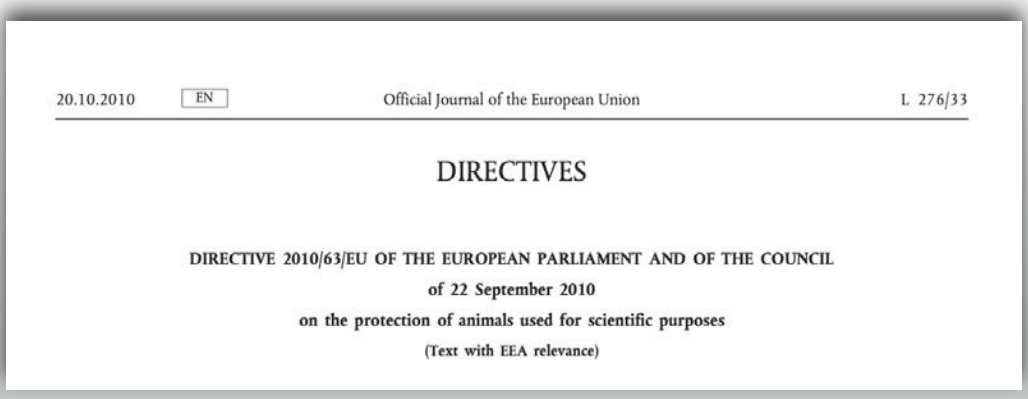
Improving nonclinical research practices: way forward

LAS webinar series organized by CroLASA in collaboration with SLAS

How should we assess the severity of procedures in experimental animals? ….and how should we judge the impact of refinements?



Severity assessment is just a regulatory exercise…..

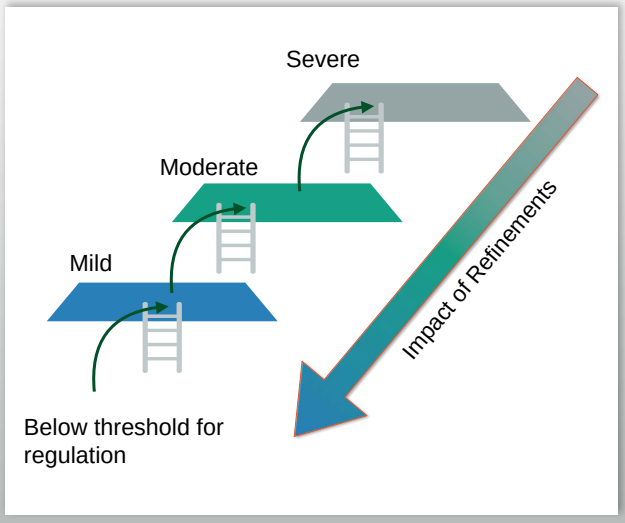


20.10.2010 EN Official Journal of the European Union L 276/33

DIRECTIVES

DIRECTIVE 2010/63/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 22 September 2010
on the protection of animals used for scientific purposes
(Text with EEA relevance)

Severity assessment is more than a regulatory exercise…..



FLAIRE LEARNING

Let us just use the examples in the EC document..

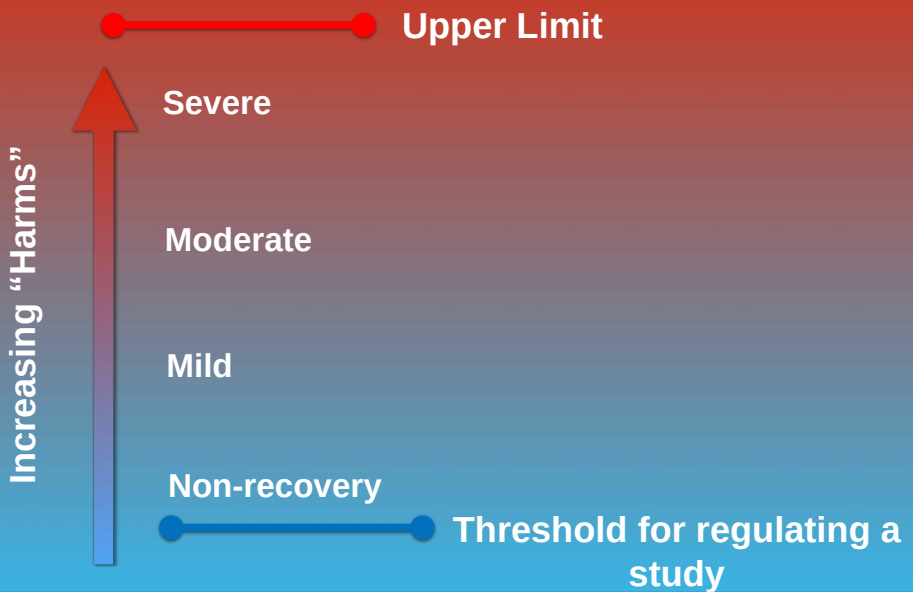
Or the FELASA/ECLAM/ESLAV Working Group report. Laboratory Animals 2018, Vol. 52(1S) 5–57

FLAIRE LEARNING

So how well are you doing at present?

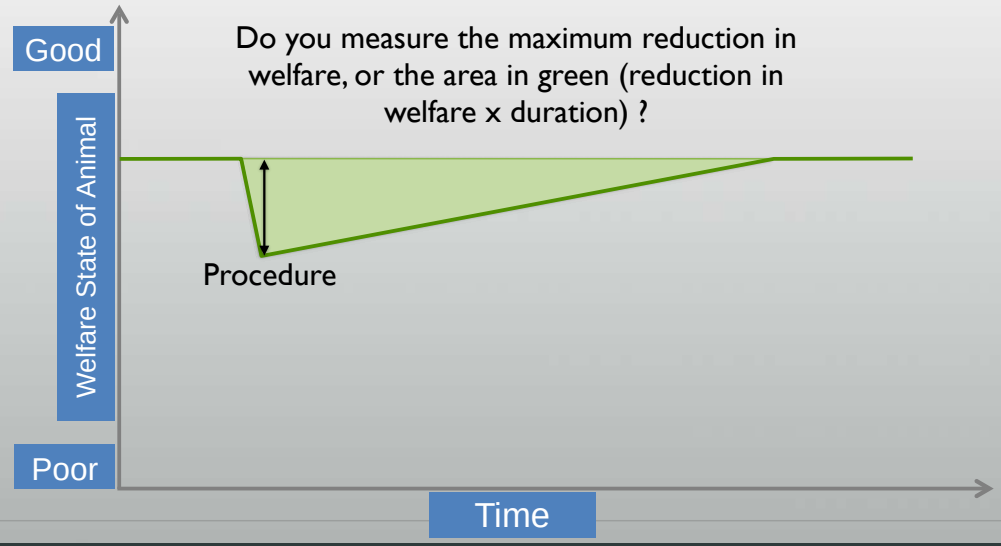
FLAIRE LEARNING

We need to recognise the uncertainty of the process of severity assessment



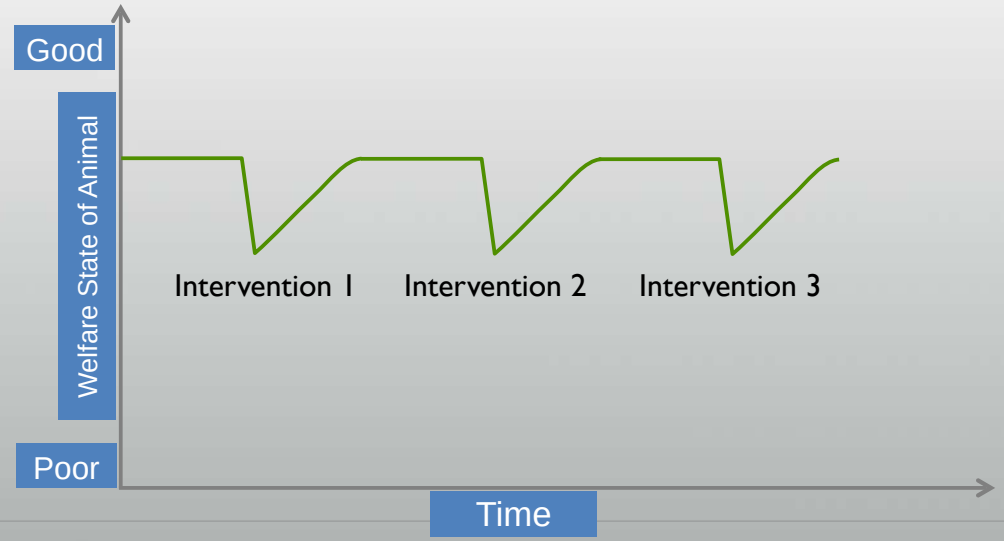
FLAIRE LEARNING

Research procedures cause a decrease in the welfare state of the animal, which then either recovers or continues to deteriorate



FLAIRE LEARNING

We also need to consider multistep procedures



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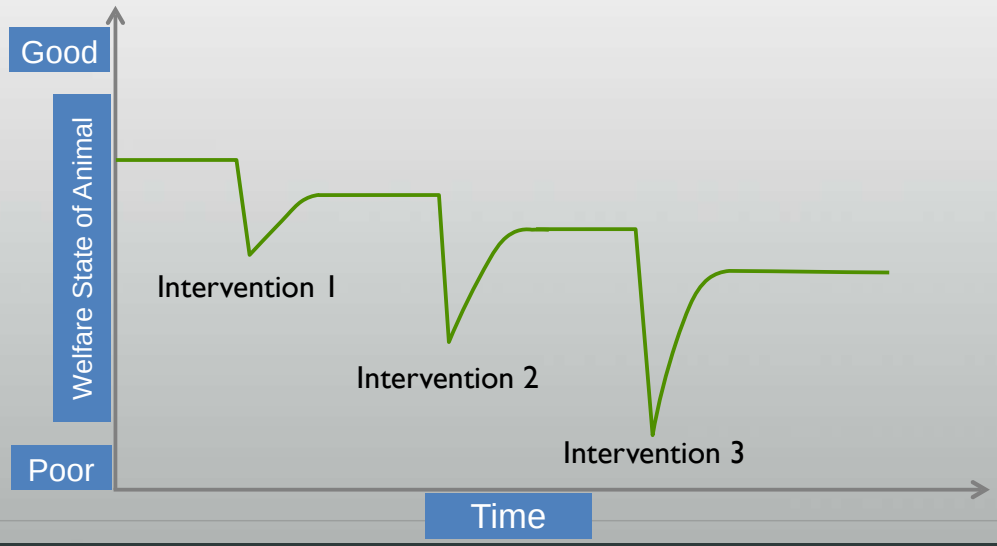

FLAIRE LEARNING

Adding up all the harms may not give us an adequate assessment of severity

The animals - transport, housing, health status, acclimatisation

Anaesthesia a surgery - perioperativ care, skills c ir

Onset of disease - Degree of clinical effects, duration of disease cess, ation of endpoints

Frequency of monitoring, what is monitored, what supportive care?

Substance administration - what volume, ? irritancy, use of positive reinforcement, handling method

FLAIRE LEARNING

So we should consider all sources of harms and how they might contribute to “severity”, but are all harms the same? How do we add up pain, hunger, thirst, “sickness” etc.?

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We have some metrics we can use for “cage side” assessment of the effects of procedures

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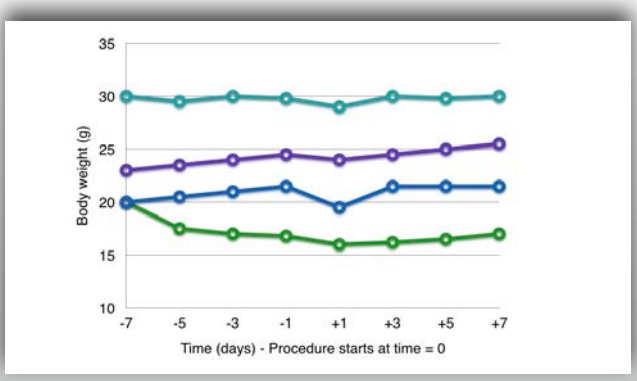

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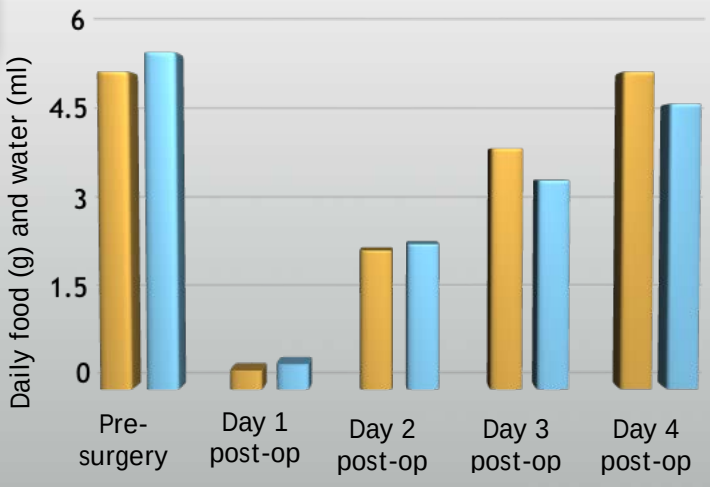
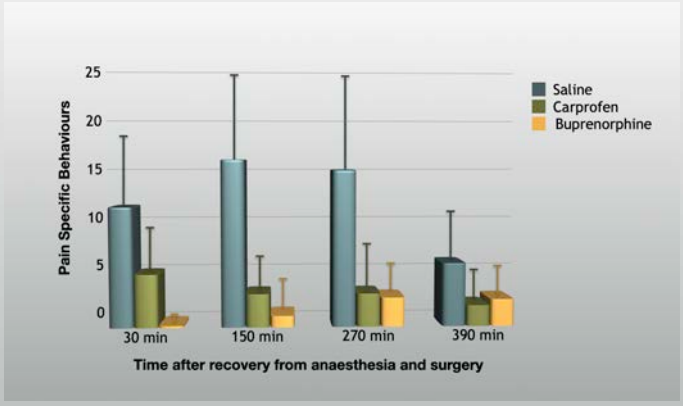


FLAIRE LEARNING

Data redrawn from Hayes et al, 2000

We have some metrics we can use for “cage side” assessment of the effects of procedures



FLAIRE LEARNING

We have some metrics we can use for “cage side” assessment of the effects of procedures

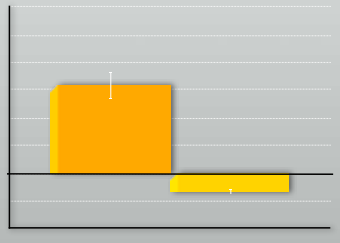
FLAIRE LEARNING

We can at least structure and record our assessments using score-sheets

	Score	1	2	3	4
1	Coat- general	Normal	Slight lack of grooming	Starey	
2	Skin tone	Normal	Mildly dehydrated	Moderately dehydrated	Severely dehydrated
3	Behaviour	Normal	Slightly dull or lethargic	Aggressive or apathetic and inactive	
4	Abdominal distension	None	Mild ascites	Obvious ascites	
5	Jaundice	None	Slighty jaundiced appearance	Mild jaundice present	Moderate jaundice present
6	Surgical wound(s)	No abnormalities noted	Mild inflammation	Wound breakdown	

FLAIRE LEARNING

We can “calibrate” our assessments from research data using cognitive bias, conditioned place preference etc.



Johanssen et al, 2001 PNAS 98, 8077-8082

FLAIRE LEARNING

Affective (emotional state) of an animal may reflect severity and can be assessed using cognitive bias and other measures

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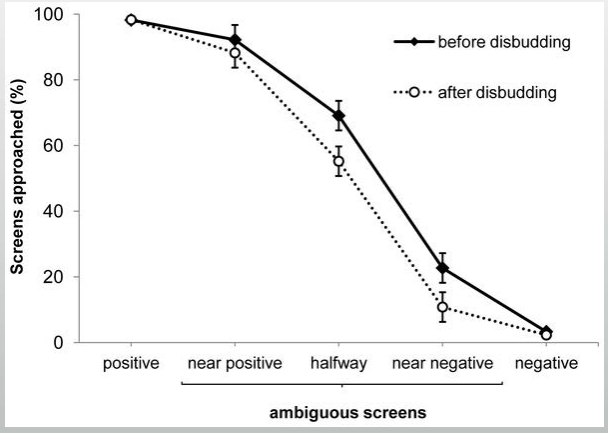


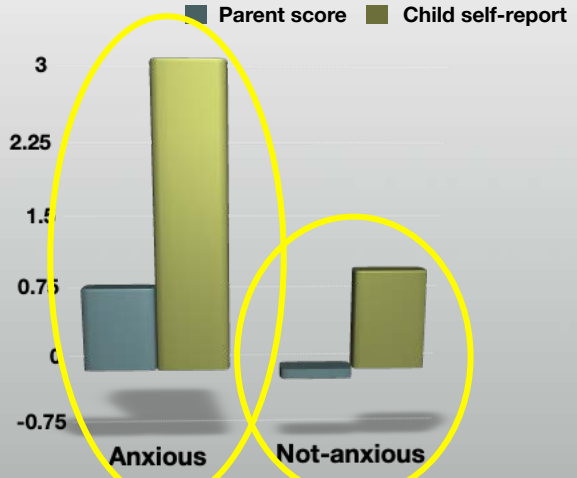
Mean ± SE approach responses of calves to each screen colour before and after disbudding.

FLAIRE LEARNING

Neave HW, Daros RR, Costa JHC, von Keyserlingk MAG, Weary DM (2013) Pain and Pessimism: Dairy Calves Exhibit Negative Judgement Bias following Hot-Iron Disbudding. PLOS ONE 8(12): e80556. https://doi.org/10.1371/journal.pone.0080556
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0080556

The affective state of the animals will influence the severity of a procedure

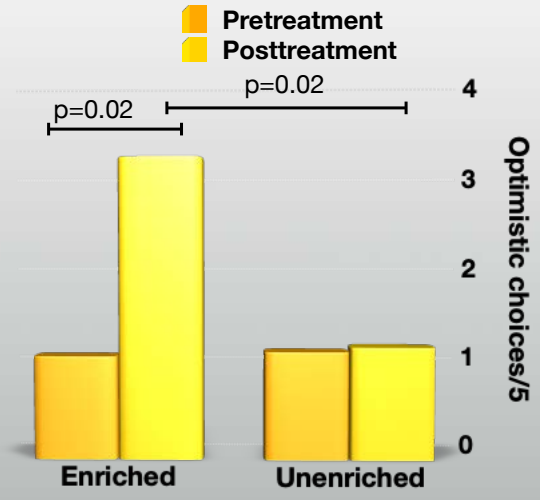
Post-operative pain score and post-operative pain threshold in children and rats



Data redrawn from: Kain, Z.N., Mayes, L.C., Caldwell-Andrews, A.A., Karas, D.E. and McClain, B.C., 2006. Pediatrics, 118(2), pp.651-658.

Data redrawn from: Liu, Y., Hou, B., Zhang, W., Sun, Y.E., Li, L., Ma, Z. and Gu, X., 2015. European Journal of Pain, 19(5), pp.733-740.

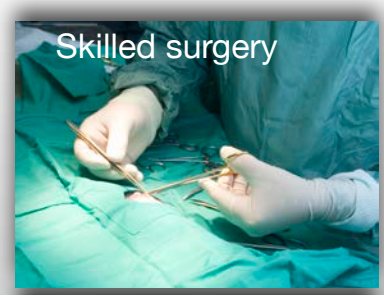
Environmental enrichment and affective state state



FLAIRE LEARNING

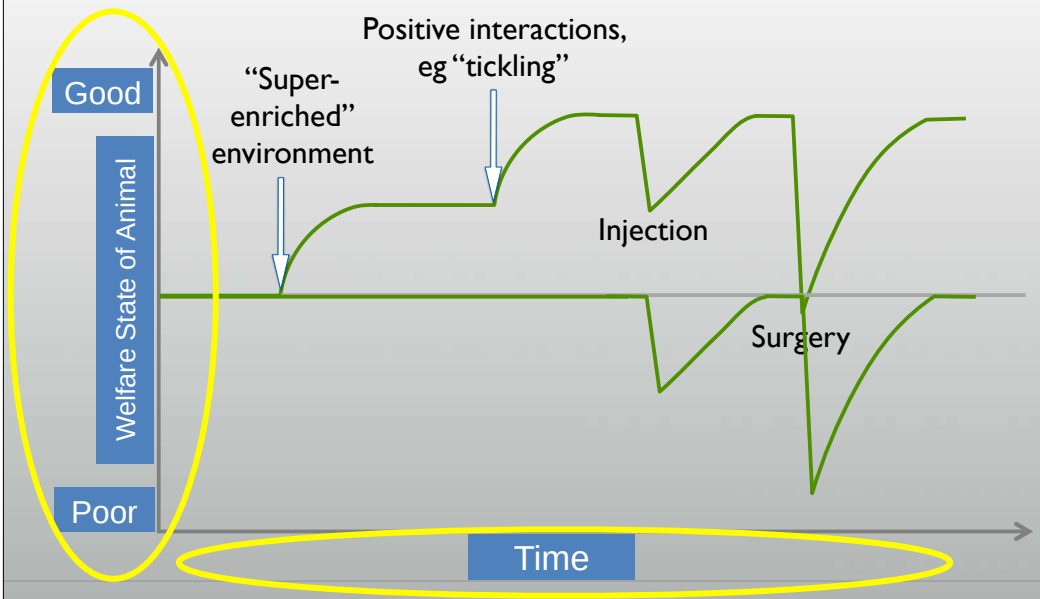
Data redrawn from Brydges, et al. "Environmental enrichment induces optimistic cognitive bias in rats." *Animal Behaviour* 81.1 (2011): 169-175.

We can induce a positive affective state by modifying handling and housing conditions



FLAIRE LEARNING

Can we have positive effects on animal welfare?
Could this reduce the severity of procedures?



FLAIRE LEARNING

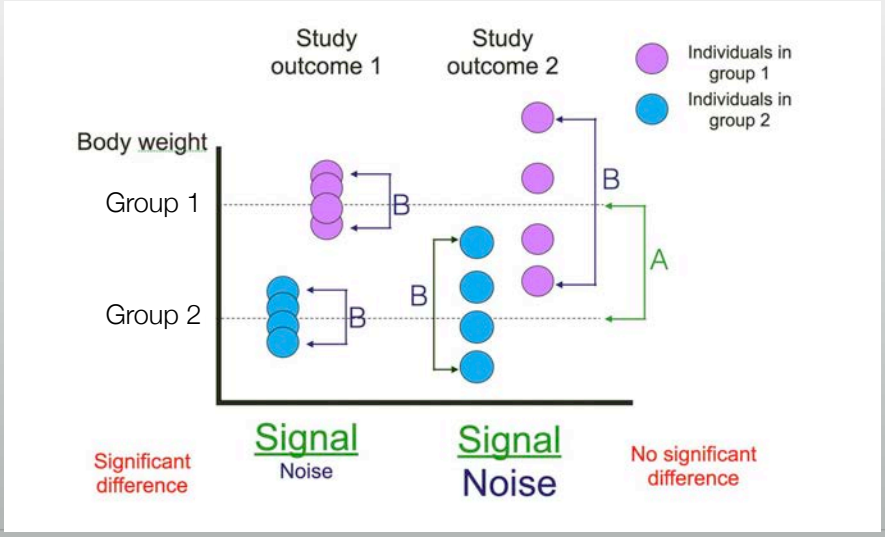
Lets look at another grading exercise

FLAIRE LEARNING

Our initial “best estimates” of severity may be based more on consensus than on metrics

FLAIRE LEARNING

Why bother? Because unnecessary harms are both detrimental to animal welfare and produce stressors that impact on experimental outcomes.



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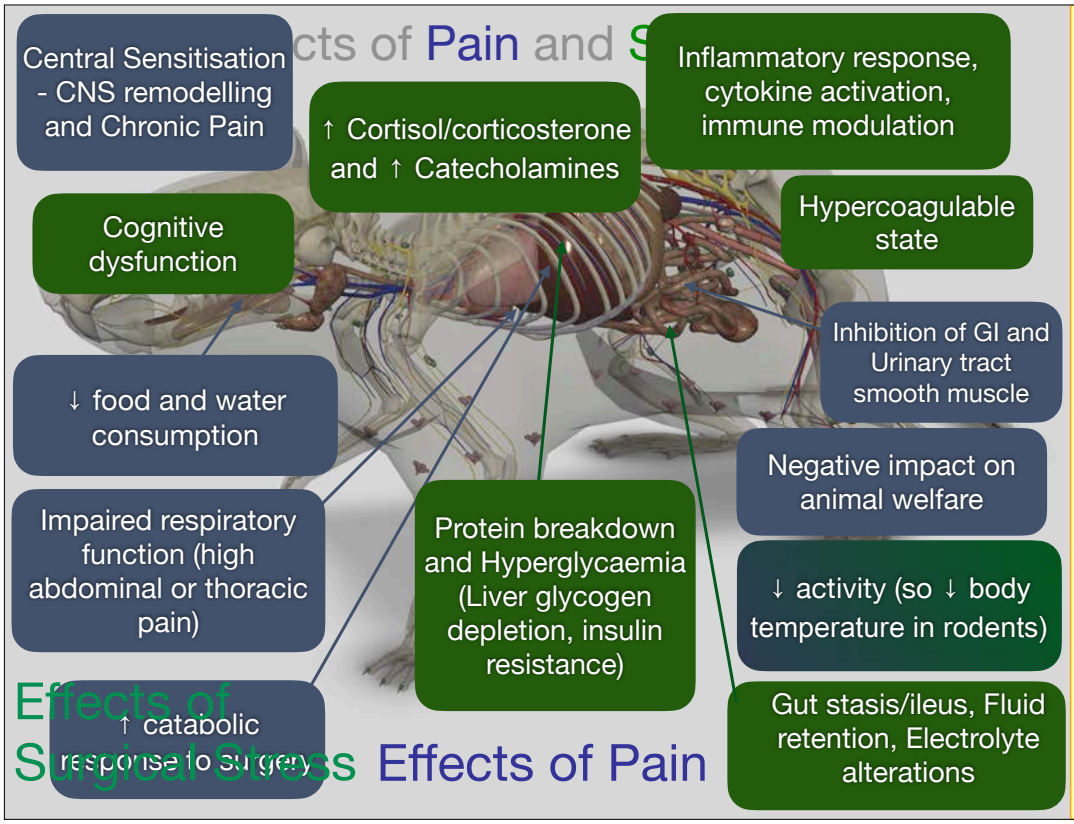

Planning stage

- Prospective severity assessment.
- Based on predicted harms and proposed refinements
- Formulate proposed. monitoring, score-sheet and humane endpoints.
- Incorporate results of review of previous study.

Review progress

- What was the welfare state of the animals?
- Review models, monitoring, score sheets, refinements and study design.
- Review severity assessment.
- Review interventions and endpoints

Study in Progress

- Assess welfare before conducting any procedures.
- Commence use of score sheet and record base-line data.

Study in Progress

- Are refinements effective?
- Are monitoring methods appropriate and effective?
- Is severity assessment appropriate?
- Are we applying appropriate humane endpoints?

Additional resources - e-learning modules on a range of topics