Ethical Review of Animal Research

A training resource developed for members of ethics committees

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In conjunction with RSPCA International

Contents

Introduction

This document originated as a handbook to accompany an RSPCA training course conducted for members of ethics committees in Poland in 2006.

The content of the document has since been revised to provide a training resource relevant to a wider audience. Though based on experience with the UK system, this document is designed to be relevant to ethics committees more widely.

Being effective in your role

- **You need a good understanding of:**
  - the type of establishment and nature of the animal research
  - how your own ethics committee operates
  - factors to consider in harm/benefit judgements
  - what you should contribute
- **Confidence and good communication skills are very important!**

Value of lay members

- **Acting as animals advocate**
- **Helping ensure the integrity of the process**
- **Providing an independent, novel perspective**
- **Supplying a measure of public representation**

The establishment

To participate effectively in ethical review it is important to have an understanding about the establishment involved.

- Is it academic, industry, contract research?
- What research area (basic or applied), species, types of procedure? How is it funded?
- Who decides what research is done

Your local ethics committee

Understand how it operates

- what it covers including what the functions and objectives are
- membership
- practical organisation
- how decisions are implemented

Factors in harm/benefit

Focus on ethical and animal welfare issues:

- assess benefit, need and justification for animal use
- assess *all* harms and weigh against benefits
- use alternatives where possible
- use minimum numbers of animals
- cause least possible suffering
- provide appropriate housing, husbandry and care
- ensure the benefits are maximised and applied

Communication and confidence

- **Facing difficulties**
  - Expressing opinions can be difficult when surrounded by ‘experts’
  - Disagreeing with the majority can be difficult
- **Feeling confident**
  - Gather information
  - Do not worry about lack of expertise
  - Ask any question you feel is important
  - Get support from lay and other members

What are the important issues that you expect to arise within your own ethics committee?

Evaluating harms and benefits

- Needs to be examined case by case
- Requires knowledge and understanding of harms and benefits
- Involves 'value' judgements which depend on *relative values* placed on animals versus scientific, individual, societal interests. These depend on:
  - the time, place and culture
  - developing understanding of animals and their needs
  - changing sociological and philosophical perspectives

Benefits: points to consider

Make sure the objectives are clearly described

- Are objectives relevant, realistic, timely, measurable?
- What is the nature of the benefit (scientific, clinical, educational, economic, regulatory)?
- Could the application of the results have any disadvantages?

Benefits: points to consider

- Is the research scientifically valid?
- Will there be new scientific insights?
- How does it relate to other studies?
- Will results be shared and published?
- How will the benefits be applied?

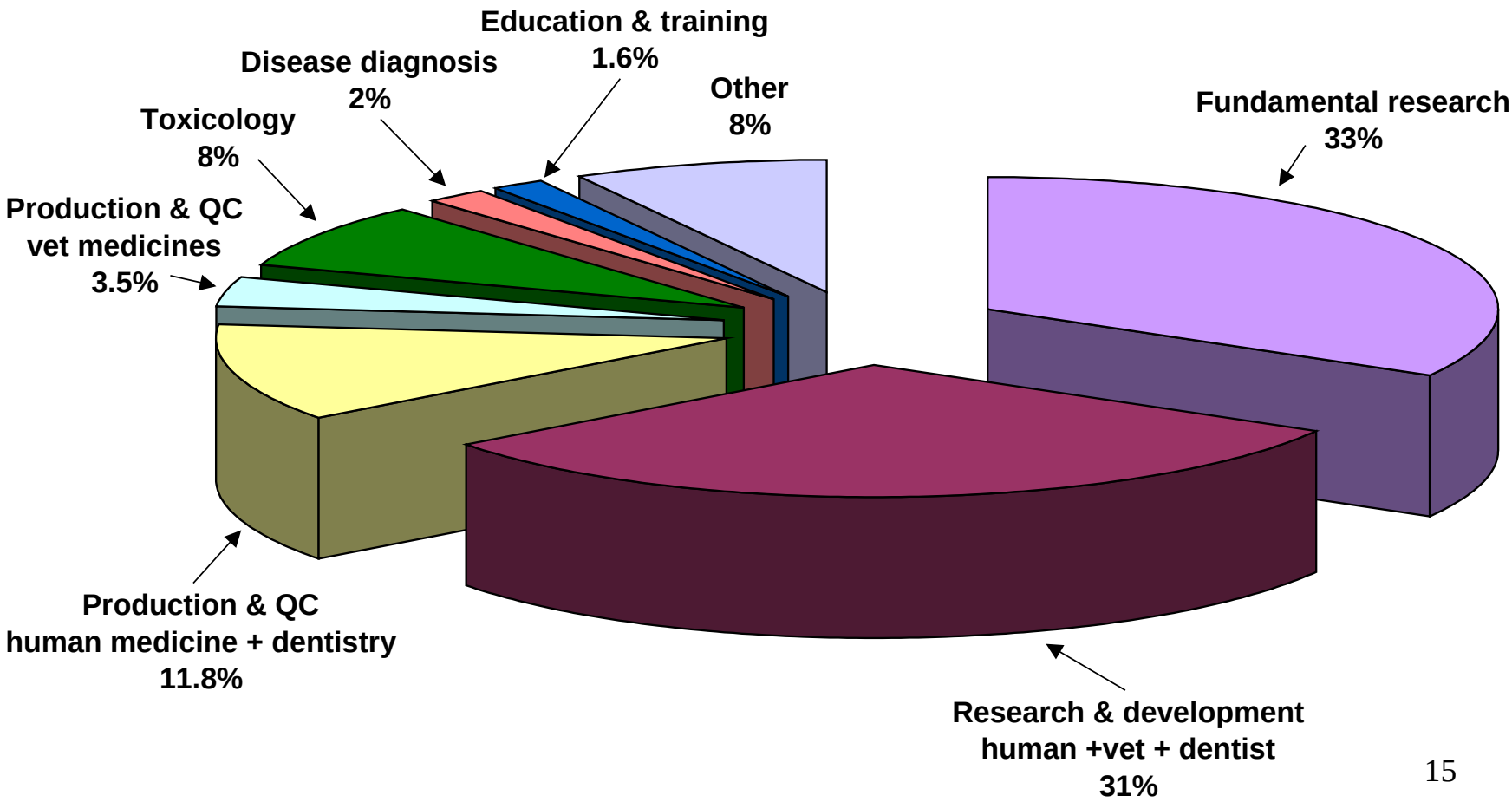
Nature of benefits

Reasons for using animals:

- developing and testing human and animal medicines and vaccines
- acquiring knowledge in science and medicine
- assessing environmental safety of agricultural and industrial chemicals
- safety testing of ingredients for household products, food additives, new foods, cosmetics

Categories of animal use

Animal use in the EU during 2005



Harms: points to consider

Harm = pain, suffering, distress (or death?)

In experimental protocols it is important to recognise and identify:

- Sources of harms
- Nature of the harms
- Levels of suffering
- How the harms can be reduced

Sources of harms

Consider full lifetime experience

- source
- transport
- housing and husbandry
- handling and restraint
- identification
- scientific procedures
- pain management
- euthanasia or rehoming

Harms from procedures

Make sure all of these are considered:

- The effect of the *technical* aspects
- *Expected* adverse effects
- *Unexpected* adverse effects

Nature and level of harms

Harms may be:

- Physiological
  - e.g. pain, nausea, fever, respiratory distress, skin irritation, organ malfunction, convulsions, paralysis
- Psychological
  - e.g. behavioural disorders, boredom, anxiety, distress
- Mild to severe

Make sure all harms are documented, reported, reviewed and acted on at the end of the experiment

Categorising suffering

Some countries grade harms into categories of severity

- There is a diversity of approaches:
  - 3 - 5 categories
  - Use numbers or descriptive words
  - UK - mild, moderate, substantial, and unclassified (e.g. for terminal procedures under deep anaesthesia)
  - NZ - no, little, moderate, severe, and very severe (unacceptable) suffering
- Grades can be applied to whole experiments or individual procedures
- Usually based on anticipated levels of suffering that may be modified as a result of retrospective review

Why grade severity?

- The process encourages consideration of levels of suffering and ways that it can be reduced
- Allows upper limits of suffering to be set and helps define and implement humane end-points
- Highlights potential problem protocols
- Helps with the weighing of harms and benefits
- Can provide public information

Difficulties grading severity

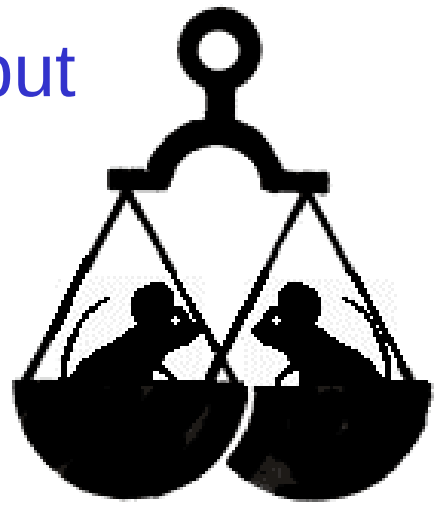
- Can feel arbitrary
- Adverse effects can be unpredictable
- Need to reflect level and duration of adverse effects
- Often prospective, and so does not reflect actual suffering
- Hard to find appropriate terminology

Severity assessments should

- Focus on the individual animal not the ‘average’
- Be assessed from the animal’s point of view
- Assess total impact on normal wellbeing
- Include all factors (transport, husbandry, procedures, duration…..)
- Encompass stress, anxiety, nausea as well as pain
- Reflect the probability that the effect occurs
- Reflect actual suffering, not just the suffering that is anticipated

Weighing harms and benefits

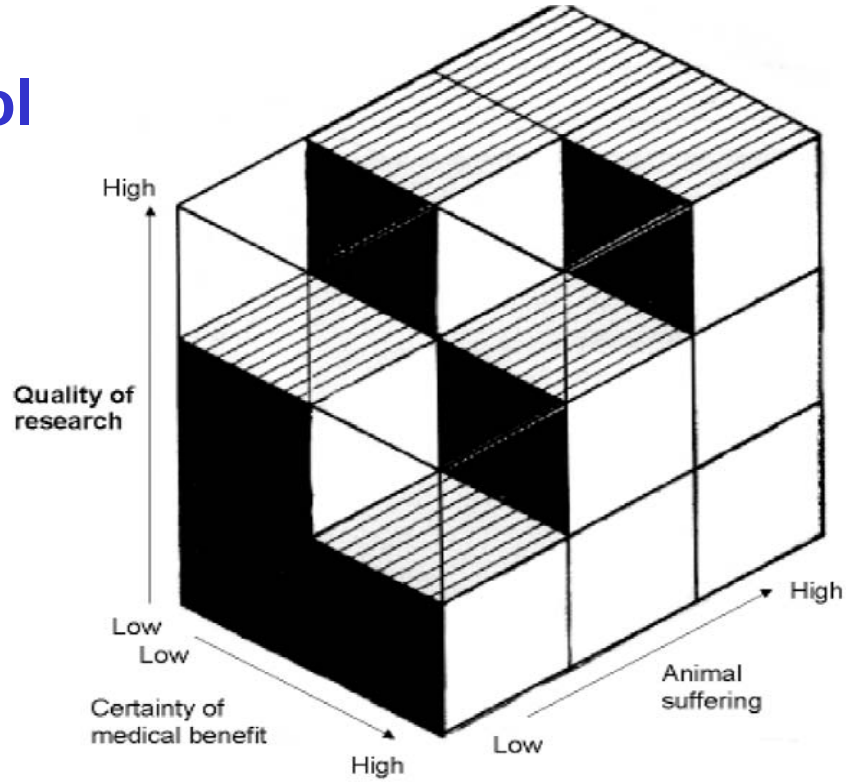
- Involves ‘value’ judgements
- There is no set ‘formula’ to provide answers
- Animal welfare representatives are as qualified as anyone to judge
- You are there to provide a different (but informed) perspective



Weighing harms and benefits

Bateson's Cube - a useful tool

"When a research project falls into the opaque part of the cube, the experimental work should not be done"



(Bateson, P. 1986. When to experiment on animals. *New Scientist* 20: 30-32.)

Continuous evaluation

It is very important to examine *actual* harms and *actual* benefits as the research progresses and at its completion to:

- implement ongoing improvements
- inform future judgements

This is described as ‘Retrospective Review’

The importance of good welfare

- Good welfare = good science
- Seemingly minor welfare problems can compromise the quality of data
- Data collected from stressed animals may be flawed

The 3Rs

- **Reduction:** reducing the number of animals involved
- **Replacement:** replacing animals with humane alternatives
- **Refinement:** adapting procedures and husbandry to reduce suffering and improve welfare

CONSIDER THE LIFETIME EXPERIENCE

The 3Rs principles

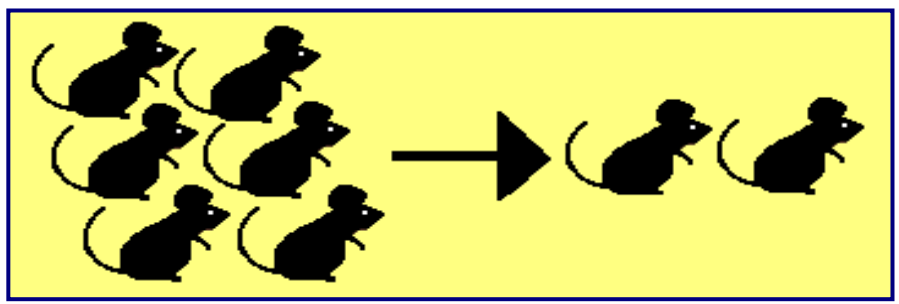
We are trying to minimise the potential for suffering in research

It can be a mistake to concentrate on one principle to the detriment of others...

… and it may be necessary to compromise one principle to improve the others

Reduction

- Well defined research strategy and objectives
- Consider a pilot study
- **Control variation**
- **Good experimental design**
- Appropriate group sizes
- Use results to inform future studies



Sources of variation

- **Environment**
- **Animals**
- **People**
- **Experimental**

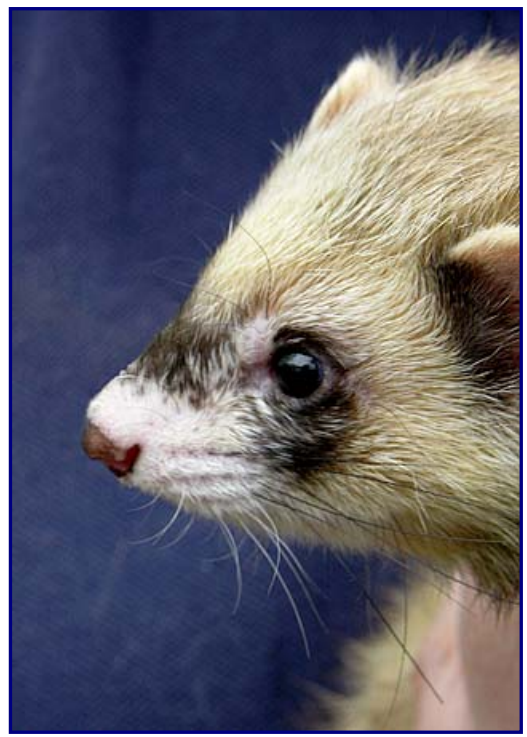
Good experimental design

- Based on an understanding of statistics
- Statistical methods should be used to:
  - select the best design for the experiment
  - determine animal group sizes
  - decide how results will be analysed before starting the experiment
- Scientists should be trained in statistics or have access to a qualified statistician

STATISTICS ARE AS IMPORTANT IN THE PLANNING OF AN EXPERIMENT AS IN ITS ANALYSIS

Reviewing results for future use

- Calculation of the most appropriate group sizes is possible if data is available from similar studies.
- The level of significance of the results may indicate that fewer animals could have been used.
- May highlight opportunities for improving the design of subsequent experiments?



What questions can you ask?

How were group sizes determined?

Has a statistician been consulted?

Do results from similar experiments suggest fewer animals could be used?

Will a pilot study be performed?

What steps are being taken to control variation?

Could animals that were more genetically similar be used so that fewer are needed?

Replacement

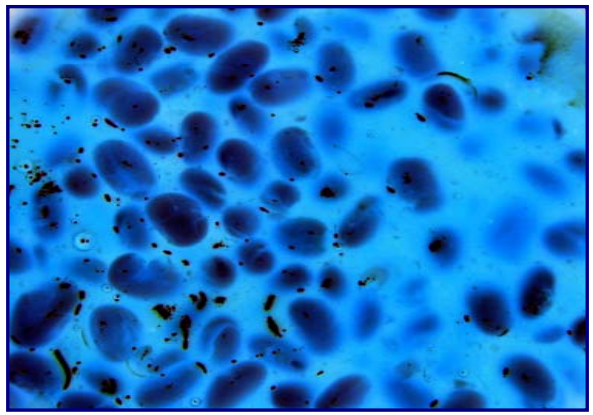
EU law requires that replacement methods must be used if they are available. Directive 86/609 states:

- **“**An experiment shall not be performed if another scientifically satisfactory method of obtaining the result sought, not entailing the use of an animal, is reasonably and practically available”.

Replacement

- **Complete replacement**
  - Method does not require any animal derived biological material
- **Incomplete replacement**
  - Method requires biological material obtained from living or killed animals

  or
  - Uses embryonic stages or invertebrates



Non-animal methods

- May be used to answer questions that animal tests cannot address.
- May be an addition to animal methods rather than a replacement, but may reduce the suffering and total number of animals used
- Alternative approaches may enable the avoidance of animal use

What questions can you ask?

Could non-animal methods be used to achieve the research objectives?

Could non-animal methods be used to replace a part of the research program?

What efforts have been made to find alternative methods?

Could an invertebrate model be used instead?

What are the barriers to replacing animal experiments with humane alternatives?

How could the questions be answered if animals were not available?

Refinement

- Aims to reduce suffering and improve welfare
- Applies to birth to death experience:
  - breeding and source issues
  - transport
  - housing and care
  - handling, identification, restraint
  - experimental and veterinary procedures
  - euthanasia

Your input

- During project review
- In developing overall standards for the establishment

  Remember, people may differ:

  – in awareness of suffering

  – on what constitutes a ‘high standard’, for example of husbandry or procedures

  – about whether pain relief is necessary.

Housing and care

General principles:

- Housing and care should satisfy the physiological and behavioural needs
- Consider:
  - social housing for social species
  - cage space and structure
  - environmental enrichment
  - food and feeding
  - environment (light, sound, temp, humidity)
  - cleaning regimes

Housing and care

Environmental enrichment is very important. It is the provision of stimuli that:

- allows animals some control over their environment
- encourages them to interact with their environment
- stimulates natural behaviour and mental activity
- helps prevent the development of abnormal behaviours

Housing and care: Rodents

- ✓ Group housing
- ✓ Plenty of space and height
- ✓ Solid floor
- ✓ Wood shavings for digging
- ✓ Shelter and/or tunnel
- ✓ Nesting material
- ✓ Something to gnaw
- ✓ Opportunities to forage for preferred foods
- ✓ Appropriate lighting levels
- ✓ Acceptable levels of ultrasound

Housing and care: Guinea pigs

- ✓ Group housing
- ✓ Plenty of space
- ✓ Solid floor with wood shavings
- ✓ Hay to burrow in
- ✓ Covered refuge areas
- ✓ Something to gnaw
- ✓ Dietary enrichment and the ability to forage

Housing and care: Rabbits

- ✓ Group housing
- ✓ Plenty of space and height
- ✓ Solid floor with substrate
- ✓ Straw or shredded paper bedding
- ✓ Nest box for breeding females
- ✓ Refuges
- ✓ Raised areas
- ✓ Something to gnaw and dietary enrichment

Housing and care: Dogs

- ✓ Group housing
- ✓ Spacious pens
- ✓ Solid floors
- ✓ Daily access to in/outdoor runs
- ✓ Warm, dry resting area
- ✓ Raised areas
- ✓ Balanced diet
- ✓ Toys and items to chew
- ✓ Protection from excess noise

Housing and care: Pigs

- ✓ Group housing in plenty of space
- ✓ Solid floors
- ✓ Material to manipulate with their noses
- ✓ A comfortable area to lie
- ✓ A means of keeping cool
- ✓ Adequate feeder space
- ✓ Nesting material for pregnant females
- ✓ Toys and things to keep them occupied
- ✓ Human interaction

Housing and care: Chickens

- ✓ Group housing
- ✓ Large pens (not cages)
- ✓ Solid floor
- ✓ Sand or wood shavings and chopped straw
- ✓ Dust baths
- ✓ Objects to peck
- ✓ Nest box and material (laying hens)
- ✓ 15cm perch per bird at varying heights
- ✓ 15cm feeder length per bird

Housing: Action points

- Make sure you know how animals are housed
- Ask to visit the animal house and see for yourself
- Compare standards with the check-lists
- Discuss any differences and the reasons for these
- Remember - good welfare=good science

Refinements in procedures

- Identification
- Restraint
- Administration of substances
- Blood sampling
- Telemetry

Procedures: Identification

- Is individual identification necessary?
  e.g. can you just label the cage?
- Is there a non-invasive method?
  e.g.coat colour, natural marks, marker pen, collars
- What is the least invasive method?
  e.g.microchips, ear notch
- Avoid using invasive methods twice
- Use anaesthesia for tattoos.
- Never toe clip

Procedures: Restraint

Handling and restraint should be:

- appropriate to species, individual animal
- gentle but firm and cause minimal distress
- carried out by trained staff

Can restraint be avoided by training animals to co-operate or using methods that do not need it?

Can equipment or process be modified to reduce effect? e.g. method, time restrained, providing a companion

Procedures: general principles

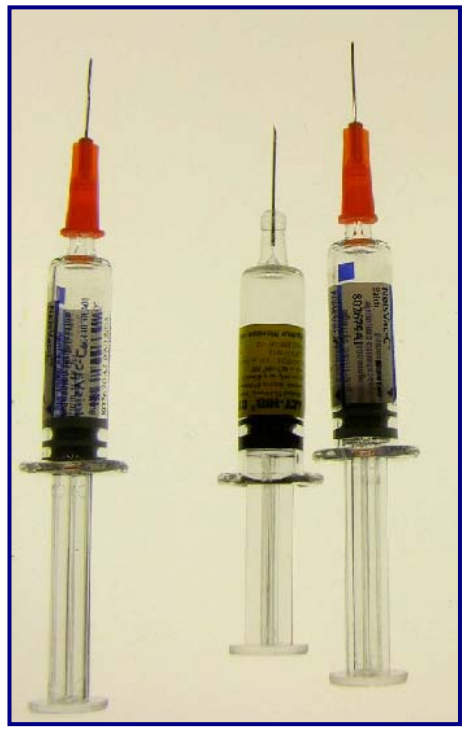
General principles for ALL procedures:

Review ALL factors and consider not only ‘can it be done’ but should it be done’

- Is the technique appropriate for the species and individual animal?
- Have the animals been given enough time to acclimatise to the laboratory and the procedures?
- Would a pilot study help assess likely effects?
- Are there any constraints on housing?
- Is everything well planned?

Administration of substances

- Route, site, volume, frequency
- Technique and equipment
- The properties of the substance (includes solvents, vehicles and adjuvants)



Route, volume and technique

- Route
  - **least severe possible**
  - **may require anaesthesia**
- Volume
  - **use smallest possible**
  - **will vary depending on route, species and animal size**
- Technique and equipment
  - **special means of restraint?**
  - **needle size?**
  - **tube design?**
  - **type of infusion device?**

Blood sampling

- Has the most appropriate technique and equipment been chosen?
- Is the smallest volume possible being collected?
- Could samples be taken less frequently?
- Why has the site been chosen? Is it the least invasive?
- What are the adverse effects and how will they be controlled?

Metabolism cages

Used for complete collection of urine and faeces. Housing can be very stressful.

- Is there an alternative?
- Group house animals?
- Pair animals and use paired results?
- Place met cage in main enclosure?
- Reduce time in cage?
- Enrich the cage?

Telemetry

Potential benefits

- Possible to get more and better scientific data from animals
- Possible reduction in animal numbers due to better quality data
- Restraint not necessary so animals can behave more normally

Potential harms

- Surgery to implant device
- Physical impact of the device on the animal - can be 20 % of body mass
- Can cause impaired wellbeing for up to 2 weeks
- Distress due to housing animals individually or by prolonged housing in the laboratory

Telemetry: Points to consider

- Housing and equipment and the potential to group-house animals
- Technical problems, and potential for wasted animals
- The impact of the weight, size and shape of the device
- Whether external or internal devices are best - important to consider from the animal's point of view
- Who should fit the devices
- Whether pain relief and post-operative care is adequate

Concluding comments

- Refinement has great potential for reducing suffering and improving science
- Never assume that established methods are the best
- Always be prepared to ask questions even if you feel you have little knowledge of the subject
- Refinements are constantly being developed and reported
- It is very important for all establishments to keep up to date

Further sources of information

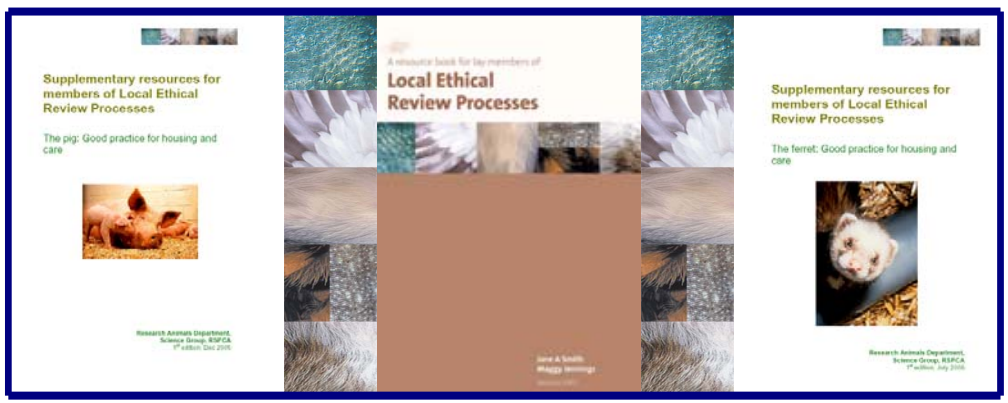
- People
  - Official Inspectors (e.g. Home Office Inspectors in the UK)
  - Veterinary staff
  - Animal care staff
  - Scientific staff
  - Other members of the committee
  - Animal welfare and behaviour experts
  - RSPCA - email: research_animals@rspca.org.uk
- Internet resources
- Published material

RSPCA resources on the internet

RSPCA Ethical Review

www.rspca.org.uk/ethicalreview

The web-site contains essential information on ethical review together with a range of documents for download that have been designed as resources for members of ethics committees.

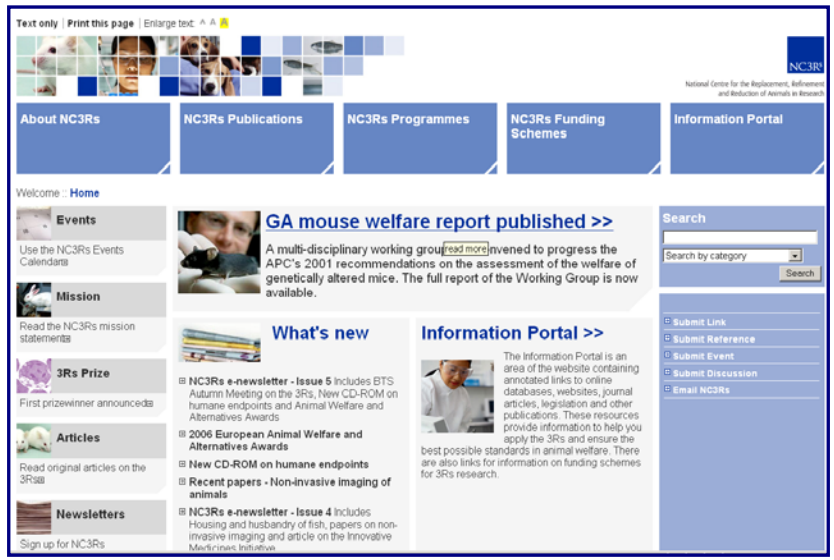


Other 3Rs resources on the internet

National Centre for the 3Rs

Website contains:

- Information and articles on the
- 3Rs
- Details of funding opportunities
- Links to other relevant:
  - databases
  - web-sites
  - journal articles



www.nc3Rs.org.uk

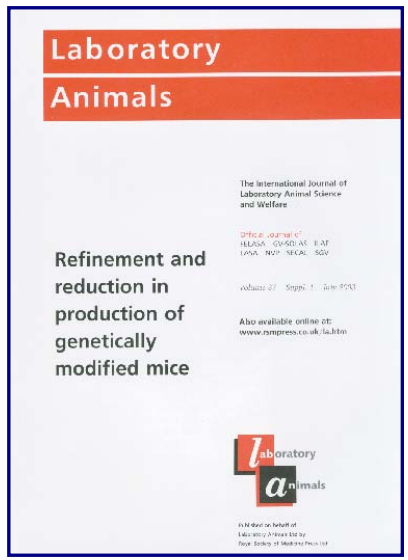
Scientific Literature

Data bases on the internet

- PubMed www.pubmed.gov
- Google Scholar www.scholar.google.com

Journals

- Contemporary Topics in Laboratory Animal Science
- ATLA - Alternatives to Laboratory Animals
- Laboratory Animals
- Lab Animal and Lab Animal Europe
- Animal Technology and Welfare
- ILAR Journal
- Animal Welfare



Questions to ask

Has a database search been conducted to look for alternative techniques

Have a variety of databases been used?

Has a literature review been performed to ensure that this work does not repeat the work of other researchers?

Are there been any refinements to this technique that have been published recently in the scientific literature?

Does the establishment subscribe to any of the journals that report on developments in the 3Rs

Feedback please!

We are are happy to provide advice to anyone setting up a committee or serving on one, or even from people considering joining a committee.

If you found this resource useful, if you think it can be improved in any way, or if there are other topics you would like us to address in this format please contact us.

Your help is invaluable as we continue to revise and develop our resources.

Please email any comments, suggestions or requests for more information to:

erp-laymembers@rspca.org.uk