Working together to end 'severe' suffering

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ANIMALS IN SCIENCE DEPARTMENT

Within the UK and the European Union, 'severe' procedures are those where animals used in science are likely to experience:
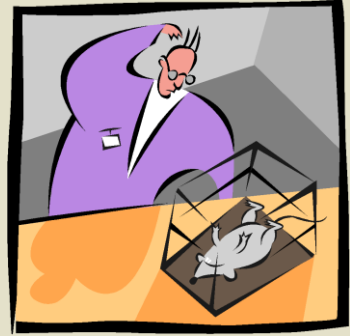
- severe pain, suffering or distress
- long-lasting moderate pain, suffering or distress, or
- severe impairment to their wellbeing or general condition
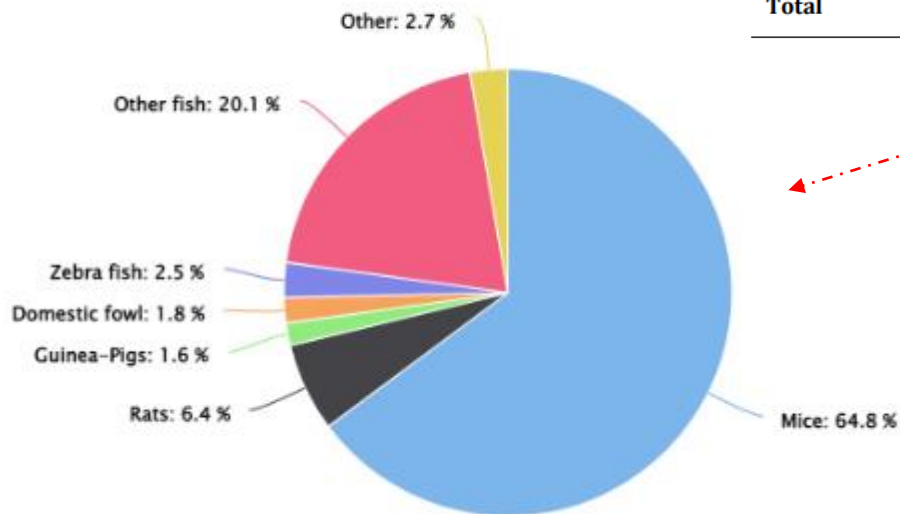
Causes of severe suffering

THREE MAIN REASONS

- Animals may be used in studies of **diseases or conditions** that by their nature can cause severe suffering
- A **combination** or series of less severe factors can combine to lead to an increase in overall suffering
- Where animals **die unexpectedly**, or where the **death** of an animal is used an **'endpoint'** of the study

	2017	2018 (EU-28 incl. NO)	2019 (EU-28 incl. NO)
Non-recovery	6% (621,054)	6% (612,094)	6% (586,373)
Mild [up to and including]	51% (4,865,721)	50% (5,469,214)	52% (5,512,134)
Moderate	32% (3,071,828)	34% (3,658,621)	33% (3,510,993)
Severe	11% (1,023,138)	10% (1,064,925)	9% (999,264)
Total	100% (9,581,741)	100% (10,804,854)	100% (10,608,764)

Uses by species

source : alures published data

Other: 2.7 %
Other fish: 20.1 %
Zebra fish: 2.5 %
Domestic fowl: 1.8 %
Guinea-Pigs: 1.6 %
Rats: 6.4 %
Mice: 64.8 %

Highcharts.com

https://ec.europa.eu/environment/chemicals/lab_animals/reports_en.htm

Member State	Uses of animals causing 'severe' suffering	% of total use
AUSTRIA	20245	9.24
BELGIUM	63134	14.20
CROATIA	2253	8.07
CYPRUS	0	0.00
CZECHIA	30653	12.98
DENMARK	4112	1.65
ESTONIA	0	0.00
FINLAND	6368	6.86
FRANCE	258440	14.55
GERMANY	97024	5.23
GREECE	12817	26.78
HUNGARY	19831	14.64
IRELAND	18543	13.39
ITALY	112087	20.37
LATVIA	82	1.93
LITHUANIA	0	0.00
LUXEMBOURG	344	3.08
MALTA	0	0.00
NETHERLANDS	4811	1.26
POLAND	83626	29.57
PORTUGAL	11170	14.82
ROMANIA	1055	7.75
SLOVAKIA	952	5.31
SLOVENIA	57	1.07
SPAIN	60119	7.94
SWEDEN	26842	11.39
NORWAY	91434	7.20
UK (GB+NI)	73265	4.18
EU + Norway total	999264	9.42

https://ec.europa.eu/environment/chemicals/lab_animals/reports_en.htm

10M

animals across the world experience severe suffering each year
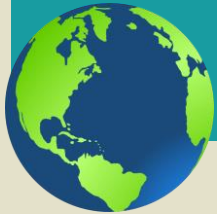
*estimate
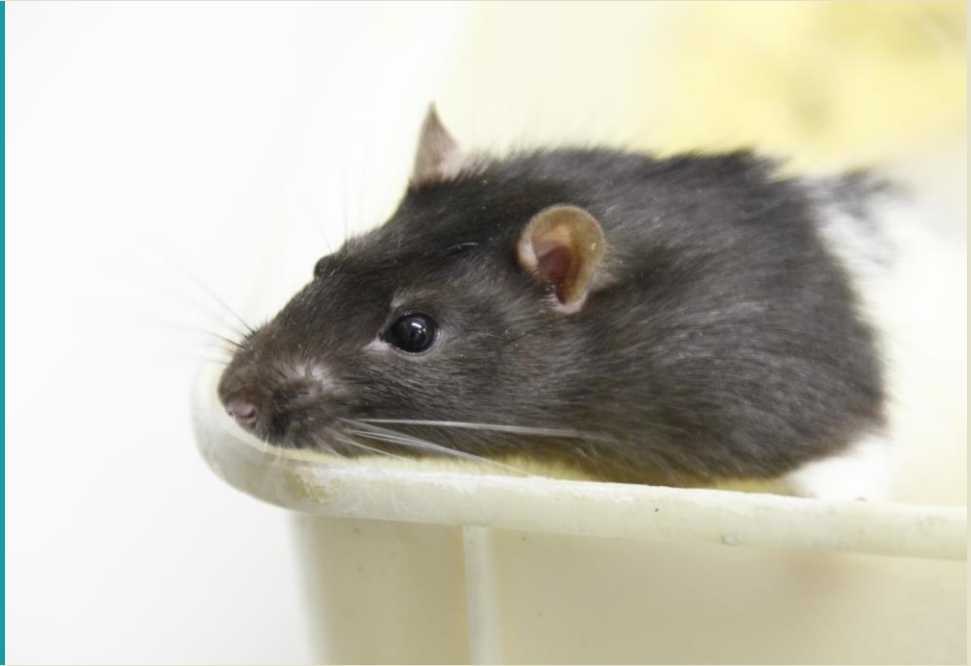
All laboratory animal suffering is a concern, but reducing and avoiding 'severe' suffering should be a top priority

✔ **Ethical** and animal welfare benefits
✔ **Legal** requirements to minimise suffering
✔ **Societal** concerns about harms to animals
✔ **Scientific** benefits - better welfare means better science

Everyone has a part to play

- Scientists
- Animal technologists
- Persons with responsibilities under Articles 24 and 25 (attending veterinarians, staff responsible for ensuring information access, training and competency etc)
- Animal Welfare Bodies
- Competent authorities
- National Committees
- National 3Rs centres
- NGOs

Our initiative

Since 2012, the RSPCA has been **working collaboratively** with the scientific community in the UK, EU and internationally, to initiate and promote a range of activities aimed at identifying and promoting **practical steps** which will help people to **reduce** or, ideally, **avoid** 'severe' suffering.

Key objectives

- Refine models to bring them to a lower severity limit where possible

  - applies to other levels of suffering too

- Ensure there has been robust discussion and a rationale that justifies the need for severe limits, where they still exist
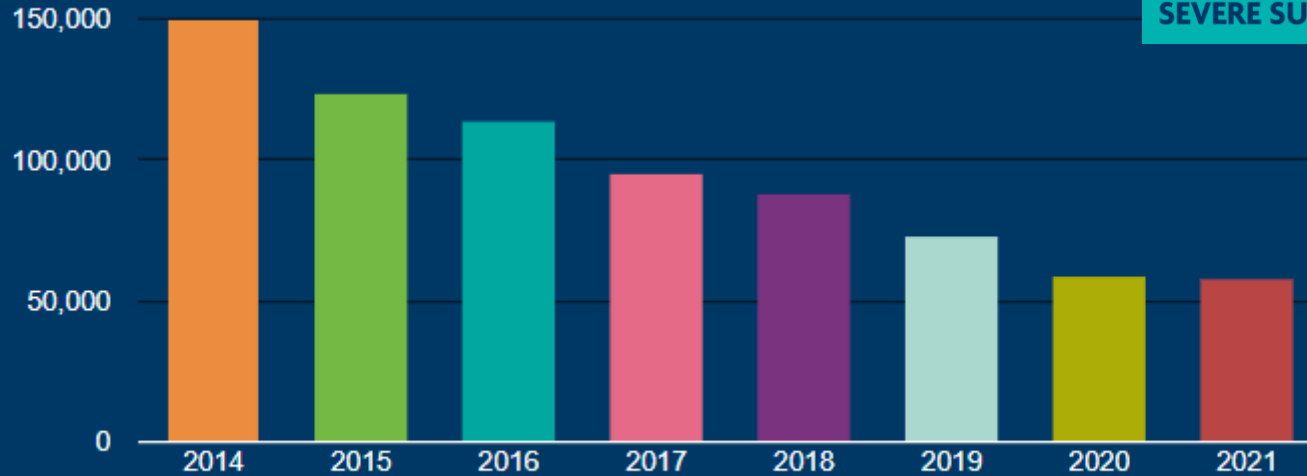
61% reduction in experimental procedures causing severe suffering in the **UK** since 2014

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EXAMPLES OF POTENTIALLY 'SEVERE' PROCEDURES

Batch potency testing of vaccines (where control animals experience 'severe' disease symptoms) **and other biologics** e.g. botulinum toxin, for regulatory purposes

Studies involving infectious disease models, including the development of vaccines or other treatments, where animals may experience 'severe' disease symptoms

Various tests involved in regulatory toxicology, including ecotoxicology, especially where animals may become moribund or die

Monoclonal antibody production using the mouse ascites method – NB this method has not been used in the UK since 2012 but is still used elsewhere in the world

Some cancer models – involving large tumours, resection, bone metastasis, brain tumours, pancreatic tumours

Some heart disease models – myocardial infarction induction; monocrotaline (MCT)-induced pulmonary arterial hypertension; transverse aortic constriction/banding

Multi-organ failure models

Demyelination of the central nervous system (CNS)

Models of motor neurone disease (MND)

Spinal cord injury models

Neuroscience studies using non-human primates, involving the cumulative effects of numerous surgeries, regular and long periods of restraint, and/or fluid or food control

Tamoxifen as an inducer of gene function

Irradiation with reconstitution of bone marrow

Cerebral malaria in rodents

Pancreatitis models

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NEW DATA ON 'SEVERE' SUFFERING IN THE EU AND NORWAY

1st August 2022

The most up-to-date data currently available on the use of animals in research and testing in the European Union (EU), and Norway, was published by the European Commission on 15 July 2022. This information is important for openness and transparency and can also help to focus 3Rs efforts more effectively. Below is a summary of the data, which is for 2019, setting out the number of animals reported to have experienced 'severe' suffering, and in which areas of science.

As in previous years, the mouse is the species most likely to experience 'severe' suffering, and batch potency testing of vaccines and other substances (such as botulinum toxin) is the category responsible for the largest proportion of 'severe' animal uses.

But on a positive note, the number of 'severe' animal uses fell by 65,661 in comparison with the 2018 data. This means that the percentage of 'severe' uses decreased from 10% to 9%, which is a small step in the right direction.

999,264 uses of animals (9% of the total) were reported as causing 'severe' pain, suffering, distress or lasting harm. This included:

- 344,582 in basic research *(7.2% of all uses for basic research involved severe suffering)*
- 310,367 in applied research *(10.9% of all uses for applied research involved severe suffering)*
- 291,166 for regulatory purposes *(12.2% of all uses for 'regulatory' purposes involved severe suffering)*

Main categories of use causing severe suffering

- 215,735 – Batch potency testing *(represents 21.6% of all uses of animals that were 'severe')*
- 132,695 – Studies of animal diseases and disorders *(represents 13.3% of all uses of animals that were 'severe')*
- 104,164 – Nervous system *(represents 10.4% of all uses of animals that were 'severe')*
- 77,654 – Immune system *(represents 7.8% of all uses of animals that were 'severe')*
- 52,574 – Oncology *(represents 5.3% of all uses of animals that were 'severe')*

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Expert Working Groups

- Seizures, convulsions and epilepsy
- Experimental autoimmune encephalomyelitis (EAE)
- Rheumatoid arthritis
- Sepsis
- Spinal cord injury
- Bone marrow ablation and reconstitution

- Avoiding mortality

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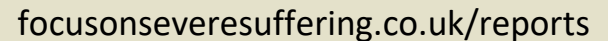
Events

- **Brussels**, Belgium - 2016
- **Berlin**, Germany - 2017
- **Stevenage**, UK - 2019
- **Athens**, Greece - 2019
- **Manchester**, UK - 2022
- **Stockholm**, Sweden - 2022
- Leiden, Netherlands - 2023

100s of participants: regulators, scientists, veterinarians, animal technologists and care staff, members of Animal Welfare Bodies and National Committees etc.

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Potentially severe procedures

- Batch potency testing of vaccines and other biologics
- Infectious disease models with severe symptoms, e.g. some vaccine development
- Studies of diseases that cause severe suffering in humans, e.g. rheumatoid arthritis, sepsis, spinal cord injury
- Some regulatory toxicology tests, e.g. acute toxicology, ecotoxicity

efpia

RSPCA

How the pharmaceutical industry is tackling 'severe' suffering in animals used in science

An online event co-organised by EFPIA and the RSPCA

Wednesday 26 January 2022: 14:30 - 16.00 CET

Website

focusonseveresuffering.co.uk

PERCEIVED OR ACTUAL REGULATORY REQUIREMENTS

The OECD recognises that *'with increasing knowledge and experience, investigators in animal research will be able to identify more specific, early humane endpoints in the form of clinical signs for impending death or severe pain and distress. This would permit international harmonisation of these humane endpoints'*. Researchers and establishments should challenge regulatory bodies to accept evidence that death can be predicted and to accept data from tests in which humane endpoints have been defined and implemented.

PREDICTING ANIMAL DEATHS

There is always scope to better predict mortality, and to challenge any assumptions that a proportion of deaths is 'inevitable' or that endpoints cannot be refined. Perceptions about the ability to predict death often change; for example, telemetered body temperature using microchips has improved the ability to define humane endpoints and avoid severe suffering in a number of fields. It is good practice to keep up with the literature and to identify any new approaches that may be suitable for trialling at the facility.

ACTIONS FOR THE AWERB (OR EQUIVALENT BODY)

The AWERB, AWB, IACUC or AEC should ask for explanations of humane endpoints, including how they are defined, refined and implemented. They can also ask to see, and discuss, animal 'fate' data, including a breakdown of animals humanely killed as part of the experiment, found dead, killed because they are close to a humane endpoint, or because they are not needed (surplus). This will allow the institution to monitor wastage, identify where endpoints may need to be revised and see where additional welfare monitoring should be applied.

For further information about humane endpoints, see www.humane-endpoints.info and www.nc3rs.org.uk/humane-endpoints

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Avoiding mortality
Hawkins et al. (2019)
Avoiding mortality in animal research and testing.
ISBN: 978-0-901098-17-7A

Experimental Autoimmune Encephalomyelitis (EAE)
Wolfensohn et al. (2013)
Reducing suffering in experimental autoimmune encephalomyelitis (EAE).
Journal of Pharmacological & Toxicological Methods 67, 169-176

Rheumatoid arthritis
Hawkins et al. (2015)
Applying refinement to the use of mice and rats in rheumatoid arthritis research.
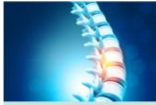Inflammopharmacology 23, 131-150

Seizures, convulsions and epilepsy
Wolfensohn et al. (2013)
Reducing suffering in animal models and procedures involving seizures, convulsions and epilepsy.
Journal of Pharmacological & Toxicological Methods 67, 9-15
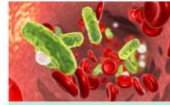
Sepsis
Lilley et al. (2015)
Refinement of animal models of sepsis and septic shock.
Shock 43, 304-316

Spinal cord injury
Lilley et al. (2020)
Refining rodent models of spinal cord injury.
Experimental Neurology 328, 113273

CUMULATIVE SEVERITY

Apart from experimental procedures and their impacts, each animal experiences many other **events during their lifetime** – including transport, marking for identification, capture, handling, restraint, laboratory housing and husbandry, and humane killing. Some of these events can be anxiety-inducing, painful or distressing, and may affect the animal's ability to cope with experimental procedures.

It is important to consider how the effects of all these events may interact with one another. The term 'cumulative severity' is often used, but harms do not 'accumulate', or simply add up – although animals may become sensitised to certain procedures (e.g. repeated injections), so the distress associated with each one is increased. As another example, if recovery time is not sufficient following stressful events (such as cage cleaning and change) before conducting a procedure, then the severity of the procedure may increase. The cumulative impact of some procedures (e.g. surgery without the most effective perioperative analgesia regime) may be long-lasting or permanent.

Alternatively, animals may habituate (become used) to repeated procedures, which can reduce suffering, especially if they can be trained using positive reinforcement techniques to avoid restraint.

It is critically important not to make subjective assumptions about cumulative severity either 'increasing or decreasing – expert input and monitoring systems are both necessary to ensure that the animal's **lifetime** experiences are understood and that welfare issues, and refinements, are identified.

Regarding severe suffering, two key questions are:

Might a procedure that does not prospectively appear to be severe, actually end up being severe in practice, because of cumulative effects?

Can we use the concept of cumulative severity to make multiple refinements (or 'marginal gains'), which will combine to significantly reduce severity?

For more information, see section 3.3. of the UK Animals in Science Committee **review of harm-benefit analysis**

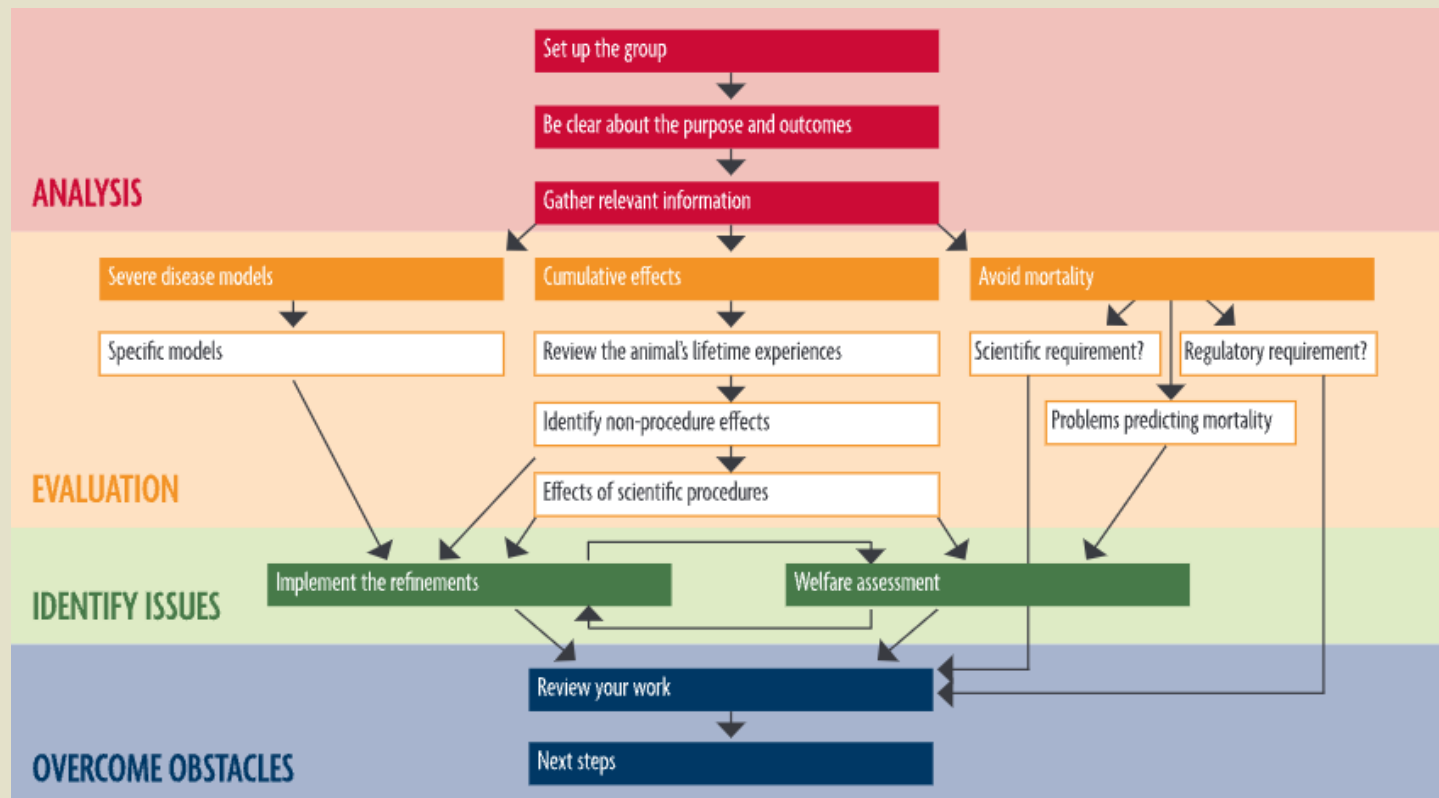◀ SEVERE PROCEDURES   MORTALITY ▶

A commitment to address severe suffering

- Agreement as a priority area for attention and action

- Institutional strategy and responsibilities

- Setting of clear objectives

Consider as part of the 'Culture of Care'

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ANALYSIS

- Set up the group
- Be clear about the purpose and outcomes
- Gather relevant information

EVALUATION

- Severe disease models
  - Specific models
- Cumulative effects
  - Review the animal's lifetime experiences
  - Identify non-procedure effects
  - Effects of scientific procedures
- Avoid mortality
  - Scientific requirement?
  - Regulatory requirement?
  - Problems predicting mortality

IDENTIFY ISSUES

- Implement the refinements
- Welfare assessment

OVERCOME OBSTACLES

- Review your work
- Next steps

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Breeding >

Capture from the wild >

Transport >

Marking for identification >

Genotyping >

Housing >

Husbandry procedures >

Handling and restraint >

Scientific procedures >

Effects of procedures >
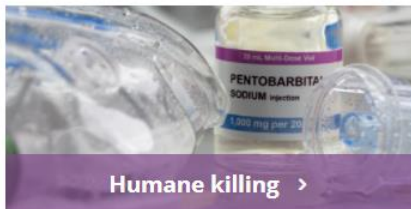
Humane killing >

Rehoming or release >

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Factor	Experience of the animal	Welfare issues	Ways of mitigating these
Sourcing	Mice are bred in-house. Supply and demand are carefully matched and animals provided with litter, nest boxes and nesting material. Cages are cleaned weekly.	Distress due to separation of dam and pups at weaning.	Ensure removal from dam is appropriately timed and keep litters together wherever possible. Review frequency of cage change (e.g. fortnightly?) to ensure cage is sufficiently clean but with minimal disturbance.
Transport	Once, between rooms within the same building before procedures begin.	Stress and anxiety due to movement.	Move in home cages, minimise distance, think about timing, ensure sufficient time to recover before any other interventions or procedures.
Marking for identification	Animals are identified using microchips, which involves capture and restraint for insertion.	Distress due to restraint, short term pain of chip insertion.	Trial less aversive capture techniques (see below). Research pros and cons of sedating or anaesthetising mice. Ensure adequate checks in case of longer term discomfort.

What does this study involve doing to the animals?	What will the animals experience? How much suffering might it cause? What might make it worse?	How will suffering be reduced to a minimum?	
	Adverse effects and indicators of these	Methodology and interventions	Humane endpoints
Administration of rheumatoid arthritis inducer	Capture and restraint – distress. Aggression, vocalisation, unwilling to be caught.

Administration i.d. or s.c. – pain. Flinching, vocalisation, aggression.

Pain or ulceration around injection site. Attention to site, reduction in nest quality, body weight/food intake reduction, | Competent, empathetic capture (e.g. not by tail) and handling, habituate to handling and restraint.

Use gaseous anaesthesia for i.d.; inject into rump, not tail base (if tail base is painful, restraint by the tail will hurt). Minimise volumes and doses, use multiple sites if large volumes. Ensure injectate formulated to minimise adverse effects

Inject into rump (less risk of ulceration); never inject into the foot; if attention paid to site apply topical anaesthesia and review | Humane endpoints with respect to administration of inducer in general:
- Ulceration that is painful, shows no signs of healing or becomes infected.
- If an ulcer reaches >5 mm, the vet or senior animal technologist should be informed and consulted about treatment. Animal should be humanely killed if no signs of healing within 3 days. |

Examples of questions to consider

- Why is severe suffering needed? Is there a robust scientific justification?

- Could the protocol be run with a moderate severity limit?

- Is the 'model' translatable? How significant are the proposed benefits of the work?

- Is there a regulatory requirement for the experimental design and 'endpoint'? Can this be challenged?

- Are welfare assessment and monitoring protocols optimised?

- What more could be done to mitigate impacts on animals?

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From presentation by Thomas Bertelsen (tsbt@novonordisk.com) at 'Refining severe disease models and procedures' international meeting - August 2022
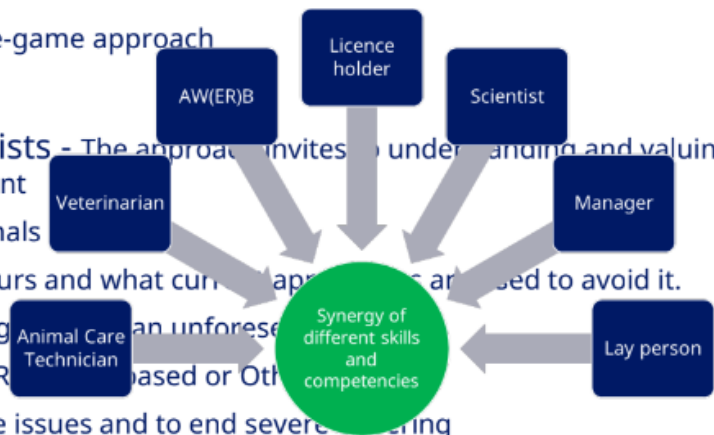
Why the roadmap works

- The RSPCA approach facilitates a **cooperative response** from licence holders and scientists, because:
  - Objective, data driven, systematic and no blame-game approach

- Dialogue with licence holders and scientists - The approach invites to understanding and valuing the roles of different people within an establishment
  - Data check: Is the scoring as 'severe' for all animals
  - Evaluation: Looking at why severe suffering occurs and what current approaches are used to avoid it.
  - Is the harm prospective or does severe suffering an unforeseen
  - Define obstacles: Are the obstacles, - Scientific, Regulatory based or Other
  - Overcome obstacles: Set out a plan to overcome issues and to end severe suffering
  - Action plan
  - Evaluate

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