Practical approaches for avoiding and reducing ‘severe’ suffering

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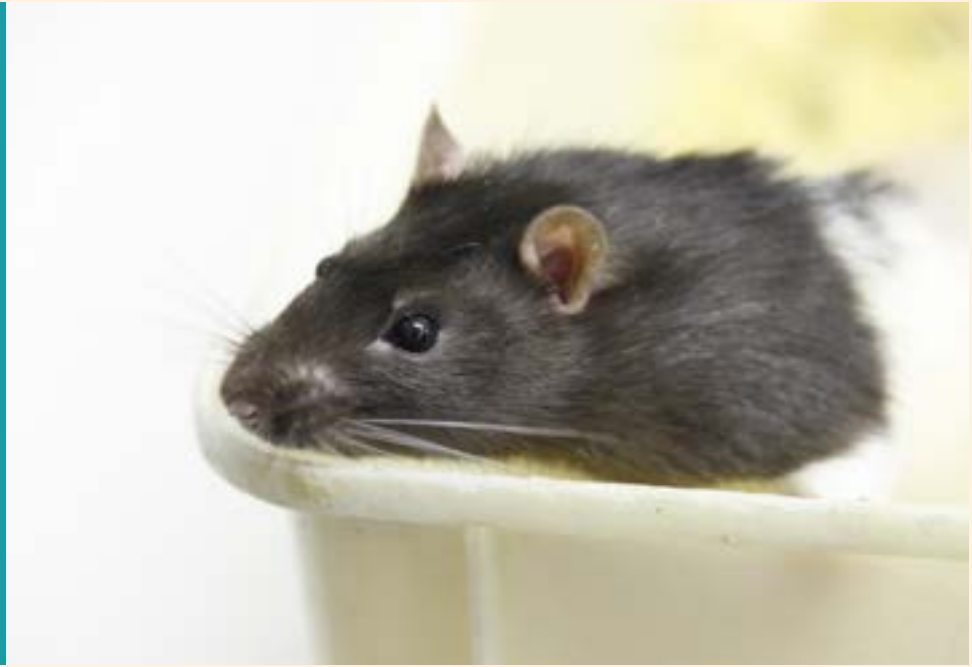
10M

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
- ✔ **Societal** concerns about harms to animals
- ✔ **Legal** requirements to minimise suffering
- ✔ **Scientific** benefits - better welfare means better science
- ✔ **Human welfare** - severe procedures are associated with emotional burnout

Everyone has a role

- Scientists
- Animal technologists
- Designated veterinarians
- Staff responsible for ensuring access to information; training and competency
- IACUCs or similar bodies
- National ethics or science committees
- Governments and regulators
- 3Rs centres
- NGOs

Our initiative

RSPCA has been **working collaboratively** with the international scientific community to identify and promote **practical steps** to **help people reduce or, ideally, avoid ‘severe’ suffering**.

Key objectives

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

  - these actions can be applied to all other levels of suffering too

- Ensure there has been **robust discussion** of the ethical issues, and a rationale that **justifies** the scientific need for ‘severe’ limits, where they still exist


PHYSICAL PAIN
PSYCHOLOGICAL DISTRESS
SICKNESS OR NAUSEA

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

Expert reports

- Avoiding mortality
- Seizures, convulsions and epilepsy
- Experimental autoimmune encephalomyelitis (EAE)
- Rheumatoid arthritis
- Sepsis
- Spinal cord injury
- Bone marrow ablation and reconstitution
- Models involving respiratory distress - *current*

focusonseveresuffering.co.uk/reports

Events

- **Brussels**, Belgium - 2016
- **Berlin**, Germany - 2017
- **Stevenage**, UK - 2019
- **Athens**, Greece - 2019
- **Manchester**, UK - 2022
- **Stockholm**, Sweden - 2022
- **Leiden**, Netherlands - 2023
- **Newcastle**, UK - 2024
- **Paris**, France - 2024

Participants: regulators, scientists, veterinarians, animal technologists and care staff, members of Animal Welfare Bodies, animal ethics committees, and National Committees etc.

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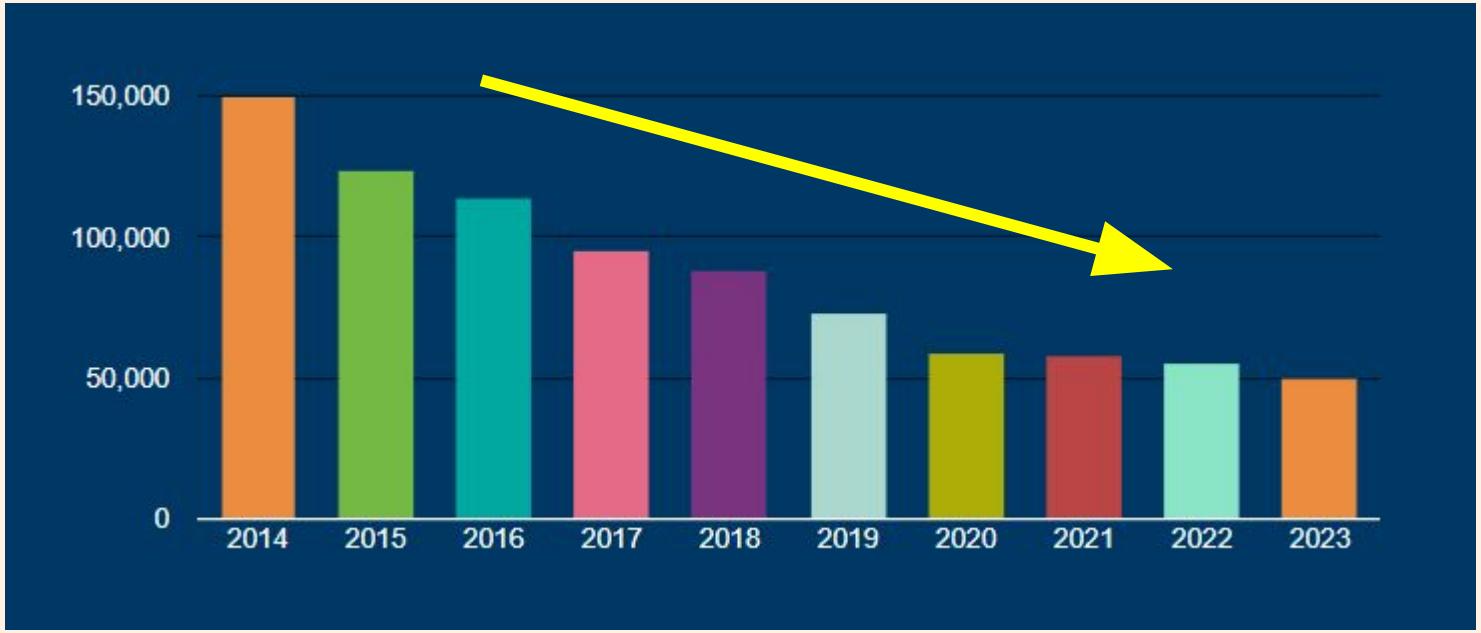


67% reduction

in experimental procedures causing severe suffering in the **UK** since 2014

How this was achieved

Experimental design

- Earlier scientific and humane endpoints
- Use of alternatives, or models at earlier disease stages
- Better husbandry and support
- Use of technology

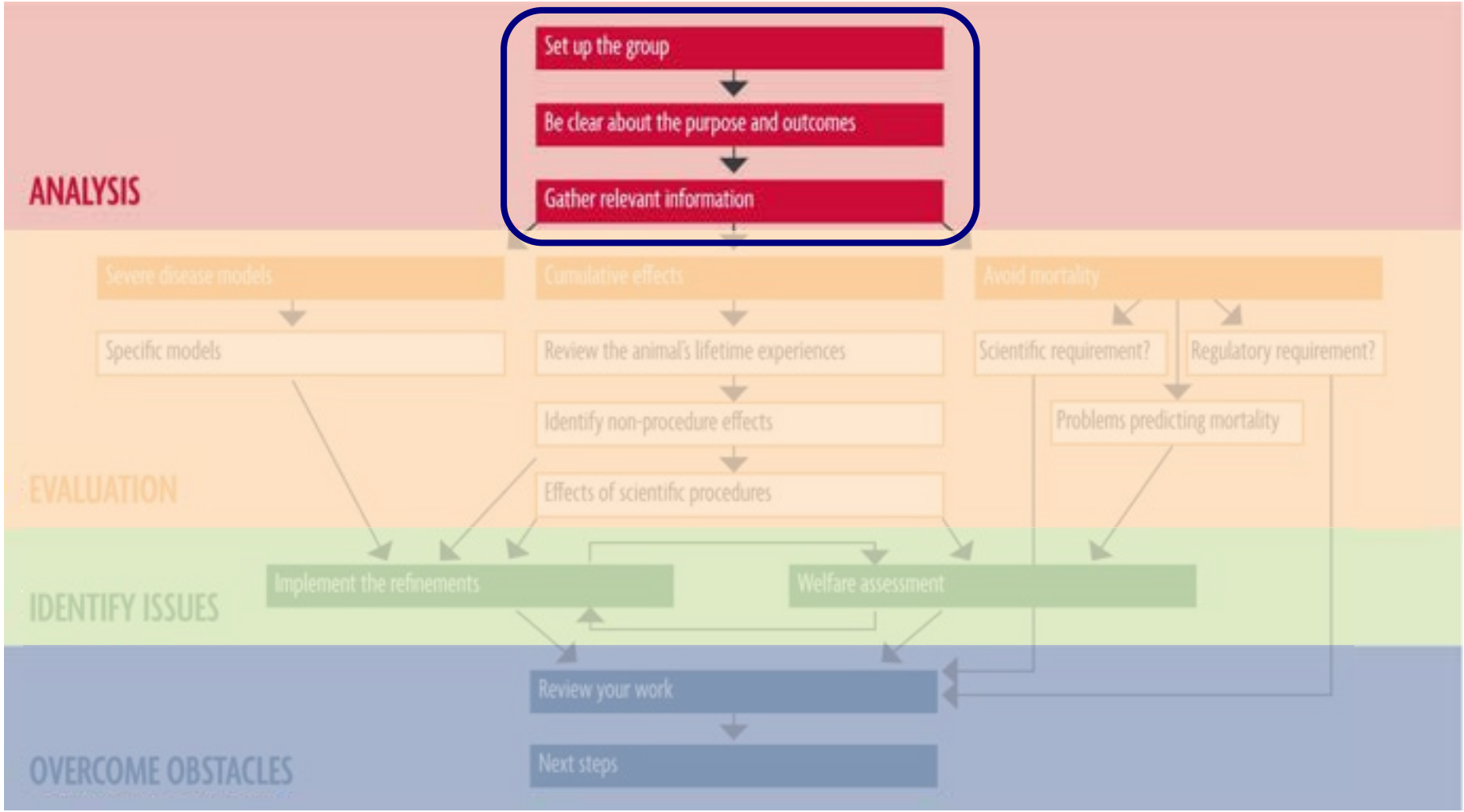
Cultural factors

- Better communication within teams
- More project review meetings, analysis of records
- More involvement of animal technologists e.g. around identifying clinical signs
- IACUC involvement

Individual institutions should adopt 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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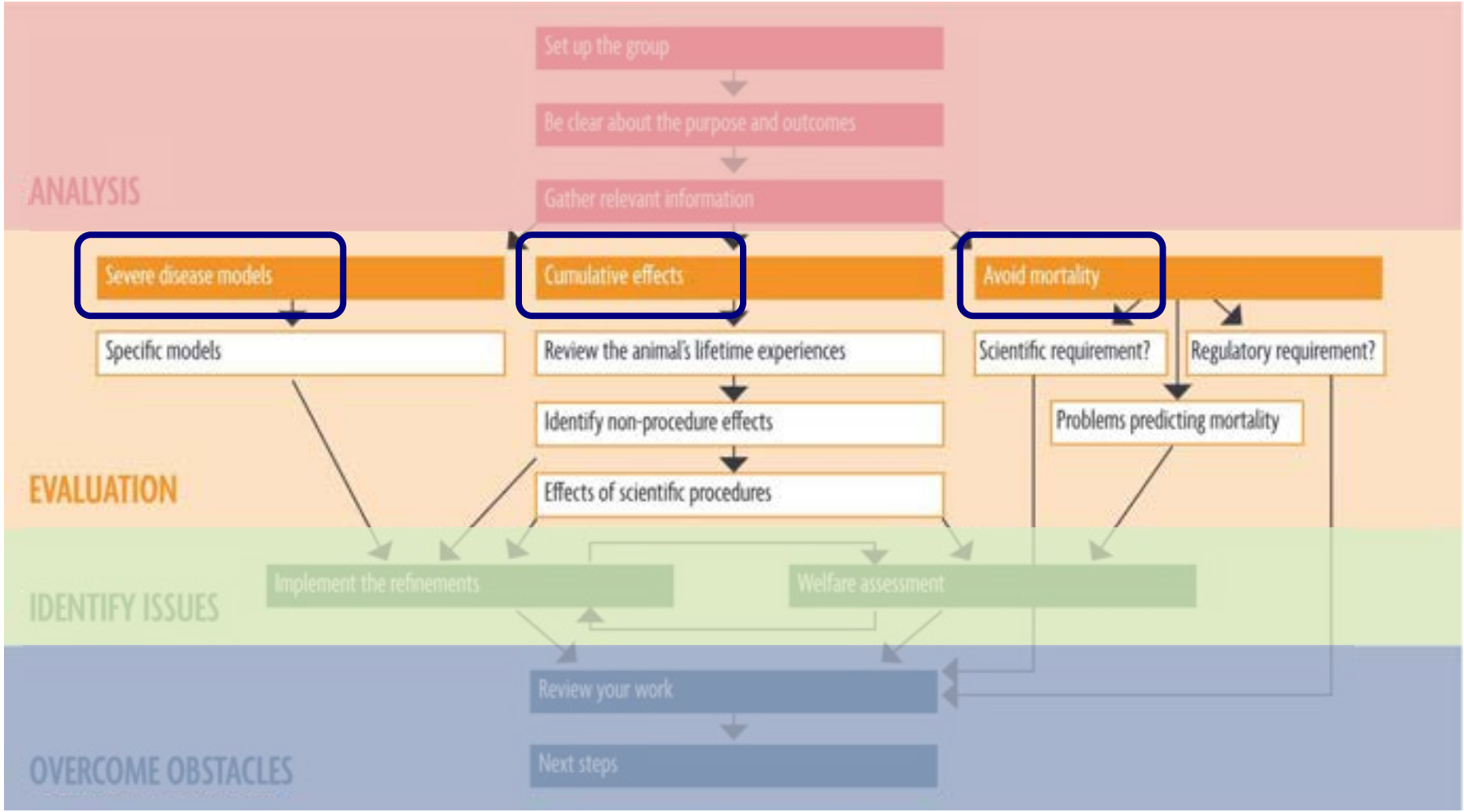
Set up the group
Be clear about the purpose and outcomes
Gather relevant information
Severe disease models
Cumulative effects
Avoid mortality
Specific models
Review the animal's lifetime experiences
Scientific requirement?
Regulatory requirement?
Identify non-procedure effects
Problems predicting mortality
EVALUATION
Effects of scientific procedures
IDENTIFY ISSUES
Implement the refinements
Welfare assessment
Review your work
OVERCOME OBSTACLES
Next steps

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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Effects of scientific procedures

Avoid mortality

Scientific requirement?

Regulatory requirement?

Problems predicting mortality

EVALUATION

Husbandry procedures

Events such as cage cleaning, and feeding, are essential for health and welfare. But they can also cause anxiety and stress, e.g. by moving mice into clean cages with none of their scent markings, or involving noisy and disturbing practices such as filling food hoppers and cleaning the holding rooms.

Examples of actions: Ensure full cage changes are done at appropriate intervals and refined to reduce stress. Minimise noise and other disturbances in the animal facility that animals find aversive, e.g. ultrasound for mice. Think about the timing of noisy practices and how this fits with circadian patterns, lighting regimes and scientific procedures. Consider what food is provided, how it is presented to the animals, and how they might interact with it, e.g. will manipulating it ready for consumption provide physical or mental stimulation?

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

Project licence number	70/6524
Protocol number	2

Non-procedure-related impacts

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.

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Procedure-related impacts

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.*	*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.*	*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.*

Mouse models of rheumatoid arthritis

A pharmaceutical company introduced the G6PI, CIA and CAIA mouse models of rheumatoid arthritis, which have the potential to cause severe suffering. This prompted a re-evaluation of the company's welfare scoring sheets and husbandry refinement protocols, with the aim of reducing suffering. The scientists and animal technologists worked together to tailor and refine monitoring systems, husbandry and procedures.

Mice used in G6PI and CAIA studies were very carefully monitored by scientists and animal technologists, to identify indicators of adverse effects and collate data on weight loss and disease scores. The observations were specific to each model, although standardised terminology was created to describe indicators. As a result, the following refinements were adopted:

- the humane endpoint for weight loss was reduced from 25% to 20%, and another endpoint added of a 15% weight loss that persisted for 5 days
- the tailored indicators (such as soft stools for CAIA) enabled study length to be reduced; e.g. the CIA studies were reduced from 30 days to 20
- disease scores were revised to include a range of indicators, as opposed to paw volume only, capturing severity more effectively and enabling endpoints to be further refined
- additional refuges are provided for DBA/1 male mice, eliminating aggression
- non-tangling nesting material is provided
- when mobility is restricted, longer sipper nozzles are fitted and food given in dishes on the cage floor
- the Mouse Grimace Scale is used to help assess acute pain

Case study

Avoiding mortality

- Is mortality difficult to predict in the strain or model?
- Is there a scientific requirement for death as an endpoint?
- Is there a regulatory requirement for mortality?

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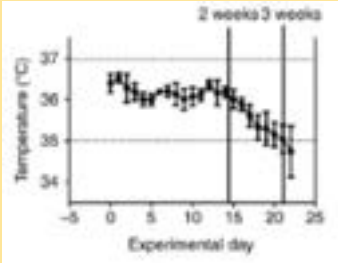
Improving ability to predict death

Review records and refine welfare assessment protocols

- What clinical signs looking for?
- How often looking?
  (frequency of monitoring)
- When looking?
  (e.g. after specific interventions; day vs night)
- How looking?
  (e.g. use of latest technology)



"all mice that had a mean decrease in body temperature of 0.7°C or greater had lymph nodes heavier than 0.5 g (100% sensitivity)"

Hunter et al 2014
https://pubmed.ncbi.nlm.nih.gov/24407190

Justification - 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?

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, R based or Oth
  - Overcome obstacles: Set out a plan to overcome issues and to end severe ering
  - Action plan
  - Evaluate

For more information

Visit our website

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Contact us

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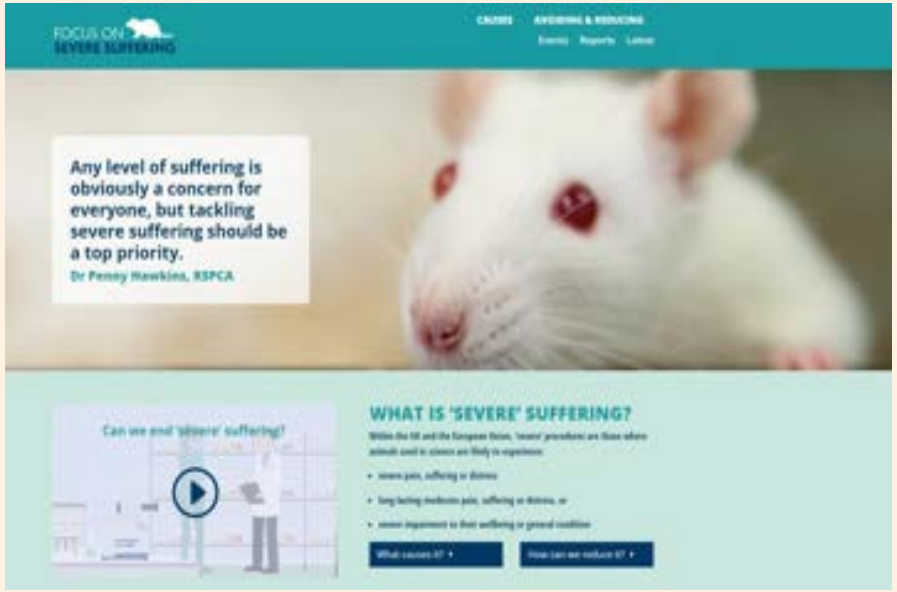

SCAN ME

RSPCA
ANIMALS IN SCIENCE