figure 2. Elements of cost, benefit and means

humane endpoints and veterinary treatments. Even though legislation describes the needs for facilities, training, veterinary care, *etc*., these are only minimum requirements. Animal welfare must be safeguarded, and as yet legislation provides no precise guidelines *e.g.* for humane endpoints.

In Figure 1 the means are incorporated into the cost-benefit analysis scheme of Bateson. It is imperative that means are evaluated where costs are medium-severe, and benefits moderate-high. By reducing the costs, the ethics decision may move to the "Permit" zone. Where costs are higher than benefits, there is no chance for approval and then it is of no use to evaluate the means, unless there is a possibility of drastic cost reduction.

Is it possible to reach consensus on the outcome after ethical evaluation?

The possible outcome of an ethical evaluation is to accept, reject, or accept conditionally, provided that specified modifications will be undertaken. The advice of an ethics committee can be advisory or obligatory, which depends on legislative and managerial regulations. In all circumstances, it is advisable to offer the possibility for appeal, as it can be that the decision has been based on incomplete information or incorrect interpretation of the information given.

Cost-Means-Benefit Evaluation in practice

To test the two-dimensional evaluation model *(Bateson, 1986)* in practice, two applications submitted to ethics committees from a Nordic country were evaluated. After a general discussion, each participant made the ethical evaluation anonymously.

Case study 1

The aim, design and benefits of the study: This project looked for new gene therapy to a hereditary human disease caused by a gene defect resulting in a kidney disorder (Alperts disease). About 4 % of the human patients needing dialysis suffer from this disease which is painful for the patients and costly for society. There is an animal model for the disease: a colony of mongrel dogs having this very gene defect has been bred at the University of Texas. In dogs, the defect is inherited only by males and if left untreated, the dog will die at about the age of one year. Clinical signs of kidney dysfunction are observed in the late stages of the disease. *In vitro* models are not suitable for this kind of research.

The research group behind the application is experienced and has previously succeeded in using gene transplantation to reverse the effects of the defective gene. However, in spite of that there have been side effects leading to kidney dysfunction. The purpose of the present project is to study the reasons for the side effects, try to find ways to overcome them, and ultimately develop a gene transfer technique for human patients.

Costs to the animals: A total number of 30 dogs will be transported at the age of 3 months by air from Texas. After an acclimatisation period of three months, the gene transfer will be performed. One month later, some of the dogs will be euthanized. If the protocol can be carried out successfully without side effects, the rest of the dogs will be maintained up to old age.

The dogs will be housed in groups in indoor pens having free access to an outdoor pen. After a quarantine period they are taken for a walk regularly. During the first days after the operation, the dogs are kept singly in pens where they have olfactory, visual and auditory contacts to each other.

For the gene transfer, the dogs will be anesthetised with Domitor® and pentothal prior to induction of inhalation anaesthesia. Anaesthesia will be maintained with oxygen/nitrous oxide/isoflurane mixture and an intravenous injection of pethidine given for analgesia. The operation will take three hours and the dogs will be observed continuously until awake. Pethidine analgesia will be provided by intramuscular injections every two hours during the first postoperative day and thereafter as necessary. Cortisone and Sendoxan® will be given to diminish the immune response.

After the operation, the dogs will be observed for signs of reduced well-being on a daily basis. From previous experience, it is known that the dogs can be expected to be eating, drinking and playing at about twelve hours after the operation. Possible complications are bleeding – which has never been observed so far – and infections with skin necrosis. The possibility of collapse of kidney function is low. In the previous studies, most of the complications have been caused by infections. Humane endpoints are defined and if major complications are observed, the dogs will be euthanized. Every third week, a kidney biopsy is performed under anaesthesia.

Questions and discussion: The following points were discussed before the evaluation:

1. What information was obtained in the previous study which resulted in serious side effects?
2. Why do the researchers have expectations for better chances to succeed in this new experiment? Are they planning to repeat the experiment in the same way as previously or are there any improvements in the experimental design?
3. To assess the benefits, more information on realistic possibilities to treat human or animal patients with the gene transfer technique in the future is needed.
4. The costs to the animals: could the transportation from Texas be postponed to a later age to be less stressful for the dogs? Is the nature of the complications always such that euthanasia is the only alternative, is it not possible to treat the symptoms?
5. Would we pay as much attention to the animal welfare aspects if the animals used were rats or pigs instead of dogs?

The results of the evaluation: Each participant marked the result of the individual cost-benefit analysis on the Bateson model and indicated if the experiment was ethically acceptable or not. The results are shown in the Figure 3. The results suggest that cost modifiers would be useful to increase the ethical acceptability of the research proposal.

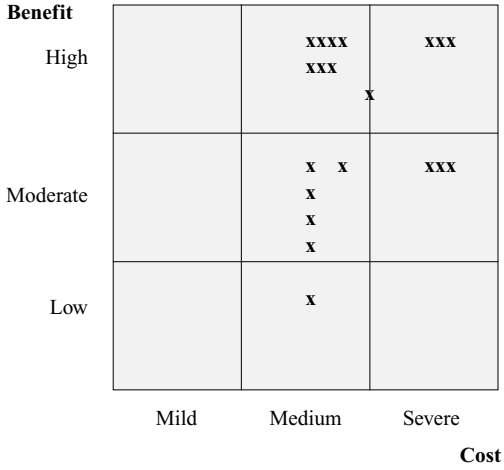

Figure 3. The results of the evaluation of case study 1. The x-marks indicate the individual ethical evaluation scores by each of the workshop participants.

Case study 2

The aim, design and benefits of the study: Diamond-Blackfan anaemia is a serious genetic disease in young children. In addition to anaemia, other symptoms such as skeletal disorders, retarded growth and heart dysfunctions are common. The disease is relatively rare, about one child out of 200 000 born suffers from this disease. Without therapy, the patients will die within two to ten years. Some forms of therapy are available, but risk of serious side effects is high. The disease is associated with a defect in a gene participating in the production of a ribosomal protein. A knock-out mouse model for the disease is available.

The aim of the study is to investigate the ability of the mice to produce new blood cells in response to an experimentally induced anaemia. The study will provide information on the role of the defective gene product in the formation of red blood cells and the gene's role in developing anaemia. If the study is successful, the knock-out mice could later be used as a model for gene therapy for human patients. Studies on gene therapy in cell cultures from human patients have been promising.

Costs to the animals: A total of 50 knock-out mice will be used in the experiment. The experimental as well as control mice will be given an intravenous injection of phenylhydrazine dissolved in saline to induce anaemia. After the injection the mice will be observed for at least an hour and after that every two hours, according to a predetermined schedule. The signs of anaemia will be observed. If suffering or discomfort is observed the animals will be killed immediately with carbon dioxide. A capillary blood sample (20 µl) will be taken before and 12, 24, 48, 72 and 92 hours after the injection and before euthanasia at seven days after the injection. The samples will be taken from the tail vein without anaesthesia. The mice will be housed in groups until the induction of anaemia and thereafter singly. The cages are provided with aspen wood shavings, wooden gnawing blocks and unbleached paper as nesting material.

Questions and discussion: The evaluation of the benefits of the study was considered problematic. The disease is lethal and causes much suffering to the patients. Thus, a therapy for this disease should in principle be highly beneficial. However, realistic possibilities to treat the patients with gene therapy appeared unclear. Would it not be ethically more correct to prevent the birth of these human beings through screening of foetuses for this disease? The expected benefit would be higher if a more general aim of increasing knowledge would be the case. If one wished to assess the costs, some more information would have been useful; especially the reason for housing the mice singly after the phenylhydrazine injection was not made clear.

The results of the ethical evaluation: Altogether 23 participants evaluated the experimental plan, the individual scores are presented in Figure 4.

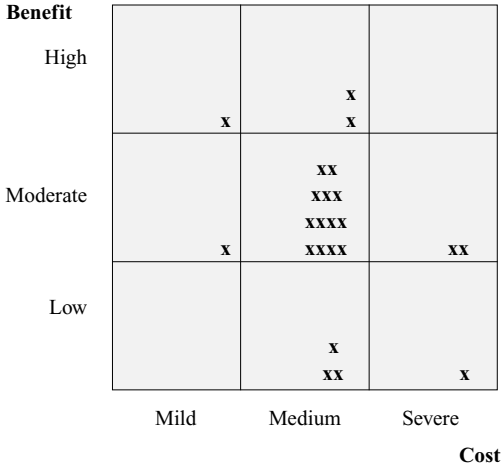

Figure 4. The results of the evaluation of case study 2. The x-marks indicate the individual evaluation scores by the workshop participants.

Summary of the two evaluations:

The results of the ethical evaluation of both case studies clearly demonstrate the large interindividual variation in the decision of the outcome of an ethical review. Both cases involved studies of severe human diseases, which in principle would lead to the expectation that the benefit would "automatically" be high. Indeed, the majority of participants did score the benefit of both cases as being moderate-high. Also the majority thought the two experiments were ethically acceptable, indicating that the benefits were assessed as being higher than the costs. However, fewer acceptance votes were given in the second case as compared to the first case, and the role of cost modifiers became more apparent in the decision making process in the second case. This was a remarkable result, as the costs were rated at about the same level in both cases and even more remarkable in the light of the fact that dogs were used in case study one: the use of dogs usually leads to more ethical concerns than (genetically modified) mice. An initial high ranking of the benefit can become modified by the probability of success. The ranking of costs can be modified by refinements in the experimental design, also influencing the ultimate ethical balancing process. The various elements in the ethical evaluation process are weighed differently by individuals, emphasizing the need for more discussion on harmonisation in the ethical review process.

Conclusions

In the currently preferred ethical evaluation systems, costs are weighed against benefits. Experiments can only be considered as ethically justifiable if the benefits are rated higher than the costs. Costs refer to the costs paid by the animals, and the benefits refer to the benefits accruing to science or society. Cost modifiers can be used to reduce the costs, thereby increasing the chances of ethical acceptability. Mathematical scoring systems used to reach an ethical decision are not considered appropriate, as they provide a false impression of accuracy and the idea that scoring is additive. Instead, a two-dimensional model is advised, where three grading categories for costs and benefits are defined. The cost modifiers must be critically evaluated in detail where the costs are higher than the benefits in case there is a chance of ethical approval of a certain experiment. It is important that checklists for the evaluation of benefits, costs and cost modifiers are rational and logical so as to avoid too much bureaucracy, as this may increase the risk of non-compliance. It is important that there is a good dialogue between the researcher and the ethical committees; thus educational aspects are considered a valuable part of the work. Increasing the ethical consciousness of everyone involved is a major step forward. Further debate is required to decide on the level of detail needed in the application forms to the ethics committees. The level of detail needed may depend on the situation.

A large inter-individual variation exist in ethical judgements, showing that more education and training is needed. In order to achieve more harmonisation, it is also important to strive for similar guidelines. In Europe several initiatives have been taken already in order to move towards a more harmonised ethical review process. The EU has financed a research task at Utrecht University, for improving the ethical evaluation process. A FELASA working group (www.felasa.org) has made an inventory of the systems that are used throughout European countries, and will produce guidelines on a harmonised ethical evaluation in the near future.

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Appendix A

Application form produced by the ethics committee Utrecht University

Application must be written for each individual experiment

A. Project information

1. Administrative information (responsible researcher, title, etc.)
2. Earlier submissions
3. Funding (funding means "scientific approval")
4. Background, aim
5. Scientific and social interests
6. Hypothesis
7. Scientific quality reviewed by other institutions

B. Animal information

1. Animals asked for and used in the year before
2. Species, strains, number, source, use of surplus animals?
3. Housing: where, individual/group, bedding, enrichment
4. Transport to other rooms: where and how long
5. After experiment: euthanasia, re-used, other purpose
6. Justification of the numbers
7. Justification of the species/strains
8. Efforts made to restrict numbers
9. Are GMO's used – check with other licenses

C. Description of different parts of the experiments

1. Species and number
2. Description of experimental procedure
3. Pharmaca used

A score is given for the duration of the procedure (score 1,2,3), the frequency (score 1,2,3) and the suffering (score 1,2,3). Also suffering is scored on a scale from 1-5. In case the score is 5 (very severe suffering), the study is transferred to the central ethics committee.

Additional questions to be asked in case the suffering is (very) severe (score 4-5):

- Describe clinical effects
- Is anaesthesia used
- Are analgesics used
- Are there other methods of refinement thinkable?
- Is there a humane endpoint?
- Will animals be re-used?
- Are GMO's used – is there suffering from the fact that they are GMO?

Appendix B

Swedish application form for ethics committees

A. Personal information: researcher, address, etc.
B. Use of GMO's –
1. production of special strain
2. use of special strain
3. permission number
C. Classification of degree of suffering light – moderate – considerable
D. Title of the project
E. Purpose of the experiment and account for previous results.
F. Discussion on other methods to achieve the same goal, with or without the use of animals, must be provided.
G. Demands for documentation in case (inter)national regulations require that these experiments are carried out, this documentation must be provided for.
H. Motivate choice of species, breed, strain and characterisation of the animals.
I. Time plan – a detailed description of the experiment, emphasizing procedures that affect the animals, the duration that animals are subjected to these procedures, etc. Starting and finishing date must be provided as well.
J. Care and housing
K. Description of the costs of the animals – provide argumentation for the classification of the degree of suffering, are humane endpoints used?
L. Anaesthesia and euthanasia. Specify use of anaesthetics, analgesics, sedatives and method of euthanasia.

This application is also signed by the responsible supervisor (veterinarian), acknowledging that he/she has been informed about the experimental plan.
The experimental plan is also sent to the responsible animal technician, before it is sent to the ethics committee.

Appendix C

List of participants

Denmark
Michael K. Bauer
Merel Ritskes-Hoitinga
Dorte Bratbo Sørensen

Estonia
Aavo Lang

Finland
Kristiina Haasio
Paula Hirsjärvi
Esa Hohtola
Ulla-Marjut Jaakkola
Eila Kaliste
Tarja Kohila
Hanna Leskinen
Pekka Männistö
Timo Nevalainen
Matti Poutanen
Liisa Pyhälä
Risto Rydman
Hannu Saloniemi
Hannu Sariola
Matti Sarvas
Teija Seppä
Esa Soppi
Jouko Tuomisto
Outi Vainio
Hanna-Marja Voipio

Iceland
Sveinbjörn Gizurarson

Latvia
Viktor Veliks

Lithuania
Osvaldas Rukšénas

Norway
Roald Bøe
Robert Murison
Sophia Salicath

Sweden
Katarina Cvek-Hopkins
Kristina Dahlborn
Ann-Christine Eklöf
Lennart Lindberg
Mats Sjöquist

The Netherlands
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