

# **Humane Endpoints: Experiences of the UK Home Office Inspectorate**

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# Types of humane endpoints

- ◆ 1) severity cut-off - animal killed, or taken off experiment, to avoid further suffering,
- ◆ 2) “objective-achieved” endpoint - sufficient data obtained for the purpose of the experiment to be met
- ◆ 3) an “objective-cannot-be-achieved” point - unlikely to be sufficient valid data if continued.
- ◆ ?4) decision point – to different path, when the first has met one or more of the three types of end-points above.

# UK Animal Scientific Procedures Inspectors

- ◆ Part of the Home Office (best government department location for keeping science/animal welfare balance)
- ◆ Required by the law to be medics or vets
- ◆ Usually also have biomedical science qualifications or experience
- ◆ Advise on applications for licences and certificates as well as visiting and reporting
- ◆ Must be consulted by the minister before the granting of a licence
- ◆ Each assess ~3% of the UK's licensable scientific work on animals
- ◆ Make assessments on a wide range of programmes of experimental work

- ◆ The assessment is usually interactive
- ◆ The legal requirements and conditions give useful tools in promoting humane endpoints

# Animals (Scientific Procedures) Act (ASPA) - Brief legal requirements

For scientific work on vertebrates which may involve pain, suffering, distress or lasting harm

- ◆ The **Person** working must have a licence
- ◆ The **Programme** of work ("project") must be licensed
- ◆ The **Place** at which the work is done must have a certificate

So there is control on Who What and Where

# There is legal specification ...

- A project licence is a licence granted by the Secretary of State specifying a programme of work
- and authorising the application, as part of that programme, of specified regulated procedures
- to animals of specified descriptions at a specified place or specified places.

Note a “regulated procedure” is an intervention or omission for a scientific purpose that may cause pain suffering distress or lasting harm

## And legal constraints ....

5(5) The Secretary of State shall not grant a project licence unless he is satisfied -

(b) that the regulated procedures to be used are those which ..... cause the least pain, suffering, distress or lasting harm, and are most likely to produce satisfactory results.

# There is also control during use - licence conditions

6. For any procedure, the degree of severity imposed shall be the minimum consistent with the attainment of the objectives of the procedure, and this shall not exceed the severity limit attached to the procedure. The minimum number of animals of the lowest neurophysiological sensitivity shall be used in procedures causing the least pain, suffering, distress or lasting harm.

(Home Office Guidance: lowest neurophysiological sensitivity = the least capacity to experience pain, suffering or distress)

# Inspectors use the 3Bs

◆ Bribery

◆ "It'll be easier for me to recommend grant if..."

◆ Blackmail

◆ "If you do not keep to this endpoint you'll be reported for not complying with condition 6"

◆ Bloodymindedness

◆ Persistence that tires out opposition

The licence application prompts may help  
Objective should be specified  
(otherwise difficult to set objective-related endpoints)

### 17a Objectives of the programme

List below overall aim (if appropriate) and specific objectives. Each objective should be one sentence long. An objective should not be too broad and should lead to a definable outcome.

and adverse effects must be listed ....

#### (v) Description of the procedure,

List the steps of the experimental protocol, indicating which are optional.

(vi) For each step in subsection (v) above give the specific adverse events/frequency/controls and endpoints. }

# Examples of routine end-points

- ◆ Animals whose body weight falls more than 25% below the initial weight will be humanely killed
- ◆ Animals which show eye discharge that does not respond to treatment will be humanely killed
- ◆ Mice with a tumour of more than 15mm on average of two diameters taken at right angles will be humanely killed

Typical score sheet – used for setting “tolerable severity” endpoint

ANIMAL IDENTIFICATION		SCORE
<b>APPEARANCE</b>		
Normal		0
General lack of grooming		1
Coat staring/Piloerection, hunched up		2
<b>FOOD AND WATER INTAKE</b>		
Normal		0
Body weight down <5%		1
Body weight down <10-15%		2
Body weight down > 15% or fails to eat food offered		3
<b>NATURAL BEHAVIOUR</b>		
Normal		0
Minor changes		1
Less mobile and alert, isolated		2
Self mutilation, cachexia		3
<b>PROVOKED BEHAVIOUR</b>		
Normal		0
Minor depression		1
Less mobile		2
Very weak and precomatose		3

**OVERALL JUDGEMENT:**

0-3	Treat as normal
4-8	Monitor carefully
>8	Kill humanely

Any animal scoring a 3 in any category will be humanely killed

Any animal losing 20% of its maximum body weight will be humanely killed

Any animal with a lesion >14mm will be humanely killed

# Severity endpoints

- ◆ Recognisable signs or combinations which give level at which no further suffering is tolerated
- ◆ Prediction features the give reliable guide to end-effect e.g.
  - Pallor shows effectiveness of anticoagulant rodenticides
  - Body temperature fall below 35°C useful endpoint in infectious agent challenge studies

Allow for flexibility - This score sheet – was unusable in practice!

ANIMAL IDENTIFICATION		SCORE
<b>APPEARANCE</b>		
Normal		0
General lack of grooming		1
Coat staring/Piloerection, hunched up		2
<b>FOOD AND WATER INTAKE</b>		
Normal		0
Body weight down <5%		1
Body weight down <10-15%		2
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# Objectives:

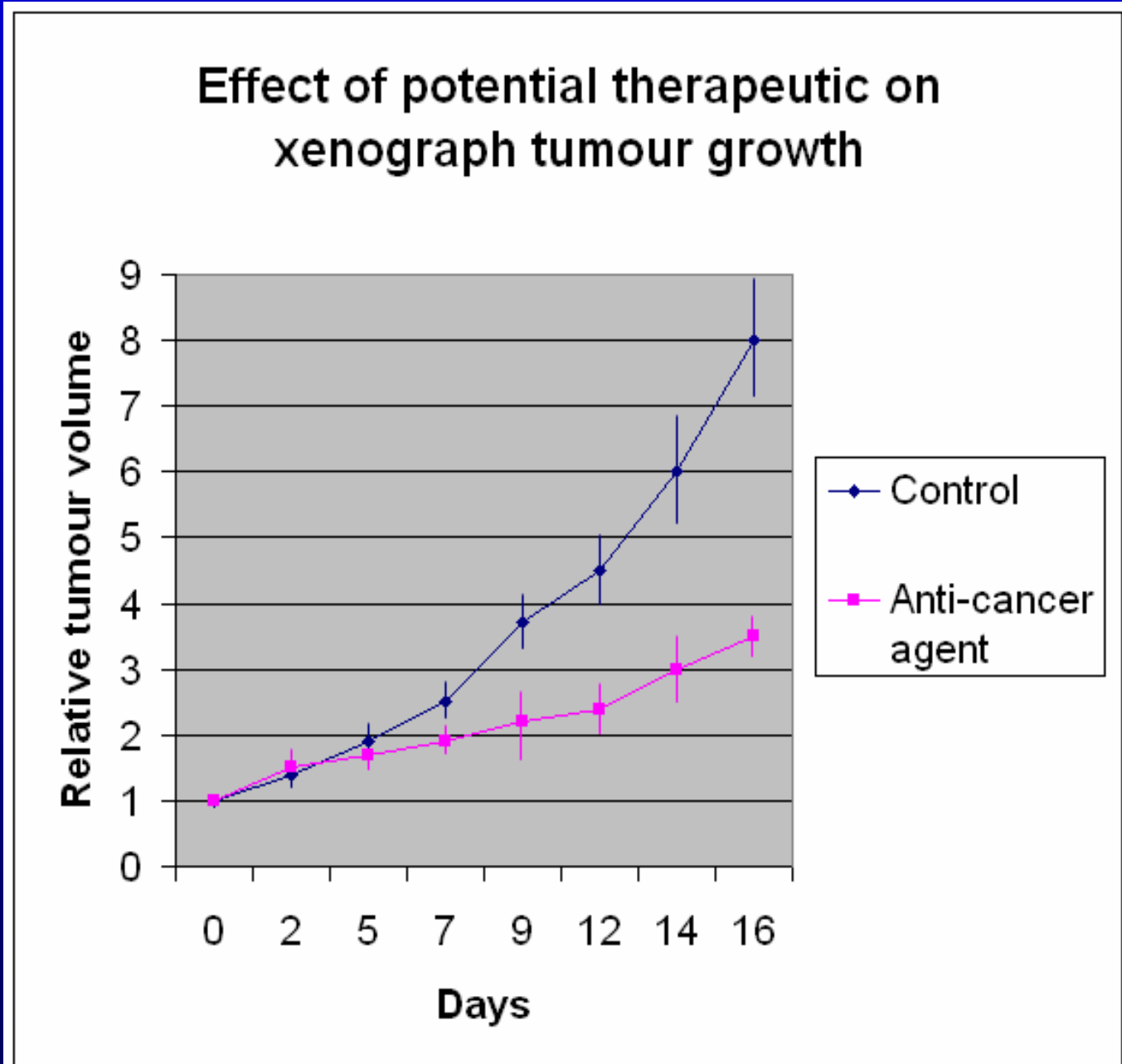
- Objective  $\equiv$  what you want to achieve
- Not in legislation but in conditions
- integral to assessment of “most likely to produce satisfactory results”
- and to setting objective-related end-points

# Example of when an objective-achieved end-point could be set

There is a clear difference before day 12.

Objective - achieved humane end-point could be set by day 12.

The rest is unjustifiable suffering



# Objective-related endpoints

- ◆ Particularly applicable when results to date can be determined before next collection point
- ◆ Also for serial designs
- ◆ Could also be set from pilot experiments

# Serial designs (simplistic!)

- ◆ Set criterion
- ◆ 1<sup>st</sup> result – Y, N, ? for meeting criterion
- ◆ If equally probable –  $P=0.33$  for each
- ◆ 2<sup>nd</sup> result – if same as first  $P$  (chance) = .1
- ◆ 3<sup>rd</sup> result – if same as others  $P = .03$
- ◆ If objective is to obtain that degree of chance probability, then that is end-point

# Pilot experiments

- ◆ Trials with small numbers
- ◆ Allow note of adverse effects, time to treatment effect, general variability, technical problems, etc.
- ◆ Guard against over optimism
- ◆ Adverse effects noted can help set severity endpoints
- ◆ Time to treatment effect can set objective-related endpoint

# Pilot experiment example

- ◆ Objective – will a particular type of radiofrequency probe give control of bleeding after hepatic surgery?
- ◆ Technical problems sorted out in terminally anaesthetised animals
- ◆ 2 animals used with hepatic surgery and recovery to assess when bleeding controlled and time after which continued bleeding shows failure
- ◆ Objective –achieved or not achievable endpoint set at that time point

# UK Inspectors at work

- ◆ 53 projects seen for consistency, workload management, special referrals in 2004
- ◆ All show evidence of efforts to minimise severity
- ◆ Half show evidence of seeking specific severity endpoints
- ◆ Some 10% show evidence of seeking objective-related endpoints
- ◆ But much of the negotiation is not written down.

# In conclusion

- ◆ I think we're getting there
- ◆ But the message to pursue humane endpoints is still worth repeating
- ◆ And there are still useful new endpoints to find