Beagle Dreams

An AWF Case Study

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A CASE EXPLORING THE ROLE OF VETS WITHIN THE ANIMALS (SCIENTIFIC PROCEDURES) ACT 1986 ACTING IN THE INTEREST OF WELFARE WHEN THERE ARE STRONG COMPETING INTERESTS AND PRESSURES

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Beagle Dreams

The novel pharmaceutical compound (test substance) on study is certain to be a 'wonder drug'; it is a new treatment that will revolutionise cancer therapy and save the lives of many women with breast tumours. Much money (approx. $15 million) has already been invested in the development of this medicine and it is on the verge of starting clinical trials (in humans).

In this study, conscious dogs are given either vehicle (placebo) or the test substance by slow intravenous injection over 2 minutes while an ECG is being recorded. The dogs receiving vehicle (2 males, 2 females) show absolutely no clinical signs and their ECGs are normal.

The dogs receiving test substance (2 males, 2 females) all collapse within 15 seconds of receiving the test substance. They lose consciousness and appear to be 'dreaming' violently. Once the infusion stops they all regain consciousness within 1 minute; most seem to remain 'confused' or dazed for a considerable period after the injection but all made a full recovery. On examination the ECGs show a series of severe (life-threatening) dysrhythmias.

The company wishes to proceed with the second stage of this study injecting a total of 24 dogs with test substance. The 'test substance' cannot proceed to clinical trials without this next part of the study. There is a lot of money at stake.

The ECGs showed really profound changes: tachycardia ➔increase in T wave polarity ➔ reversal of T wave ➔ profound bradycardia ➔ AV dissociation ➔ escape complexes ➔ premature complexes ➔ 1st degree AV block etc. But the ECGs returned to normal after 5 minutes with no apparent lasting harm.

You are the veterinary cardiologist charged with reporting the ECG findings. Should these dogs be put on study? After all, they all recovered and this drug will save many human lives. Did they actually 'suffer' during this episode? They lost consciousness – surely a bad dream didn't hurt them?

If you refuse to let the company perform the next study they will take it to a contract laboratory in the Far East, where animal welfare is not important, and your company will lose the contract It's your call as MRCVS and veterinary cardiologist.

What should you do? (continue for answers)

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Stakeholders and relevant considerations

- **The dogs**

Did the dogs suffer? Was their welfare compromised? From the “fit and healthy” perspective it was compromised because their biological fitness was reduced (they collapsed and had abnormal heart function). From the “mental/subjective” perspective they appeared to be dazed and confused which is likely to be stressful and be associated with a negative mental state.

We should also consider the impact of housing and husbandry on the welfare of experimental animals. Dogs are likely to be housed in a kennel and run with a platform. They may have controlled access to a play room (e.g. 1 hour daily).

- **Personal licence holder (doing the experiments)**

They carry out the scientific procedures, under the A(SP)A, so need to be compassionate and well trained.

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Stakeholders and relevant considerations

- Veterinary cardiologist

Every new medicine is tested to see if it produces the expected result i.e. a positive pharmacological action but the test procedure is also used to determine if there are any adverse reactions (known as side effects). Side effects may be seen during the study (as clinical signs) or picked up after the study by:

- A pathologist who will examine the tissues post mortem
- A veterinary cardiologist who examines the ECGs taken during the study

Occasionally (as in this case) the severity of clinical signs dictates that a veterinary cardiologist looks at the traces during the study. Once the cardiologist looks at the traces, they may decide that the findings are sufficiently severe to call into question the continuation of the study. A discussion between the veterinary cardiologist and the Study Director will be the starting point but as an MRCVS, the Home Office would support your stance on terminating the study.

As an MRCVS, your constant endeavour will be to ensure the welfare of the animals committed to your care (even via ECG traces).

- You could argue that your job is to act in the interests of the animals – leaving others (the Study Director, the client company, the Named Veterinary Surgeon and the Home Office Inspector) to decide whether, ethically, it should proceed to stage 2.
- Your decision may mean that this potentially life-saving drug may not complete pre-clinical trials and therefore may not reach clinical trials.

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Stakeholders and relevant considerations

- **American pharmaceutical company**

They have a strong commercial interest to proceed; this compound looks like a sure-fire commercial winner. Animal welfare is unlikely to be their top priority. What is the discomfort of a few dogs compared to the earning power of a billion-dollar medicine?

- **Study director (SD) who holds a Personal Licence**

The SD organises all the study components from the study protocol (study plan) to the final report with all the dosing and testing in between. In overall charge of this specific study; the SD will be the main liaison between the client and the company. The SD wants their client company to be successful, but is keen to uphold high standards of animal welfare as well.

- **Home Office inspector**

The A(SP)A is administered by the Secretary of State at the Home Office, through a network of Home Office Inspectors. They visit research establishments and study applications for licences to work on animals, to ensure the work is justified.

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Stakeholders and relevant considerations

- **Project licence holder**

Usually a senior person within the company with overall responsibility for a study performed under the A(SP)A. They ensure that the work is done within the conditions of the licence and that personal licensees are suitably trained.

- **British contract research company**

Performs work for a range of different companies. Want to be commercially successful, but probably want to ensure high standards of animal welfare as well. Not doing so could damage their reputation and lose further contracts.

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Relevant legislation and professional guidance

"…constant endeavour will be to ensure the welfare of the animals committed to my care." RCVS declaration

"Make animal welfare your first consideration in seeking to provide the most appropriate attention for animals committed to your care." RCVS GPC

The **Animals (Scientific Procedures) Act 1986** covers regulated procedures performed on protected animals and aims to ensure that any research using animals is original and justified, and has no alternative. Under the **ASPA** there are strict controls that ensure the study is conducted within carefully defined parameters. Perhaps most relevant to this case is the **severity** banding – this states exactly how much pain and / or suffering the animals are expected to experience. The bands are mild, moderate and substantial.

Experiments with a moderate or substantial banding will have had to undergo a rigorous interrogation from the company's **Ethical Review Committee (ERC)**, which has at least 50% lay members. The ERC looks at the cost (in terms of severity) to the animal and the benefit (in terms of therapy) to the final patient before giving a study the go-ahead.

This test substance was cleared for a moderate severity band.

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Relevant legislation and professional guidance

ASPA terminology:

Certificate of designation – given to a person of seniority and authority at the establishment

Certificate holder – has overall legal responsibility for all the animal facilities and for all the procedures carried out in an institute or research facility.

Project licence – held by a senior researcher and covers a programme of work with a single theme or purpose. Application must explain the background, objectives and justification for the work and consider the cost-benefit analysis and must take into account the 3Rs – replacement, reduction, refinement – and use alternatives where possible. Licences last for a maximum of 5 years.

Project licence holder – directs and supervises a particular project

Personal licence – authorises the holder to perform specialised techniques on particular animals. May be granted to applicants after attendance at an accredited training course, where competence is assessed.

Named Animal Care and Welfare Officer (NACWO) – responsible for ensuring the animals are kept in the required conditions and are checked daily. They would also be involved on a study if the animal's welfare was called into question.

Named Veterinary Surgeon (NVS) – advises on the health and welfare of the animals and the performance of techniques. Diagnoses and treat diseases. Often involved in training licensees, drafting of new project licence applications and is a member of animal care and ethical committees.

The problem

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- Seriously large amounts of money have been spent on this test compound already.
- This reaction was seen in dogs – it might not give the same reaction in primates or humans but without the experiment continuing in dogs, it will be impossible to titrate the dose for other species.
- The client company is seriously annoyed at this (your) interruption to the clear passage through the pre-clinical trials.
- In all other respects the medicine is ‘clean’ and they had every intention of starting clinical trials when they received your company’s report.

What could happen next?

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A very cross American company is demanding that there is a telephone conference with you and the SD. They say that their (human) cardiologists want to speak to you to persuade you that it would be OK to proceed with further studies.

You are absolutely convinced that this is not in the best interests of the animals – who knows if dogs hallucinate? And those dysrhythmias were life-threatening. They say: “they recovered, didn’t they?”

You would rather they didn’t conduct any more experiments using this test substance but they point out that it is almost certain to save many women’s lives – can you be responsible for preventing this progressing? They say: “You are a woman, after all…”

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What could be done in practice?

After discussion with the Home Officer inspector, the SD and the Project Licence holder, your employer company decides to file its report, including your cardiology report that recommends in the strongest possible terms that this test substance should never be given to dogs again.

Your employer company (to its credit) declines to take on more work involving this test substance knowing that it will lose considerable revenue. In fact, there is a risk that this client company will withdraw all its work – there are after all, many more contract research laboratories keen for the work.

But your company backs your opinion that the welfare of the animals was severely compromised during this study exceeding the severity banding. Your opinion (as an MRCVS) has been completely vindicated.

It is not known if this novel compound ever made it onto the market. It is also not known if the experimental work continued overseas in laboratories where animal welfare is of secondary importance to making money.

What could be done in policy?

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Veterinary associations could put pressure on those responsible for allocating funding to furtherance of the 3Rs – replacement, reduction, refinement.

All those working with experimental animals (including veterinary surgeons) should be up to date with outcome-based welfare assessment of experimental animals (e.g. Leach and Main), as well as latest scientific thinking on enrichment and humane experimental technique.

A few facts from the Home Office Report on Statistics on Scientific Procedures on Living Animals (2010).

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About AWF

The Animal Welfare Foundation (AWF) aims to alleviate unnecessary pain and suffering in all animals including working and livestock animals, wildlife, and pets. We do this by focusing out charitable activities on three main areas:

Providing a forum for discussion to highlight and promote animal welfare best practice

Research

Debate

Education

Grant funding research which has a direct impact on animal welfare.

Investing in education for the public and veterinary professions, particularly students, on animal welfare issues

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