Severity classification – before and after the project

Severity classification in theory and in practice
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Severity assessment
Legal framework under 2010/63/EC

- Article 4(3) …eliminating or reducing to the minimum any possible pain, suffering, distress or lasting harm to animals
- Article 15(1) …all procedures are classified as non-recovery, mild, moderate or severe on case-by-case basis using assignment criteria set out in Annex VIII
- Article 15(2) … a procedure is not performed if it involves severe pain, suffering or distress that is likely to be long-lasting and cannot be ameliorated
- Article 54 (2) Member States shall collect and make publicly available, on an annual basis, statistical information on the use of animals in procedures, including information on the actual severity of the procedures and on the origin and species of non-human primates used in procedures.
Why do we need Severity Classification?

- Welfare of animals
  - More precise pre-evaluation of pain and stress
  - Documented follow-up during the study
  - More information for refinement and reduction for now and future
  - More information for possible re-use

- Increased communication between researchers and animal facility

- Transparency for general public

- PR-function?
Severity assessment – a continuous process

**PROJECT PLANNING**
- Develop *project, species and strain specific* severity assessment
- Decide on monitoring tools, frequency, type of scoring
- Agree on actions when signs of pain, distress or suffering observed

**DURING THE PROJECT**
- Consistency in observations / trained staff
- Effective day-to-day monitoring
- Good communication among all involved
- Ongoing review of assessment protocol as necessary

**AFTER THE PROJECT**
- Analysis and feedback
- Assessment and scoring of actual severity
- Statistical information
- Retrospective project assessment
- Feedback for future studies
- Reflect on further opportunities to implement Three Rs

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Severity classification in harm assessment

- Pain, suffering, distress and lasting harm to the animals are assessed before the experiment and classified

  Non-recovery (SV1)
  Mild (SV2)
  Moderate (SV3)
  Severe (SV4)

- Not only the pain but also suffering
Severity classification

Non-recovery \text{ sv1 }

- Procedures which are performed entirely under general anaesthesia from which the animal shall not recover consciousness
- The animal is euthanatized under the same anaesthesia
Severity classification

Mild sv2

- Procedures on animals as a result of which the animals are likely to experience short-term mild pain, suffering or distress; as well as procedures with no significant impairment of the well-being or general condition
Severity classification
Mild sv2

- Administration of substances with appropriate volumes
- Pharmacocinetic study with a single dose and limited number of blood samples
- Non-invasive imaging with appropriate anesthesia
- Superficial procedures like ear and tail biopsies, non-surgical sc mini-pump implantation
- Induction of tumours, or spontaneous tumours, that cause no detectable clinical adverse effects
- Short-term restraint in metabolic cage < 24 hours
- Short-term deprivation of social partners
Severity classification

Moderate sv3

- Procedures on animals as a result of which the animals are likely to experience short-term moderate pain, suffering or distress, or long-lasting mild pain, suffering or distress, as well as procedures that are likely to cause moderate impairment of the well-being or general condition.
Severity classification

Moderate sv₃

- Frequent application of test substances which produce moderate clinical effects
- Surgical operations, like thoracotomy, craniotomy, laparotomy, orthopaedic surgery with effective stabilisation and wound management; appropriate analgesia and anesthesia
- Tumours which are expected to cause moderate pain or distress
- Creation of genetically altered animals through surgical procedures
- Metabolic cages up to 5 days
- Withdrawal of food for 48 hours in adult rats
Severity classification

Severe sv4

- Procedures on animals as a result of which the animals are likely to experience severe pain, suffering or distress, or long-lasting moderate pain, suffering or distress, as well as procedures that are likely to cause severe impairment of the well-being or general condition.
Severity classification
Severe sv4

- Toxicity testing where death is the end point
- Tumours that are expected to cause progressive lethal disease
- Surgical and other interventions in animals under general anaesthesia which are expected to result in severe or persistent moderate postoperative pain; thoracotomy without analgesia
- Use of metabolic cages involving severe restriction of movement over a prolonged period
- Complete isolation for prolonged periods of social species
- Immobilisation stress to induce gastric ulcers or cardiac failure in rats
How to do the preliminary assessment?

- What will be done to the animals?
- Go through all the procedures to an individual animal
- Take the cumulative effect into account
- One injection is mild but 200 injections is not
- Refinement may have effect on severity: try always find refinement possibilities
- Early humane end point can change the class – even from severe to moderate
- Examples in the directive can help
- Class severe is very severe
- The final class is chosen according to the most severe procedure to an animal
- Subprojects may have different classes
Assessment in ELLA licence

- Severity assessment is mandatory in the project license application
- ELLA (Animal experiment board) may change the class based on the directive examples, experience etc.
- Refinement and early humane end points can change the class even in the ELLA-process
Specific humane end points

Earlier end point may change severity

Fig. 4 Appearance of mouse front paws with progressively severe CIA arthritis. In this example scheme, 0 normal, 1 digit swollen, 2 digits and pad swollen, 3 wrist/tangle, pad and digits swollen. (Courtesy Remi Oloye, Alex Vugler; UCB Celltech)

Assessment during the project

- Often team work
  - Researchers, animal technicians, veterinarian
- Create appropriate protocols and scoring systems for assessing behaviour and clinical sings
- Continuous observations
  - Responses to the procedures
  - Clinical signs, any changes in behaviour etc.
- Proper documentation is important

- The procedure can be more severe than expected. If so, you need to inform ELLA and apply for the change.
## Example of scoring

<table>
<thead>
<tr>
<th>General clinical signs</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Appearance</strong></td>
<td></td>
</tr>
<tr>
<td>5-10% weight loss</td>
<td>1</td>
</tr>
<tr>
<td>11-15 % weight loss</td>
<td>2</td>
</tr>
<tr>
<td>16-20% weight loss</td>
<td>3</td>
</tr>
<tr>
<td>20% + weight loss</td>
<td>HEP</td>
</tr>
<tr>
<td>Coat slightly unkempt</td>
<td>1</td>
</tr>
<tr>
<td>Slight piloerection</td>
<td>2</td>
</tr>
<tr>
<td>Marked piloerection</td>
<td>3</td>
</tr>
<tr>
<td><strong>Body function</strong></td>
<td></td>
</tr>
<tr>
<td>Rapid, slow or deep breathing-slight</td>
<td>1</td>
</tr>
<tr>
<td>Rapid, slow or deep breathing-moderate</td>
<td>2</td>
</tr>
<tr>
<td>Rapid, slow or deep breathing-marked</td>
<td>3</td>
</tr>
<tr>
<td>Food and water intake</td>
<td></td>
</tr>
<tr>
<td>Not drinking up to 10% of body wt per 24 hrs</td>
<td>1</td>
</tr>
<tr>
<td>Not drinking at all</td>
<td>3</td>
</tr>
<tr>
<td>Reduced food intake</td>
<td>1</td>
</tr>
<tr>
<td>Anorexia</td>
<td>3</td>
</tr>
<tr>
<td><strong>Behaviour</strong></td>
<td></td>
</tr>
<tr>
<td>Slightly decreased mobility</td>
<td>1</td>
</tr>
<tr>
<td>Markedly decreased mobility</td>
<td>2</td>
</tr>
<tr>
<td>Significant mobility problems</td>
<td>3</td>
</tr>
<tr>
<td>Immobility &gt;24h</td>
<td>HEP</td>
</tr>
<tr>
<td>Tense and nervous on handling</td>
<td>2</td>
</tr>
<tr>
<td>Markedly distressed on handling, e.g. shaking, vocalizing, aggressive</td>
<td>3</td>
</tr>
</tbody>
</table>
Actual severity

- Actual severity classification must be done to every individual animal – do it immediately after the final procedure.

- How much pain, distress and suffering did the procedures cause in reality – during the whole project?

- The class can differ to that expected – both ways.

- Remember the possible cumulative pain, suffering and distress.

- Each animal’s whole-life experience.

- Previous procedures in the case of re-use.

- Information will be sent to authorities.
What if an animal is found dead?

- If an animal is found dead (not euthanized) this may be a consequence of the experimental procedure or unrelated causes.

- The actual severity should be reported severe unless it is known that animal did not experience severe suffering before death.

- If it is unlikely that there was severe suffering before death, the actual severity is classified according to the known experience before death.

- If the death was caused by unrelated reasons like disease or injury the classification must be based on the harm caused by experimental procedures.
Retrospective assessment

- When the project was originally classified as severe
- Always in the projects where the non-human primates have been used
- The researcher will provide authorities (in Finland ESAVI) all the information
  - How well the aims of the project were achieved
  - Animal species and number used
  - The actual severity of the procedures
  - Could the knowledge gained from the project use to help implementation of 3Rs in other projects
Severity classification aims also at refinement

- In severity classification, you need to go through all the procedures on animals – and find out the refinement possibilities in each step
- Actual severity assessment may bring up some new ideas for the next time
- In retrospective assessment, you need to explain what refinement has been used and developed during the project
- New refinement methods for similar projects
Refinement – even during project

- **Spinal cord injury studies, EAE models, other studies with hind leg paralyses**
  - Improve the cage bottom with a grid, it helps moving
  - Provide easy access to tasty food, adaptation beforehand
  - Soft bedding, extra heating under cage or in room
  - Other supportive treatment
Questions?