Home Office

NON-TECHNICAL SUMMARY

Investigating the dog as a naturally occurring model of epilepsy and its neurodevelopmental comorbidities

Project duration

Years **5**
Months **0**

Project purpose

- (b) Translational or applied research with one of the following aims:
  - (i) Avoidance, prevention, diagnosis or treatment of disease, ill-health or abnormality, or their effects, in man, animals or plants.

Retrospective assessment

The Secretary of State has determined that a retrospective review of this licence is required, and should be submitted within 6 months of the licence's revocation date.

Objectives and benefits

Description of the project's objectives, for example the scientific unknowns or clinical or scientific needs it's addressing.

What is the aim of this project?

Epilepsy, defined by spontaneous recurrent seizure activity, is a common and serious disorder, affecting around 1 in every 26 people. The dog is a recognised model of human epilepsy, with striking

similarities in the cause, clinical manifestation, and disease course when compared to human patients. Although seizures can be induced in normal dogs by electrical or chemical means, a large population of pet dogs with spontaneous recurrent seizures exist, with the dog considered to be affected by epilepsy more than other domestic species, making canine epilepsy a disease of considerable comparative medical interest. It is increasingly recognised that epilepsy is no simply a seizure disorder, and is a more global brain disorder with multiple manifestations. Neurodevelopmental disorders such as autism and ADHD are commonly seen in people with epilepsy, and are termed ‘co-morbidities’. It is possible that altered neurobiological mechanisms involved in early brain development lead to the co-development of one or more these disorders. It is not yet known whether these co-morbidities are seen in dogs with canine epilepsy.

This project will answer the following questions:

1) Do dogs with epilepsy show increased levels of autism and/or ADHD-like behaviours in comparison to healthy control dogs?

(2) Are there differences in the brain structure and function of dogs that show autism or ADHD-like behaviour compared to controls?

(3) Is the presence of autism or ADHD-like behaviour associated with an individual’s response to drug treatment?

(4) Does epilepsy, autism and/or ADHD have a negative impact upon the welfare of affected dogs?

Potential benefits likely to derive from the project, for example how science might be advanced or how humans, animals or the environment might benefit - these could be short-term benefits within the duration of the project or long-term benefits that accrue after the project has finished.

What are the potential benefits that will derive from this project?

In the short-medium term, the results of this study will:

- Produce objective screening tools to detect behavioural abnormalities in dogs with epilepsy, which clinicians will be able to use to screen for potential co-morbid behavioural problems in dogs they treat for epilepsy
- Allow researchers in the field of canine epilepsy to more fully characterise dogs included in their studies, and lead to genetic research to advance our understanding of their genetic cause(s)
- Enhance our abilities to use ambulatory EEG (brain activity monitoring) and MRI (brain structural scanning) to detect differences in brain activity and brain structure between dogs with epilepsy and healthy controls, and between dogs that show abnormal behaviour and those that do not, which may lead to an improved understanding of their underlying causes

In the long term, naturally occurring canine epilepsy and its neurodevelopmental comorbidities may be used more widely in epilepsy research, potentially reducing the number of genetic or induced rodent models of epilepsy that are commonly used at present.

Species and numbers of animals expected to be used

What types and approximate numbers of animals will you use over the course of this project?

Around 60 client owned dogs will be used in the studies over a 3 year period, 30 of which will be ‘case’ animals that have been diagnosed with spontaneously occurring epilepsy, and 30 of which will be controls, which are matched to the case animals on breed, sex, age and neuter status (where possible). Each dog will be enrolled to the study for two days during this period.

Predicted harms

Typical procedures done to animals, for example injections or surgical procedures, including duration of the experiment and number of procedures.

In the context of what you propose to do to the animals, what are the expected adverse effects and the likely/expected level of severity? What will happen to the animals at the end?

All dogs will be returned to their owners at the end of the study. The expected level of severity is mild, with no significant adverse effects expected. Due to studying dogs with epilepsy, there is always a risk of seizure activity occurring during the study protocols; however, all will be carried out in a veterinary hospital with assistance available in emergencies.

Application of the three Rs

1. Replacement

State why you need to use animals and why you cannot use non-animal alternatives.

The dog has been chosen as a model for this study, as epilepsy is the most common chronic neurological disorder in this species. As such, the work carried out will be of direct benefit to dogs, but will also be of translational value to humans with epilepsy. Directly studying the behaviour of dogs in a naturally occurring disease model will lead to greater understanding of epilepsy and its comorbidities in dogs compared to using experimentally induced disease in different species.

2. Reduction

Explain how you will assure the use of minimum numbers of animals.

Sample size calculations have been based on evidence from published studies to use the minimum possible number with sufficient statistical power. This sample size will allow for statistically significant differences in EEG, MRI and behavioural variables to be detected. To reduce variability only one breed of dog will be recruited from. Each case dog will be matched as closely as possible with a control dog based on age, sex and neuter status to further reduce variability between the study groups.

3. Refinement

Explain the choice of species and why the animal model(s) you will use are the most refined, having regard to the objectives. Explain the general measures you will take to minimise welfare

costs (harms) to the animals.

Selecting the dog, a naturally occurring model of epilepsy, negates the need to breed for animals with genetic epilepsy syndromes or induce seizures with electro- or chemo-convulsants.

Minimal distress is anticipated to be caused by this work; however, to mimimise any potential suffering, local anaesthesia will be used where necessary for procedures where mild pain/discomfort may occur (e.g. placement of subdermal EEG electrodes), and sedation will be used in anxious dogs to avoid restraint and/or distress. Throughout the study procedures, the behaviour of the dogs will be closely monitored, and if considered to be distressed (e.g. excessive panting, excessive vocalisation, hiding), data collection will be paused, and if distress continues or is severe, procedures will be terminated.

Habituation to testing environments and equipment will be carried out where appropriate, and the owners of study dogs will also be present during procedures where this is feasible and beneficial to the dog’s welfare. While housed at the study institution, dogs will be closely monitored by veterinary nurses, with additional observation of the epilepsy group to monitor for signs that may indicate impending seizure activity.