Scandinavian Journal of Laboratory Animal Science

2023, Volume 49, Number 2
ISSN 2002-0112

Report

Project evaluation in animal research – Possibilities for harmonization in Nordic countries

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Summary

This paper is a report of discussion, between responsible persons involved in animal research project evaluation throughout the Nordic region, on the activities, issues and problems encountered with evaluating project applications for experimental work involving the use of animals. Harmonization of the actions of responsible authorities in the evaluation of animal experimental projects is encouraged by policy makers at the European level, and the possibilities to encourage this are discussed. While the processes of evaluation and the composition of the committees are broadly similar across the region there are also differences. Applications are often made with insufficient attention, with sometimes too much non-essential information (for example details on molecular biology) given which tends to mask the important question of 'what is actually proposed to be done to the animals?'. Better guidance and simplification of the application process, in particular simplification of information required in the application document, may improve this. Lack of training was identified as a common problem, although training sources are available which could be used. The inclusion of persons with experimental design and statistical expertise is recommended. It is concluded that it would be to the benefit of each committee if there were communication between the committees in the Nordic states, to share best practice and flag common errors and problems.

Introduction

This paper summarizes the discussions at a meeting between responsible persons participating in project evaluation from the Nordic region delivering decisions on the approval of experiments involving the use of animals. This took place in a special session at the Scandinavian Society for Laboratory Animal Science (Scand-LAS) meeting in 2021 in Tallinn. Previous informal discussion showed that there is a variable approach to the management, membership, evaluations and decision-making process in response to applications for animal-included projects throughout the region. Committees may be under the direct responsibility of national ministries (agriculture and other), competent authorities or regional authorities, and decisions can be made at national or regional level. Consequently the acceptance or rejection of research projects involving animals can be inconsistent, and there is not a level playing field for scientists proposing these projects; there is a risk that projects rejected in one country may be accepted in another. While we recognize that differences in the structures of the evaluation committees do not necessarily result in differences in decisions, it has been reported that evaluation outcomes of proposed animal-involved projects from different cultures (globally) varied significantly as did the local ethics review requirements (Olsson et al. 2022). In line with the stated aim of the European Commission for the harmonization of approaches, particularly harmonization of the evaluation principles, this meeting was arranged. While this harmonization of approach could be very difficult to implement throughout the European Union, it could be facilitated by being addressed initially in the Nordic region, as the cultural backgrounds of the public and researchers are similar, the ties between countries are strong and the priorities for animal welfare are similar. In addition, there is an overarching organisation, Scand-LAS, that has members from each of the Nordic countries and is keen to facilitate such harmonization. Although the countries of the Nordic region are not all Member States of the European Union, this does not negate the drive for harmonization throughout the region, which would ensure sharing of best practice and avoidance of error. The Nordic countries represented at this meeting were: Denmark, Estonia, Finland, Norway, and Sweden, and of these the only non-EU member state, Norway, has also fully implemented Directive 2010/63/EU (European Union 2010).

The need for harmonization was one of the main reasons for replacing the previous directive (Directive 86/609/EEC (1986)) relating to the protection of animals used for scientific purposes. The preamble (point 1) of Directive 2010/63/EU (European Union 2010) states: "Since the adoption of that Directive [Directive 86/609/EEC], further disparities between Member States have emerged. Certain Member States have adopted national implementing measures that ensure a high level of protection of animals used for scientific purposes, while others only apply the minimum requirements laid down in Directive 86/609/EEC. These disparities are liable to constitute barriers to trade in products and substances the development of which involves experiments on animals. Accordingly, this Directive [Directive 2010/63/EU] should provide for more detailed rules in order to reduce such disparities by approximating the rules applicable in that area and to ensure a proper functioning of the internal market."

Also, in the preamble to Directive 2010/63/EU (European Union 2010), it is clearly stated (in point 35) that harmonization is the main objective. However, it is important to point out that within the EU legislative system, Directives aim at harmonization of objectives unlike Regulations that are directly applicable and aim at harmonization of operational procedures to achieve these objectives. Therefore, the aim of the Directive is not to harmonize the process of project evaluation but its compulsory elements and objectives. It is left to each Member State to devise their own laws and determine the most appropriate processes within their environment to attain the objectives set out in the Directive. The differences in evaluation processes have been discussed in detail by Olsson et al. (2016). The various ways in which the Directive has been implemented by Member States could provide opportunities for further harmonization by learning from each other, for example by exploring the established processes in the neighbouring Nordic countries.

EU Directive 2010/63/EU (European Union 2010) highlights the importance of the Three Rs, that animals should be used only when this is properly justified, and only when the expected benefits outweigh harm to the animals. Project applications must include information such as the justification for the use of animal models, how the project complies with the Three Rs e.g., consideration of alternative models, details of the experimental design and the origin and training needs of the animals proposed to be used.

As one of the first tasks after the adoption of the Directive, the European Commission together with Member State experts and those assigned by key stakeholder organisations developed a **guidance**

document on project evaluation to facilitate establishing an effective, efficient, and consistent project evaluation process across the Union (European Commission, Directorate-General for Environment 2019a). A similar approach was taken to develop an **EU Education and Training Framework** to facilitate meeting the requirements of the Directive for competence of all those involved in use and care of animals (European Commission, Directorate-General for Environment 2019b). Both guidance documents have been endorsed by the Member State National Contact Points responsible for the implementation of the Directive. The Education and Training Framework provides a modular approach to training. It contains Learning Outcomes for all core and function-specific modules for the key areas under the Directive, with a specific focus on the implementation of the Directive and the Three Rs. It also contains a section on the profile and training requirements for Project Evaluators and a dedicated training module for Project Evaluators.

Despite the available guidance, common difficulties were identified at the European level that included concerns about the time taken for the completion of the application process and apparent difficulty in providing "correct and complete" information. There were inconsistencies within and among Member States, and committees reported difficulties finding suitably experienced evaluators. Training for evaluators was only apparent in six of the 28 Member States at the time of Directive Review.

The European Parliament has expressed its desire for further harmonization by providing funding for the development of tools for education and training to facilitate the application of the principle of Three Rs in line with the Directive. These funds have been used *inter alia* to transform some of the key modules in the EU Education and Training Framework into open access eModules. The first six eModules have been finalised, including the module for Project Evaluators. These are free tools that can be used by individuals, establishments, authorities, and training providers alike. The eModules and other free training resources can be found on the ETPLAS platform (ETPLAS n.d.). It is suggested that, to promote best practice in project evaluation, the organisations making the evaluation should be: sufficiently resourced, include systematic initial training for members, undertake regular and frequent review of evaluations, and review and improve the application process.

Details of project evaluation in Nordic countries

Details of project evaluation in five Nordic counties are outlined below, with key aspects of the evaluation process in these countries compared in Table 1.

Denmark

In Denmark there is no legal requirement to have ethical committees for animal science, but there have been animal welfare bodies in place since 2013. There is one committee nationally, The Danish Animal Experimentation Council, within the Department of Animal Welfare and Veterinary Medicine of the Ministry of Food, Agriculture and Fisheries, which evaluates each application for animal experiments in Denmark. The applications are assessed in the council meetings where it is decided whether the application is approved or needs elaboration. This committee includes ten experts from welfare NGOs and research institutes, and it is chaired by a judge. There is a required quorum of six, and members sit for a period of four years. Licences are awarded according to a majority decision. In practice all members are usually in agreement. Where licences are awarded, these are made publically available. There is no appeal in cases of refusal. The council also prepares inspection reports and best practice guidelines. The process of evaluation includes a pre-assessment stage, by The Animal Experiments Inspectorate. Applications can be sent back to the applicant for revision and improvement. The Inspectorate also inspects a third of all animal research institutions in Denmark per year. It collects statistics on animal experiments in Denmark, advises applicants, provides current information through newsletters, and organizes meetings on issues related to Directive 2010/63/EU (European Union 2010). There is close collaboration between the inspectorate and the Danish Three Rs Centre (https://en.3rcenter.dk/).

Estonia

In Estonia there is one committee nationally, which is responsible for project evaluation and authorization for the use of animals in research and it operates under the Ministry of Rural Affairs. The Ministry helps organize the necessary activities: holding meetings, taking minutes, putting together, and storing necessary documentation. The committee consists of seventeen persons who serve for five years. Currently there are nine members from research institu-

tions, six from government institutions and two are from NGOs. Members include experts in designing projects, breeding, keeping, and taking care of animals, anaesthesia, analgesia and pharmacology, ethics, the 3Rs, veterinary medicine and the welfare of animals. There is also a dedicated statistician, a lawyer, and laypeople.

For project evaluation an application form has been produced (Maaeluministeerium 2021). This covers information on the proposed project, including a detailed overview of procedures, addressing of the 3Rs, the effects of procedures on the animals, methods used for relieving potential pain and suffering, an overview of expected outcomes and justification for the need for the project among other things. If questions arise or deficiencies are found during evaluation, the applicant is asked to send in an amended application for further evaluation. Usually 1-2 amendments are made before authorization. Meetings take place once a month and the meeting calendar has been made public, so applicants know when to send in their applications for a specific month's meeting. An average of ~20 applications are evaluated every year.

Finland

The organisation in Finland for animal research project approval is the National Project Authorization Board. Members of the Board (16 + deputies) are experts in scientific research, the care of animals used for scientific purposes and procedures, veterinary science and practical animal protection or ethical questions. The Board has a chair (lawyer) and is divided into four sections, each of them including representatives from all expertise areas. The sections evaluate project applications and authorize them if the members are unanimous. Applicants are often asked to give more details of procedures. The decisions can be appealed. The applications are pre-evaluated by two officers from the Regional State Administrative Agency. The officers also give licences for amendments of minor increases in animal numbers, short extensions of the licence period and urgent amendments (25-35/year), make retrospective assessments of projects and collect statistics. Moreover, one officer from the Agency inspects and awards licences for user research establishments. The Board receives between 100 – 120 project applications and 40-60 amendment applications per year. The time from submission to decision is 4 – 6 weeks. For simple projects there is a simplified application form in order to reduce the workload on both applicants and assessors. The Board has produced descriptions of common techniques to guide scientists and to reduce the amount of text in the applications. The use of tables is recommended, e.g., welfare scoring and details of procedures. The fees for licences (correct at the time of the meeting in November 2021) are 1,830 Euros for normal projects, 1,100 for simplified projects, and 550 for amendments assessed by the Board and 190 by the Agency.

Norway

As a non-EU country Norway has fully implemented Directive 2010/63/EU (European Union 2010) via the European Economic Area agreement. The competent authority is the Norwegian Food Safety Authority (NFSA) and project evaluation is carried out at national level by inspectors at the National Assignments Department. The decisions can be appealed to the head office of NFSA. NFSA strongly recommends that applications are reviewed at local level prior to submission, and in most institutions this review is carried out by the person responsible for overseeing the welfare and care of the animals in the establishment (c.f. Article 24 a, in Directive 2010/63/EU) and/or by the Animal Welfare Committee. The project evaluation is handled by designated employees at NFSA, at present six in number, who have backgrounds as veterinarians and researchers and work together as a team. No interest groups are involved in the evaluation (e.g., no representatives from academia, welfare groups, industry, patient organization, nor the public). In addition to project evaluation, NFSA inspectors also perform retrospective assessments of projects, consider applications for user research establishments, carry out inspections of experiments and user establishments, provide information and advice to applicants and the public, collect statistics, and ensure transparency according to the Norwegian legislation on public access to information. The department has regular meetings with user establishments, the national committee for the protection of animals used for scientific purposes and Norecopa (Norway's 3R Centre), and it also has the role of the National Contact Point and the PARERE (Network for Preliminary Assessment of Regulatory Relevance) contact in Norway. In their project evaluations NFSA weighs harm and benefits. Included in their method of evaluation is consideration of the three Rs, severity of harm, methods to be used, experimental design and humane endpoints. During the evaluation process there is often close dialogue with the applicant, literature may be

checked, external experts may be consulted, previous projects, including statistical reports by the applicants may be considered, and whether the purpose and experimental methods fit with legal requirements. Applications are submitted *via* an electronic system which is also used for reporting. Applications can be submitted in Norwegian or English languages. The required level of detail in the application form is relatively high and the number of new applications each year is about 450. There is a handling fee and full project applications cost (correct at the time of the meeting in November 2021) about 670 Euros, pilot applications 420 Euros, amendments 170 Euros, and applications for user establishments 670 Euros. The ethical guidelines on the use of research animals provided by The Norwegian National Research Ethics Committees (NENT 2019) present principles that are set by the Regulation/Directive. At present, applications involving some procedures may not be approved as the proposed procedures are restricted. Examples include retro-orbital injections, back-pack GPS tagging of birds, tagging of small fish (compared to the tag size), Carlin tagging of juvenile fish and the use of live bait for the capture of wild-living fish. Also, multi modal analgesia in mammals must be used whenever possible and following the revision of the national regulation when Directive 2010/63/EU (European Union 2010) was implemented in Norway, it was required that a competent veterinarian must be present during the immobilization of wildlife. Of stricter national measures of relevance for project authorization that were in force prior to Directive 2010/63/EU (European Union 2010), and that were transposed into the revised Norwegian regulation, project approval for studies undertaken in field circumstances are only approved for two years, while studies undertaken in approved animal facilities can be approved for up to four years. Production of antibodies from ascites have not been approved since the 1980s, and there is an ongoing effort to promote the transition to non-animal antibodies. Also, the transition from tissue to mucus sampling for the genetic identification of fish is promoted. Due to research connected to the aquaculture industry, the statistics show a high number of fish used, fluctuating between years, due to some experiments with a high number of individual fish.

Sweden

In Sweden, the responsibility for evaluating animal research projects lies in six regional committees, each in university towns. These regional committees all use the same electronic system for ethical applications; the Swedish Board of Agriculture is responsible for this, and they also appoint the members of the committees. However, all committees take their own decisions according to the knowledge and experience of their members. Therefore, the questions from the committees and what they think is acceptable or not can differ between them. The committees do not work in exactly the same way, but there are regular conferences for the chairpersons to stimulate harmonization between the committees. There is one overarching central committee that considers appeals, and this committee's members include a chair (a lawyer), four scientific members and two NGO members. For projects involving experiments with animals, including wildlife, the facility must have been approved and evaluated. Each committee consists of 14 members, including a chair and vice-chair who are both lawyers. Six of the members are researchers or animal carers and six are laypeople (two from NGOs, others are appointed by political parties). Each member sits for a period of four years, and each member has a named substitute. Some committees operate a little differently, but in general, members and their substitutes take part in preparation meetings, and these preparatory groups communicate with, and submit questions for clarification to, the applicants prior to the plenary meeting. The significance of the outcomes of the proposed research is weighed against the expected animal suffering. Purposes must be defined, and animal use must be justified. There is also an informed consent form for animal owners. There must be a time plan for the experiment, and detail of the method must be included. Descriptions of humane endpoints are considered very important.

There is a fee scale for evaluations. Amendments are (correct at the time of the meeting in November 2021) costed at 600 Euros, pilot studies at 800 Euros and other applications at 1,500 Euros. The animal research unit's animal welfare body can manage amendments that do not involve suffering for the animals and assess the likelihood of the experiment achieving its stated aims. Researchers must be able to identify and assess behavioural and clinical signs of suffering. The plan must be discussed with the NCWO (Named Care and Welfare Officer), laboratory animal veterinarian and animal care staff. The process in Sweden is very transparent. During evaluation meetings of the committees the laboratory animal veterinarians, NCWOs and the person responsible for the official control can sit in and observe the process. Applications are public docu-

Table 1. Comparison of project evaluation systems in Nordic countries.

Country	No. committees	Responsible organisation	Membership of committee(s)	Pre-evaluation possible?	Appeal possible
Denmark	1	Department of Animal Welfare and Veterinary Medicine of the Ministry of Food, Agriculture and Fisheries	10, quorum of six, specialists from NGOs and research Institutes, chaired by a judge	Yes	No
Estonia	1	Ministry of Rural Affairs	17, from research Institutes (9) Govt. Depts. (6) and NGOs (2) Includes a statistician and a lawyer,	Yes	Applicant invited to amend if unsatisfactory
Finland	1	National Project Authorization Board	16 (+ deputies) Includes a lawyer as chair.	Yes	Yes
Norway	1	National Assignments Department of the Norwegian Food Safety Authority	6, Employees at NFSA, who have backgrounds as veterinarians and researchers	Yes	Yes
Sweden	6	Swedish Board of Agriculture	14, including a chair and vice-chair who are both lawyers. Six researchers or animal carers and six laypeople (two from NGOs, others appointed by political parties).	Yes	Yes

ments. Appeals heard by the central committee are the end point of the appeals process.

Issues identified

It was noted that in Sweden the committees are not allowed to make demands that are higher than the current legislative standards unless the animals have specific needs. Other comments from all states represented at the meeting were that applications frequently appeared to have been written in too much of a hurry, often without sufficient detail. Often lacking were detailed descriptions of what will be done to the animals (including clearly defined Humane End Points). Many applicants provided non-essential information. Clarity requires some thinking and thinking takes time. If clarity is missing, this suggests that insufficient time (and effort) has been put into writing the application. An example of an indication of hurried writing and thinking; "Will I be able to fit my application in to your Board meeting next week - I started writing it this morning and I will get it ready by the evening".

There is no systematic formal training in place for project evaluators (although some committees do provide this and others are working on implementing standard training, including the development of online training, and some have information days for committee members and in some cases the boards are taken to visit facilities, observe procedures and have them explained to them). This was identified as an issue by all. It was furthermore considered that during the process of evaluation the study design may not be sufficiently considered. The biggest problems identified included the complexity of project applications, particularly large projects with a range of treatments, and it was sometimes difficult to understand why animals were planned to be used and what exactly their experience would be. Description of how the three Rs had been taken into account was often insufficient in submitted applications. Chairing project evaluation meetings can be difficult, with the need to take into account the different levels of expertise of the members of the committees. It was considered important that experienced animal caretakers are represented in the evaluation committees. Evaluating meaningfully the harm-benefit analyses can be challenging due to the complexity of applications and difficulties in understanding the experimental method. There can be language problems if the applicant is foreign (this was agreed to be a problem by all). Communication with applicants can be challenging, as can be the applicants' selection and descriptions of the proposed statistical methods. One particular issue raised by Norway and Sweden was the tagging of wild animals for scientific purposes. This requires official approval while for manage-

ment purposes it does not as Directive 2010/63/EU (European Union 2010) only regulates animals used for scientific purposes (and not population management).

And finally, it was noted that there were similar problems with applications and their evaluation across the region.

Future steps

There is a current need for improved harmonization between the bodies evaluating and authorizing project applications for research involving the use of animals. Directive 2010/63/EU (European Union 2010) has established National Committees in all Member States to ensure a coherent approach to project evaluation at national level, especially where more than one body is involved in this task. Implementing a periodic review of project evaluations to identify elements of difficulty and inconsistencies in approach could significantly improve harmonization. Should this become a regular practice in Member States, the exchange of information at EU level between National Committees would allow further harmonization across the region. Sharing best practice and problems within the Nordic region would be beneficial not only throughout the region but could serve as a model for the rest of Europe. Open access training material is available covering implementation of the Three Rs within projects and initial training for project evaluators. To improve harmonization, their use should be considered systematically, including by Member State authorities. This could perhaps be offered under the umbrella of Scand-LAS, maybe initially through ETPLAS (Education and Training Platform for Laboratory Animal Science) modules, and maybe integrating with FELASA (the Federation of European Laboratory Animal Science Associations) training modules. Indeed, this could be a starting point for harmonization across the committees in the region. Scand-LAS could provide an overview of the various committees and could share information, requirements, coordination of evaluation processes, and the provision of guidance. Committee chairs, or named persons from each committee, could take responsibility for acting as a conduit for information, reporting difficulties, sharing best practice, which would be a point of contact for the representative from each of the other Nordic committees. If allowable under current national legislation, members of these bodies from each country could on occasion sit as *ex officio* members on other Nordic committees, without voting rights or having a consultative role, but this would give an opportunity to identify problems and share best practice. This could also engender a sense of community among practitioners and members.

Conclusion

While there is clear commonality between the governance, approaches, composition and working practice of the animal research evaluation committees in the Nordic region, there are also significant differences. Likewise, common issues and problems have been identified, particularly in the content of applications and training, and understanding of committee members. It would be of benefit to share good practice and problems and experience of the committees within the region. Scand-LAS could play a role to facilitate cooperation, training, and harmonization.

Conflict of interests

All authors declare no conflict of interests.

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