

Harm-benefit assessment: EU legislation and UK experience

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Overview of presentation

1. Harm-benefit in Directive 2010/63/EU
2. Identifying, assessing and minimising harms
3. Identifying, assessing and maximising benefits
4. How do you 'weigh' harms and benefits?
5. What to aim for in an ideal system



Harm-benefit analysis in Directive 2010/63/EU



RECITAL 39

It is essential, both on **moral and scientific grounds**, to ensure that each use of an animal is carefully evaluated as to the scientific or educational validity, usefulness and relevance of the expected result of that use. The **likely harms** to the animal should be balanced against the **expected benefits** of the project

Harm-benefit analysis in Directive 2010/63/EU



ARTICLE 36: PROJECT AUTHORISATION

Member States shall ensure that no project is carried out unless a favourable project evaluation by the competent authority has been received in accordance with Article 38

Article 38.2: Project evaluation

- SHALL CONSIST IN PARTICULAR OF THE FOLLOWING:

- Objectives, predicted scientific benefit or educational value
- Compliance with the 3Rs
- Assessment and classification of severity (non-recovery, mild, moderate or severe) – worst predicted
- Whether and when retrospective assessment is required
- Harm/benefit analysis
 - Whether the harm (suffering, pain and distress) is justified by the expected outcome, taking into account ethical considerations

Article 39: Retrospective assessment

- AN EVALUATION OF THE FOLLOWING:

- Whether the objectives were achieved
- The actual harms inflicted, including numbers, species and severity
- Any elements that may contribute to further implementation of the Three Rs
 - Mandatory for all severe procedures and all procedures using primates
 - Member States may exempt 'mild' or 'non-recovery' procedures using non-primates



**National Competent Authorities for the implementation of Directive
2010/63/EU on the protection of animals used for scientific purposes**

Working document on Project Evaluation and Retrospective Assessment

Brussels, 18-19 September 2013

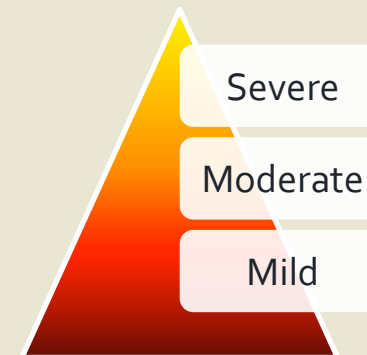
The Commission established an Expert Working Group (EWG) for Project Evaluation (PE) and Retrospective Assessment (RA) of projects to facilitate the implementation of Directive 2010/63/EU on the protection of animals used for scientific purposes. All Member States and main stakeholder organisations were invited to nominate experts to participate in the work.

The main objectives of the EWG were to develop guidance and principles for PE and RA in line with Articles 38 and 39 of the Directive to assist all those involved in the preparation, evaluation and assessment of projects. The EWG for PE & RA was convened 19-20 March 2013.

This document is the result of the work of the EWG meeting, discussions with the Member States as well as legal input from the Commission on the understanding of the requirements for these two processes, its components, participants and working tools and methods. It was endorsed by the National Competent Authorities for the implementation of Directive 2010/63/EU at their meeting of 18-19 September 2013.

Information required

ARTICLE 37 & ANNEX VI



- Relevance and justification for use of animals (species, origin, numbers, life stages) & procedures
- Application of 3Rs
- Use of anaesthesia, analgesia, other pain relief
- Reduction, avoidance & alleviation of suffering, from birth to death
- Use of humane end-points
- Experimental design and observations of animals to minimise suffering
- Re-use and its effects
- Severity classification
- Avoidance of duplication
- Housing, husbandry & care
- Methods of killing
- Competence of staff

Who does the harm/benefit assessment?

- Formal project evaluation by the competent authority
 - which varies in different countries
 - National board/ethics committee
 - National inspectorate (e.g. UK)
 - Regional boards/ethics committees
 - If the CA is not a public authority, there must be **no conflict of interest**
- Some countries have institutional ethics committees that review applications **from a local perspective** before passing them to the competent authority for formal evaluation

Harm-benefit in the UK

TWO COMPLEMENTARY STAGES

- AWERB – Animal Welfare and Ethical Review Body
 - expanded version of AWB
 - applies local values and advises Establishment Licence Holder whether to support project licence application to ...
- Home Office – performs h/b during authorisation
- [• Animals in Science Committee – ‘special cases’]

The UK AWERB

MEMBERSHIP

- **NACWO (senior animal technologist)**
- **NVS (attending veterinarian)**
- **Scientist (user establishments)**
- Other 'named persons' actively engaged
- People without responsibility under ASPA
- Independent persons
- Regulator

TASKS

- Advise ELH whether to support project proposals, from a local perspective
- Retrospective assessment
- Communicate with NC
- Promote the 'culture of care'
- Provide a forum for discussion and development of ethical advice

**Identification,
assessment and
minimisation of harms**

National Competent Authorities for the implementation of Directive 2010/63/EU on the protection of animals used for scientific purposes

Working document on a severity assessment framework

Brussels, 11-12 July 2012

The Commission established an Expert Working Group (EWG) for the assessment of severity of procedures to facilitate the implementation of Directive 2010/63/EU on the protection of animals used for scientific purposes. All Member States and main stakeholder organisations were invited to nominate experts to participate in the work.

The EWG for the assessment of severity met twice: in December 2011 with the focus on genetically altered animals, and in May 2012 discussing a general framework for assessing the actual severity experienced by animals in procedures.

This document is the result of the work of the two EWG meetings, discussions with the Member States as well as legal input from the Commission on the understanding of a severity assessment framework, its components, participants and working tools and methods. It was endorsed by the National Competent Authorities for the implementation of Directive 2010/63/EU at their meeting of 11-12 July 2012.

Disclaimer:

The following is intended as guidance to assist the Member States and others affected by this Directive to arrive at a common understanding of the provisions contained in the Directive. All comments should be considered within the context of Directive 2010/63/EU on the protection of animals used for scientific purposes.

Examples to illustrate the process of severity classification, day-to-day assessment and actual severity assessment

Brussels, 11 January 2013

on a *Severity Assessment Framework*¹ produced by the European Commission Expert Working Group and endorsed by the National Competent Authorities for the implementation of Directive 2010/63/EU on the protection of animals used for scientific purposes. In its meeting of July 2012 recommended that examples be developed to illustrate the "process of severity classification, day-to-day assessment and actual severity assessment" and that these should be made available to the scientific community.

The Expert Working Group produced a range of examples to show how the process described in the *Working Document* is applied to different procedures. These are intended to help Competent Authorities, users, animal technologists, and other relevant staff to ensure that pain, suffering and distress are effectively predicted, recognised, ameliorated, where necessary, and fully assessed during procedures. This document was endorsed by the National Competent Authorities for the implementation of Directive 2010/63/EU at their meeting of 23-24 January 2013.

A number of important factors are taken into account when using these examples:

It is essential that **good practice is implemented** throughout with respect to housing, husbandry and care; refining procedures; ensuring the welfare of animals; assessing competence; retrieving and applying current information on replacement, reduction and refinement; and ensuring the quality of experimental design.

The examples included within the examples are intended to **complement – not substitute for – the judgement of trained, experienced and competent staff**. The aim is to enable more systematic and objective observation, record keeping and assessment of procedures to complement professional judgement.

¹ [http://ec.europa.eu/chemicals/lab_animals/pdf/Consensus%20doc%20on%20severity%20assessment.pdf](#)

Examples in Annex VIII

Mild	Administration of anaesthesia except for the sole purpose of killing
Moderate	Breeding genetically altered animals resulting in a phenotype with moderate effects
Severe	Vaccine potency testing with progressive disease leading to death



The factors related to the procedure shall include:

- Type of manipulation, handling
- Nature of pain, suffering, distress or lasting harm caused by (all elements of) the procedure, and its intensity, the duration, frequency and multiplicity of techniques employed
- Cumulative suffering within a procedure
- Prevention from expressing natural behaviour including restrictions on housing, husbandry and care standards

The following additional factors shall also be taken into account:

- Type of species and genotype
- Maturity, age and gender of the animal
- Training experience of the animal with respect to the procedure
- If the animal is to be reused, the actual severity of the previous procedures
- Humane end-points



Assessment of harms



- How adverse effects are recognised
- How likely these are to occur
- Measures to prevent and control adverse effects
- Practical and realistic humane endpoints

- Thinking about:
 - Overall nature of harms – physical and psychological – from all sources
 - Duration of suffering
 - Level of severity
 - **Worst case scenario** within each procedure

Harm-benefit assessment as a tool to reduce suffering

THE APPROACH

- Consider **what will happen to each animal** during the procedure, from beginning to end
- Identify potential causes of suffering
- Research how each of these can be avoided or refined
- Define humane endpoints
- The end result should be a significant reduction in suffering

Consider everything that will happen to the animal



A SIMPLE EXAMPLE – DURING BLOOD SAMPLING, A MOUSE IS ...

1. Caught and removed from the cage
2. Restrained
3. Subjected to a **needle stick**, e.g. to access the sublingual vein
4. Possibly a second needle stick, if rehydration is necessary
5. Returned to the cage

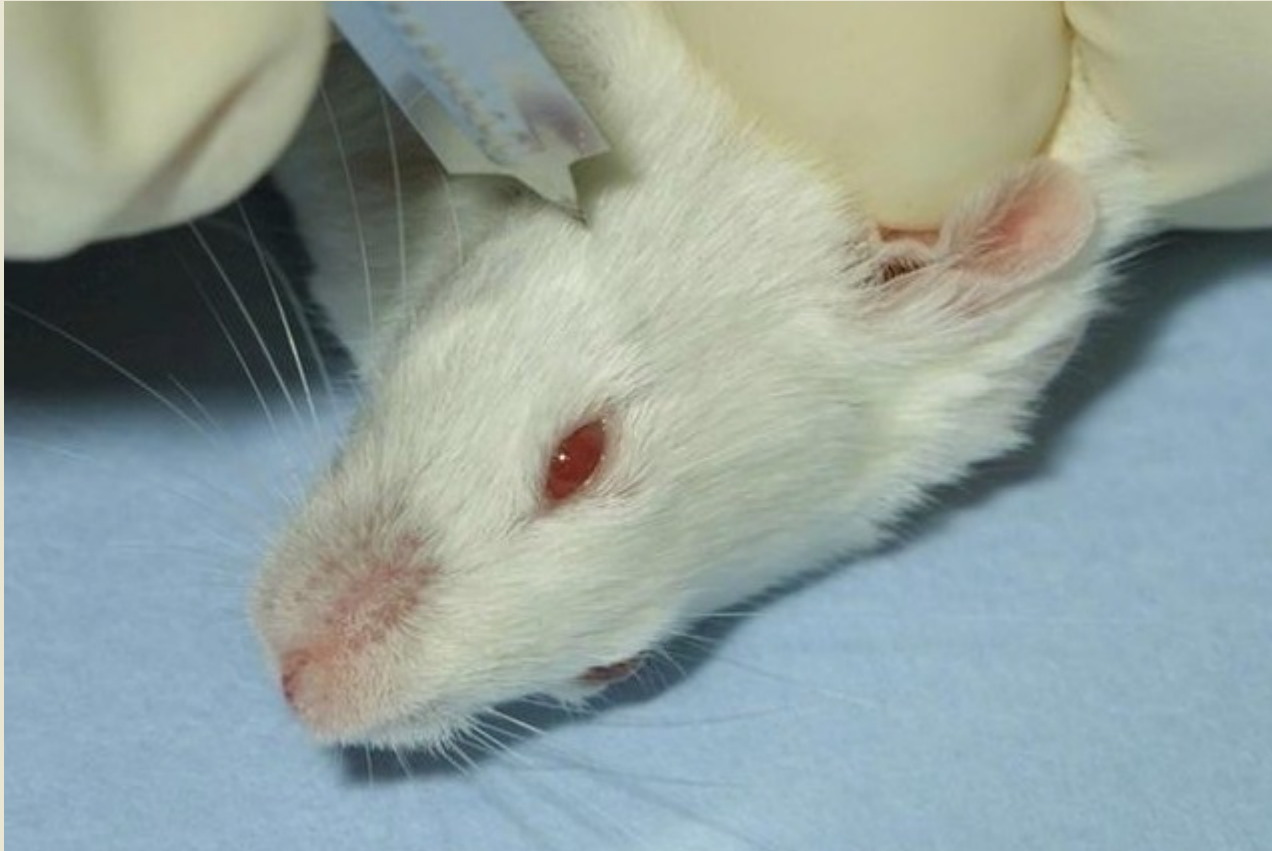
1. Caught and removed from the cage
2. Restrained
3. Subjected to a **needle stick**, e.g. to access the saphenous vein
4. Possibly a second needle stick, if rehydration is necessary
5. Returned to the cage

At the doctor's ...

Doctor: "I need to take a blood sample from you today ..."

"... I take my blood samples by sticking a knife into your neck without anaesthesia ..."

"... But don't worry, I'll inject 2 litres of fluid into your peritoneal cavity first so you don't die from loss of blood."



www.braintreesci.com

'Critical anthropomorphism'

= *empathy* + objective,
knowledge-based
consideration of what is likely
to be significant to the animal

Potential causes of suffering



Cause of discomfort, pain or distress	Nature of suffering
Capture and removal from the cage	Stress, especially when caught by the tail
Restraint	This can be very stressful
Needle stick	Pain, distress
Effects of blood removal	Dehydration, dizziness, weakness

Explain how these could be avoided or refined

Cause of discomfort, pain or distress	Nature of suffering	Refinement
Capture and removal from the cage	Stress, especially when caught by the tail	Catch by cupping in the hands or in the tunnel
Restraint	This can be very stressful	Ensure that the person restraining the mouse is trained and competent
Needle stick	Pain, distress	Ensure that the needle gauge is appropriate and choose site carefully
Effects of blood removal	Dehydration, dizziness, weakness	Ensure that only the minimum volume necessary is removed; rehydrate if required

Version Date	
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Applicant to complete version date

PPL Number:

OFFICIAL SENSITIVE



PROJECT LICENCE APPLICATION

UNDER THE ANIMALS (SCIENTIFIC PROCEDURES) ACT 1986

PROJECT TITLE (<50 characters including spaces)

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A. PROJECT LICENCE HOLDER

Under the Animals (Scientific Procedures) Act 1986, section 5, a project licence is granted by the Secretary of State which specifies a programme of work and authorises the application, as part of that programme, of specified regulated procedures to animals of specified descriptions at a specified place or specified places. The project licence holder is responsible for the overall implementation of the programme of work and for ensuring that the programme is carried out in compliance with the conditions of the licence.

a. Title (e.g. Professor, Dr, Mr)	
b. Surname	
c. Forename(s)	
d. Qualifications	
e. Position or appointment	
If you have previously been known by another name, give that name:	
f. Surname	
g. Forename(s)	

Minimising harms through the 3Rs

PROPER EXPLANATION, NOT 'BOX TICKING'

- Replacement
 - Why it is not possible without using animals
 - What alternatives considered and why unsuitable
- Reduction
 - Experimental design, sources of advice
- Refinement
 - Explain choices of species, model, methods
 - How suffering will be minimised
 - Special justification for severe procedures
 - Use of pain relief including anaesthesia & analgesia
- Confirmation of staff training, facilities etc.



THE 3Rs

Under the Animals (Scientific Procedures) Act 1986 section 5B(3) (b), in carrying out the evaluation of the programme of work, the Secretary of State must assess the compliance of the programme of work with the principles of replacement, reduction and refinement.

Refinement

- Explain your choice of species, model(s) and method(s). Explain why they are the most refined for the intended purpose.
- How will you minimise animal suffering in order to achieve your objectives?
- Provide specific justification for any protocols categorised as 'severe'.

Protocol title:	
Species of animals (state if genetically altered):	
Severity category:	

List each of the steps in this protocol. Note: It is accepted that the order of steps may be varied according to scientific need. Indicate which steps are optional and for each give the anaesthetic code. If appropriate indicate the method of killing, Schedule 1 or non-Schedule 1. Give brief details of non-Schedule 1 methods e.g. perfusion fixation (AC).

Expected adverse effects

Describe the expected adverse effects of the series of regulated procedures described above.

For each adverse effect indicate under the headings below:

- the likely incidence
- how the adverse effect will be recognised
- the refinement measures and other controls you will adopt to prevent occurrence or minimise severity
- practicable and realistic humane end-points.

Expected adverse effects and likely incidence

How the adverse effect will be recognised

Refinement control measures

Humane end-points and limits of severity

**Identification,
assessment and
maximisation of
benefits**

Explaining the benefits / scientific objectives



GUIDANCE FROM THE EUROPEAN COMMISSION

- Set out the key scientific questions to be addressed
- Include the purpose of the project (Article 5), e.g. treatment of disease, regulatory testing
- Use SMART objectives – Specific, Measurable, Achievable, Realistic, Timely

Version Date	
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Applicant to complete version date

PPL Number:

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C. SCIENTIFIC BACKGROUND

The total response to this Part must not exceed 2000 words

Background

- For research projects: What is the current position in your area of work and how will this project help to advance knowledge or meet a clinical need?
- For testing or screening projects: What are the relevant statutory requirements or regulatory guidelines?
- For service or production projects: What are the likely demands for the service or product in the lifetime of the licence?
- Where applicable, summarise relevant progress under any previous project licence.

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Benefits

Under the Animals (Scientific Procedures) Act 1986 5B (3)(d), the Secretary of State is required to carry out a harm-benefit analysis of the programme of work to assess whether the harm that would be caused is justified by the expected outcome, taking into account ethical considerations and the expected benefit to human beings, animals or the environment.



What are the expected benefits of this project? Why are they worthwhile?

What are they?

- Direct medical benefit
- Increase in knowledge
- Educational benefit
- Economic benefit?

Who are they for?

- Human/veterinary patients
- The field of research
- Individual scientists
- Society as a whole e.g. through economic benefit?

Benefits

Importance changes with time, place, culture, economics, emerging scientific issues & changing ethical values

How will they benefit?

- Better diagnosis, treatment, quality of life
- Intellectual gain
- Informing other research
- Product safety
- Scale and level of impact?

When will the benefits occur?

- Short or long term
- At completion of the project?
- 10, 20, 50 years??

Evaluating benefits – information needed

- Overall purpose and aims
 - Scientific background
 - Expected benefits and why they are worthwhile
 - Project plan
 - Justification for each protocol – how objectives will be achieved
 - How *in vitro* and *in vivo* work integrate
 - What data/products needed, how generated
- Thinking about:
 - Quality of science
 - Likelihood of achieving benefit
 - Originality
 - Relevance
 - Timeliness
 - Realistic – staff, expertise, resources etc.
 - **How results will be used and disseminated**

Important factors relating to benefit

LIKELIHOOD OF SUCCESS

- Track record of applicant (and group)
 - Publications
 - What have they achieved previously?
- Expertise, equipment, practical and technical support



And what would happen if the project didn't go ahead?

Problems with applications



SOME EXAMPLES ...

- Insufficient funding or resource to deliver benefit
- Severe disease model, when milder models are available
- Flawed disease model, with no supporting evidence
- Unrealistic/unsubstantiated benefits
- Inadequate information on Three Rs
- Insufficient information on nature and/or levels of harms

How do you 'weigh' harms and benefits?

$$\text{justification} = \frac{\text{importance of objectives} \times \text{probability of achievement}}{\text{harms to animals}}$$

No numerical 'formula'

- AND A SPECTRUM OF VIEWS



- The harm-benefit assessment involves value judgements, which depend on individual opinions on:
 1. The nature and likelihood of the benefit
 2. The value placed on animal life – may depend on species, numbers
 3. The nature and level of suffering
 4. Controversy around particular procedures
 5. The fate of the animals

Some points to consider ...

1. The nature of the benefit

WHAT CRITERIA DO WE USE TO JUSTIFY USING ANIMALS?

- In basic research, is all knowledge equally valuable?
- Are all health benefits equally valuable – does the nature and severity of a medical condition make a difference – or the number of people affected?
- What about using animals in space research, or to develop 'cures' for hangovers or jet lag?
- Are all chemical products essential?
- Does an economic benefit justify harms to animals?

2. The value of animals – are all animals equal?

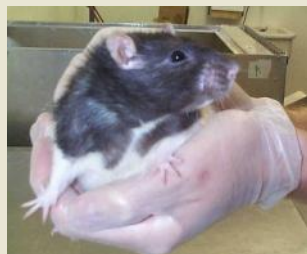


'Primates are intelligent animals occupying extensive home ranges. They have complex behaviours and social interactions. They can experience pain and distress. It is difficult to satisfy their physical and behavioural needs in a laboratory environment.'

but ...
the same can be said of pigs



or rats ...



And what about fish?

How do we make our decisions?

Is it perceived 'intelligence'? Does the size of the animal make a difference, or what they look like, or how they interact with us, or if they are a 'companion' species?



Special justification required for dog, cat, equid and primate use in UK

Small animals are not always small!

... and large animals are not
always large!

What about animal numbers?

- If the severity limit is the 'worst case scenario', do numbers make a difference?
- Would more animals, but same severity, alter the harm-benefit?
- What should come first – refinement or reduction?



3. The nature and level of suffering

- Does the level of harm it is acceptable to cause depend on the type of benefit?
- Are there harms that you think cannot be justified for any purpose?
- Directive sets limits on severe pain, suffering or distress that is likely to be **long-lasting** and **cannot be ameliorated**. How would you interpret this?
- How well do you think we assess pain, suffering and distress in animals?

4. The fate of the animal

IS DEATH A HARM IN ITSELF?

- Does it make a difference if animals are:
 - killed?
 - re-used?
 - re-homed?
 - released?



5. Controversial procedures

People can be concerned about certain procedures regardless of benefit and even if they cause no more suffering than others

- Interference with the brain or special senses
- Genetic modification where plant genes are put into animals
- Animals containing human material
- Solid organ xenotransplantation

Harms or benefits that cannot be justified

UK VOLUNTARY BANS

1997. Great Apes, alcohol product development, tobacco product development, offensive weapon testing, cosmetics product testing

1998. Cosmetics ingredient testing

2015. Household product and (some) ingredient testing

Problems encountered in UK AWBs

BELIEFS ABOUT BENEFIT

- Science is 'beyond question' – absolute belief in academic freedom and the value of (any) knowledge
- Scientists are unchallengeable, lack of confidence to question them
- Funding is approved, therefore work must be justified
- Unquestioning acceptance of economic benefit

UNDERSTANDING OF HARMS

- Lack of understanding of animals' ability to suffer and how to assess this
- Limited knowledge of how unrelieved harms can lead to poor science
- Lack of knowledge about 3Rs
- Insufficient expertise to recognise poor practice

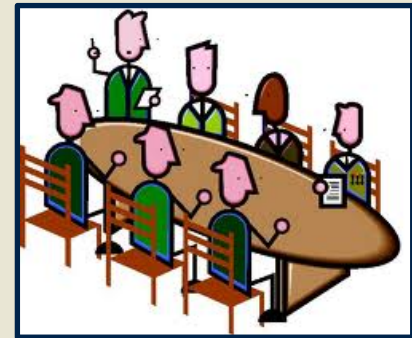
Result: an unambitious view of potential to improve or change

Conclusion:

**What to aim for in an
'ideal' system**

What to aim for [1]

- A robust system that requires an **honest description and critical assessment** of the harms and benefits and application of the 3Rs in all projects
- Those responsible for making decisions on weighing harms and benefits:
 - have the 'right' knowledge, expertise and skills
 - are able to **balance** interests of science and animal welfare
 - are **open-minded**
- Decisions are **consistent** and transparent



What to aim for [2]

Information provision

- Questions that deliver information and prompt in depth thought about, and understanding of, the issues
- Clear guidance on kind of information expected

Evaluation and judgements

A balanced, open-minded approach that:

- Does not assume claims of benefit are always correct
- Understands animal welfare implications of research
- Is prepared to turn down poorly designed and ill thought through studies
- Is prepared to set aside cultural, social, political issues and challenge outdated scientific opinion e.g. that pain relief cannot be given

What to aim for [3]

An assessor/Competent Authority that:

- Recognises the wider implications of the Directive for regulating *and advancing* animal welfare, *all* 3Rs, science and public accountability
- Includes (or can consult) experts in relevant fields

together with AWBs/ethics committees that:

- Have a clear idea of their roles, responsibilities and expected outcomes
- Incorporate a wide range of perspectives
- Select members with appropriate qualities including confidence to ask questions, deal with answers and challenge the *status quo*

Minimising conflicts of interest!

Harm-benefit is an ongoing process

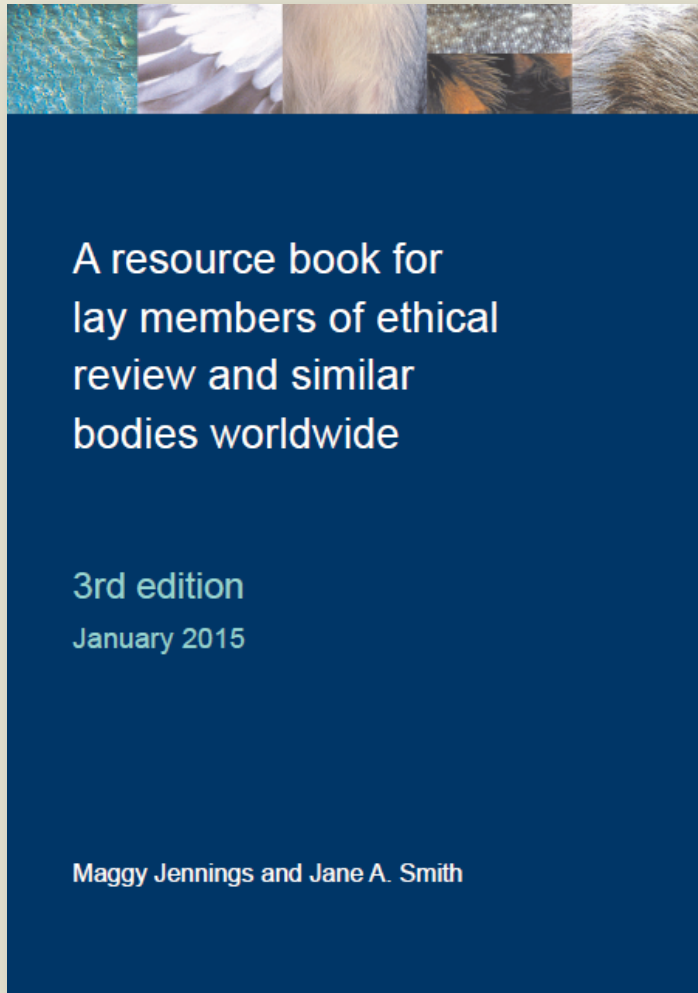
- NOT A ONE-OFF EVENT

- It is good practice to keep a check on harms and benefits as projects progress, e.g. mid-term reviews
- Actual severity *must* be reported
- Retrospective review is required for some projects but is *good practice for all*
 - check whether prospective and retrospective assessments differ and use to inform future judgements and implementation of 3Rs

Developments in the UK



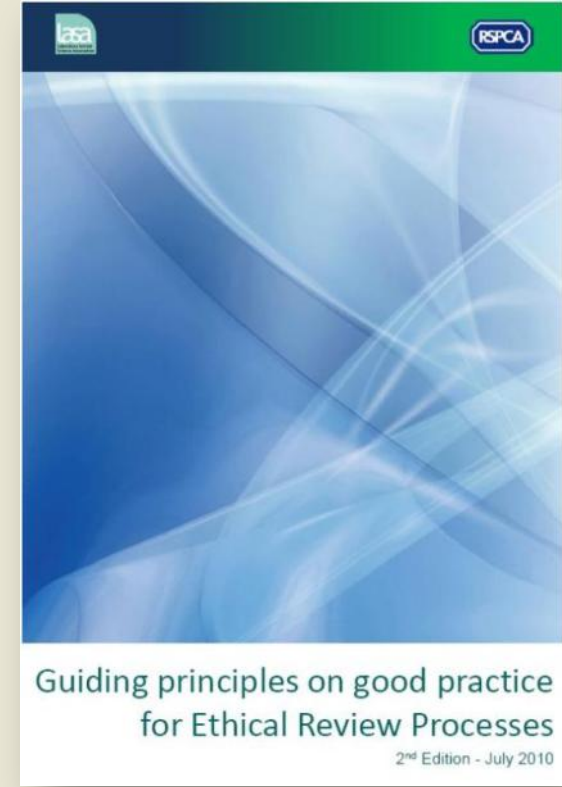
- Competent Authority is preparing a report explaining how it does harm-benefit – out soon
- Animals in Science Committee (ASC) is working on cumulative severity
- ASC is reviewing current arrangements for harm-benefit, focussing on severe procedures and a referral process



A resource book for
lay members of ethical
review and similar
bodies worldwide

3rd edition
January 2015

Maggy Jennings and Jane A. Smith



Guiding principles on good practice
for Ethical Review Processes

2nd Edition - July 2010

<http://science.rspca.org.uk/sciencegroup/researchanimals/ethicalreview>

Thank you