
Guidance Notes on Retrospective Review: A discussion
document prepared by the LASA Ethics and
Training Group

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1. Introduction

The function of 'retrospective review' of research involving animals has received attention in a number of different forums in recent years. In particular, it was an issue raised by the European Commission within the Technical Expert Working Groups set up to advise on the revision of Directive 86/609 (European Commission, 2004). In the UK, 'retrospective review' has been a requirement of the local ethical review processes (ERPs) which have been mandatory at all establishments breeding or using animals in scientific procedures since 1999 (Home Office, 2000). The precise requirement for this has not been prescribed, and as a consequence it has been interpreted in a number of different ways.

This report on the function of, and mechanism for, retrospective review has been prepared by the LASA Ethics and Training Group (LASA E&T). It arises from a workshop held in May 2003, attended by the authors of the report, which examined approaches taken by a number of different UK Designated Establishments to clarify the purpose of retrospective review and to provide guidance on how the usefulness and effectiveness of the process can be optimised. It specifically addresses UK ERPs, but the principles can be applied to any body established to review research involving the use of animals. The guidelines are also relevant to deliberations on ethical review made by funding bodies and other review panels.

The report is intended to be used as a working document and it is hoped to develop it further as more establishments gain experience in what does and does not work. Feedback on this document – its usefulness and content - would be very welcome to LASA at P.O. Box 3993, Tamworth, Staffordshire, B78 3QU www.lasa.co.uk

2. Requirements for retrospective review within the ERP

The ERP set up under the Animals (Scientific Procedures) Act 1986 (ASPA) must allow for:

“.. undertaking retrospective project reviews and continuing to apply the Three Rs¹ to all projects throughout their duration” (in Home Office, 2000)

When the Home Office published its review of the operation of the ERP, retrospective review was included as one of three key ERP functions as follows:

“Key function 3. Retrospective review of ongoing projects in order to promote the development and uptake of the Three Rs.” (Home Office, 2001)

The Home Office stated that the purpose of retrospective review is to:

¹ Reduction, refinement and replacement of animal experiments (Russell and Burch, 1959).

“.. look back on the animal welfare costs encountered and benefits realised. This permits assessment of the extent to which the original assumptions, including the severity limit of protocols, were correct when the request for authority was originally considered, and to consider if additional 3R strategies can be identified and incorporated. This information is of value to licensees and the ERP in planning future work and, as ERP records are available to the Inspectorate, it may also influence future Home Office assessments.”

Other than this, there is no definition of what retrospective review should involve, when and how it should be carried out, or how the outcomes should be utilised. As a consequence, there has been much discussion of whether current practices are ‘right’ and what was expected when the ERP was first introduced.

Local ERPs have now been mandatory for five years and in this time different establishments have interpreted the necessity for retrospective review in different ways. This has led to some interesting and useful initiatives, benefiting both animal welfare and science. One interpretation has been to equate retrospective review with cost-benefit assessment and perform a review of the actual versus predicted harms and benefits on completion of individual projects. This is generally termed ‘*end of term review*’. A more common approach has been to review a project at intervals during its life, for example at 1, 2, and 4 years in the course of a 5-year project. This has been described as ‘*interim review*’.

Both interim and end of term reviews focus on individual projects. However, some establishments have also used the process to evaluate other functions of the ERP. For example, the process may be used to examine individual procedures, or husbandry of individual species, often within one or more projects, or sometimes within the establishment as a whole. Although this is an important activity, and is an integral part of good management of bioscientific investigations involving animals within any establishment, the wording from both Home Office documents above clearly relates retrospective review to individual projects. This is also the meaning most appropriate for retrospective review by funding bodies.

However the term retrospective review is interpreted, and wherever it is applied, it is important that it is a worthwhile exercise that adds value to the overall process of ethical review. In this document we interpret retrospective review as interim and/or end of term review of individual projects, and indicate which is being discussed where appropriate.

3. Why do it ? The purpose and benefits of retrospective review

The overall focus should be to reduce the harms and increase the benefits of a project, aiming continually to improve both animal welfare and the quality of the science. However, any requirement for retrospective review needs to be set in the context of what is done *prospectively*, and of the other functions of the ethical review (or other review processes) concerned. Within the UK ERP these include:

- examining the harms and benefits of applications for work involving animals and how these balance;
- promoting the development and uptake of the Three Rs;
- considering standards of accommodation and care and humane killing;
- providing a forum for discussion of issues relating to animal use; advising on staff training; and reviewing managerial systems and protocols and procedures relating to animal use.

Taking this into account, the LASA Working Group endorsed the purposes of retrospective review briefly set out by the Home Office (see section 2 above) and sought to develop these into three objectives described below.

(i) To determine whether the actual costs and benefits are in line with those anticipated, and ensure information and experience gained during the course of the review period is applied to future assessments.

A defined interim review point sets a time during the life of a project for Project Licence holders, together with the project team, to reassess their approach and focus clearly on what they are doing. In particular, it is important to:

- re-examine the validity of the study design and outcomes, assessing whether the existing animal model is still the most appropriate for answering the scientific question, whether the results are as expected and, if not, whether any variations can be explained;
- establish whether the science is on-track and, if not, to explore why; or to determine whether there have been other scientific developments that need to be taken into account that might augment or diminish the value of the project;
- compare the actual versus the anticipated adverse effects on the animals and identify and address any problems;
- review the original harm-benefit judgement and see whether anything has changed which might alter the balance.

Review also affords an opportunity to give recognition to the Project licence holder and project team by announcing the ongoing achievements of the project, which may influence future work directions and/or funding decisions

(ii) To identify, build on, enhance and promulgate good practice and improvements in the Three Rs during the course of a project

A review provides an ideal time and an effective mechanism to reflect on and assess scientific and technical developments both in the field and in the specific project, and to describe and share advances in any of the Three Rs (bearing in mind that not all procedures and projects will necessarily present opportunities for this each year). This process should benchmark scientific progress as well as raising awareness of the Three Rs. It should also encourage adoption of improvements identified into the establishment's codes of good practice.

Issues that could be reviewed include:

- whether there are any welfare problems with the particular animal model and, if so, whether alternative animal models are available that would experience less suffering;
- any relevant new work not involving regulated procedures on animals;
- the experimental design, including the opportunity for refinement of procedures, adjustment of numbers being used or amelioration of adverse effects, e.g. changes to anaesthetic and analgesic regimes, surgical approaches, dosing routes or vehicles, humane endpoints;
- supply and transport;
- housing and care;
- records of clinical signs;

- the well being of individual animals on long term studies;
- the eventual fate of the animals – euthanasia, re-use, rehoming;
- any wastage of animals and the reasons for this;
- standard operating procedures (SOPs).

(iii) To help with project licence management

A review point provides a time-out reminder for all relevant staff to raise any concerns they may have regarding the project and work out how to resolve them. Examples might be: unexpected adverse effects; behavioural problems or mortality; poor surgical success rates; or equipment shortcomings or failures. It provides a check that the project licence holder is not too remote from the ongoing work and that the whole team is 'on the ball', so providing a reassurance against the likelihood of inadvertent mistakes or infringements.

It can also help to:

- check whether any amendments are likely to be needed so they can be dealt with in a timely fashion;
- discuss and identify training needs;
- empower the Named Animal Care and Welfare Officer and Named Veterinary Surgeon by enabling them to identify and raise issues of concern;
- disseminate information, particularly for licence holders;
- verify that the team is working well and that all members feel supported, and enhance communication between animal care staff, Personal licensees, the Project licence Holder and the ERP.

4. Achieving effective retrospective review

Three key factors contribute to an effective system for retrospective review: (i) staff need to know and understand the aims and mechanism of the review and appreciate how it can benefit them, the animals and their work; (ii) the process needs to be clearly defined, workable and manageable; (iii) the review must be adequately resourced.

4.1 Developing staff understanding of the aims and mechanisms of review

Many scientists do not yet engage with the process of ethical review and may see a requirement for retrospective review as another obstacle to their science, particularly if they believe that the harms and benefits are to be reassessed. The harm/benefit assessment is in itself difficult, whether done prospectively or retrospectively; if a project is not going well, hard and unpopular decisions may need to be made about whether it should be terminated or its direction substantially altered. A formal retrospective review mechanism may be perceived as taking responsibility from the Project licence holder, damaging ownership of the project and hence the level of innovative thought about what is being done. This can understandably create antagonism towards other staff and the ERP as a whole.

To avoid these problems and ensure that retrospective review is a constructive and useful process, stakeholders need to know exactly what retrospective review entails, what it is for (its nature and value) and what is required of them. They also need to know how the information they provide will be used. As a first step, the ERP needs to set all this out clearly, for example, using the bullet points in section 3(i) to 3(iii) above, in an easily accessible, reader-friendly format.

As a general principle it is important to involve people rather than simply dictating actions, and to be inclusive of all relevant staff. The support of project and personal licensees is particularly important, but they may feel remote from the ERP in general, since they are often less closely involved with this than animal care and veterinary staff. Face to face discussion, rather than extensive use of written documentation, is usually the easiest, most time efficient and best approach. Providing feedback to contributors on the outcome of the process is also very important, giving credit where it is due.

Training, together with wide and open communication about the functions of the ERP, including retrospective review, is particularly important in developing staff understanding of the process, and this needs to be built into the current accredited Home Office training courses for personnel working under the ASPA. In-house training (either modular, induction or continuous professional development) enables the *local* process to be explained and so is also important.

There is also benefit in ERPs organising awareness-raising events or a workshop to consider how retrospective reviews might best be performed within individual establishments. Staff can then feel that they have contributed to the development of the process rather than having it inflicted upon them.

4.2 Establishing a workable process

It is extremely important to keep the process manageable and not allow it to become just a non-productive form filling exercise. There are four key issues to consider:

- the timing of review,
- prioritisation of projects for review,
- documentation, and
- who carries it out.

4.2.1 Timing

The original Home Office process statement provides ERPs with considerable flexibility in deciding when and how projects should be reviewed. This is essential, since it is unlikely that all licenced work will require, or fit, into the same schedule. The timing of interim reviews may vary with each plan of work, and the nature, novelty and severity of the procedures involved. For example, a simple pharmacokinetic study to measure drug concentration in blood, which requires a single oral dose followed by collection of serial blood samples of small volume from superficial blood vessels, is unlikely to require frequent review. More complex projects, for example where a) a new animal model is developed, or b) a drug metabolism service is provided to a number of drug discovery projects, using a variety of different dosing routes and different types of compound, may more appropriately be reviewed on a regular (annual) basis.

It is helpful for the ERP to identify provisional dates for initial project review and to advise the certificate holder of these at the time when the application is submitted to him/her for signing. The review should be frequent enough to take account of the rapidly accumulating body of knowledge on issues such as husbandry and care, animal behaviour and refinements in procedures. Currently, the most frequent interval appears to be annual.

Some establishments use the submission of a licence amendment as the trigger to carry out a review of a project. The benefits of such a routine have to be balanced against the irregularity (or in some cases the frequency and regularity) with which amendments may be required, and (if frequent) the additional administrative burden this imposes on the Project licence holder and those involved in the ERP.

4.2.2 Prioritisation

In circumstances where a large number of projects are running concurrently, it is helpful to prioritise their review according to any particular concerns. For example, priority might be given to projects involving:

- models and/or species that are new to the laboratory;
- a particular species (e.g. dogs, cats, primates or equidae);
- procedures of substantial severity;
- procedures where there is a concern arising from their nature and/or novelty;
- large numbers of animals.

4.2.3 Documentation

The key principle is to minimise the formality of the system by limiting the need for lengthy documentation. It is important to consider what is required as *input* into the retrospective review (i.e. what information is needed, when, who from and in what form) and what records will be maintained to record the *outcome*. It is important not to 'over-document' either aspect and to keep the overall aim of the review in sight.

In many cases, the best approach may be to invite the Project licence holder to present a review of the key issues to the ERP in person. Some establishments have developed structured proforma or templates to help the Project licence holder assemble the information required. There should be no need for lengthy texts - brief written summaries of key points may be all that is necessary to structure the discussion.

The ERP needs to hold records to guide future debate and decisions, but current practice is very variable with respect to what is recorded and to whom the results are communicated. It may be that if a project is proceeding according to plan and no changes are needed, then it is only necessary to record that the review has taken place.

Practical recommendations regarding any changes to the programme of work need to be communicated directly to the relevant personnel so that they can take appropriate action and there needs to be a mechanism for ensuring that this happens. It may also be that more general problems are identified which apply to a number of projects, or are likely to apply to future work, and consequently there may be a need to develop a 'standard' solution and communicate this to relevant staff. A database of projects would allow the solution to be more easily applied to them all straight away, rather than waiting for a formal review.

4.3 Resources

Retrospective review requires resources, but it is possible to design the process to minimise these. As an example, the review can be combined with other activities. Thus, where a project is funded by a grant awarding body, an annual report needs to be prepared and this could be used to inform the retrospective review process. This approach has the additional advantage of providing the trigger to ask for top-up funding for further application of the Three Rs, something that the major funding bodies (the Medical Research Council, BBSRC and Wellcome Trust) have now agreed to consider.

Retrospective review does not always have to take place in a full ERP setting. As a minimum, the process requires the Project and Personal licensees, Named Veterinary Surgeon and Named Animal Care and Welfare Officer to check the science is on track, scrutinise any animal welfare problems and assess the outcomes of the procedures. However, subsequent feedback to the full ERP is essential.

If concerns are raised at retrospective review and any resulting recommendations are not progressed because of lack of resources, then all staff are likely to see the process negatively. Involvement of senior management in the ERP itself is critical so that they understand the importance of the whole process, and the need to provide adequate resources for all aspects of its operation, including the implementation of recommendations flowing from it.

5. Conclusion

Retrospective review of projects by local ERPs is now a requirement under the UK ASPA, although currently, understanding of what is meant by retrospective review, and the approach taken at individual establishments, varies widely. Whatever and however retrospective review is done, it must provide something useful at the end – the focus must be on its outputs. The experience of those contributing to this report is that an effective system of retrospective review enhances the culture of care at their establishments and has promoted an environment where people (and projects) can share not only ideas and successes, but also failures. In addition, it has provided a forum where the Three Rs can be promoted, recognised and celebrated.

Some outcomes identified from recent retrospective reviews have included:

- the development of a planned programme of back-up studies so that animals from a cancelled study were not wasted;
- the study of receptor profiles in various species leading to the abandoning of irrelevant models;
- the implementation of better techniques leading to less stress or fewer animals;
- an increase in the amount of work within a project which was able to be undertaken *in vitro*;
- the awarding of an annual trophy and prizes for the best contribution to the Three Rs in the year – the winner had introduced a less severe animal model and the runners-up had both used improved experimental designs involving fewer animals (with improved quality of data).

The LASA Ethics and Training Group has produced this document by drawing on the approaches of a range of establishments as a contribution to improving understanding and interpretation of the nature and benefits of retrospective review. The document also provides

ideas and practical guidance on how to achieve an effective retrospective review process which will hopefully encourage more effective – and easier – retrospective review and lead both to wider development and implementation of the Three Rs and to better science.

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