Non-technical summary: Investigations into lumpy skin disease virus

Project duration
5 years 0 months

Project purpose
(a) Basic research
(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

Key words
Poxvirus, Lumpy skin disease, Capripoxvirus, Cattle

Animal types
Cattle

Life stages
juvenile, adult, pregnant, aged, neonate

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

Reason for retrospective assessment
This may include reasons from previous versions of this licence.
Contains severe procedures

Objectives and benefits
Description of the projects objectives, for example the scientific unknowns or clinical or scientific needs it's addressing.
What's the aim of this project?
To understand the disease caused by lumpy skin disease virus, and generate knowledge that will enable better control and prevention of lumpy skin disease.

A retrospective assessment of these aims will be due by 14 December 2027
The PPL holder will be required to disclose: Is there a plan for this work to continue under another licence? Did the project achieve its aims and if not, why not?

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.
Why is it important to undertake this work?
Lumpy skin disease virus (LSDV) is a poxvirus that causes severe systemic disease in cattle and water buffalo. In the past ten years it has spread rapidly from Africa and the Middle East into Europe, Russia and throughout Asia, causing substantial loss to affected farmers and rural communities. LSDV is therefore a rapidly emerging, high impact virus. It is also a neglected virus with scant literature describing studies into the virus and the disease it causes. It is important to undertake the work described in this project licence in order to build our knowledge of the virus and the disease. This knowledge will enable and promote effective, safe and proportionate means of disease control and prevention. These may include better management practices to inhibit vector-borne virus transmission, better

diagnostic tests to improve LSD surveillance programmes, and better vaccines to provide cattle and water buffalo with protection against LSDV.

What outputs do you think you will see at the end of this project?
The outputs of the project will be new knowledge about the pathogenesis and immunology of LSD, a better understanding of the vector-borne transmission of LSDV, and information about the efficacy of novel LSD vaccines. These outputs will enable improvements to be made to LSD control and prevention. The outputs of the project will be disseminated primarily via scientific publications and conference presentations.

Who or what will benefit from these outputs, and how?
In the short term, beneficiaries will include other research groups working on LSD. They will be able to make use of more appropriate and well-defined experimental models of LSD.

In the medium term the beneficiaries will include veterinary vaccine manufacturers and companies that produce diagnostic tests for LSD, as they will be able to use the outputs of this project to develop new or improved products. Policy makers will also benefit from the new knowledge which can be used as an evidence-base to underpin decisions.

In the long term the beneficiaries will be farmers and rural communities currently affected by or at risk from LSD.

How will you look to maximise the outputs of this work?
The outputs of this project will be published in open access scientific journals, and presented at national and international conferences. Protocols will be deposited online, and datasets deposited in public repositories. Samples from the studies will be made available to collaborators in the field. Where necessary intellectual property arising from this project will be protected by patenting.

The outputs will be disseminated to industry partners via collaborations, and to policy-makers via direct discussions and participation in expert working groups. Outputs will be communicated to the general public via press releases, articles on science-themed website, and public engagement events.

Species and numbers of animals expected to be used
Cattle: 696

Predicted harms
Typical procedures done to animals, for example injections or surgical procedures, including duration of the experiment and number of procedures.
Explain why you are using these types of animals and your choice of life stages.
Lumpy skin disease virus is very species specific and causes disease only in cattle and water buffalo. A less sentient species cannot be used in experimental animal models that aim to mimic natural disease. Cattle under 8 months of age will be used for ease of handling.

Typically, what will be done to an animal used in your project?
Cattle will be inoculated with lumpy skin disease virus (LSDV) and the resultant disease studied.

Expected clinical signs include fever, swollen lymph nodes, skin lesions, and mild lethargy. Samples will be collected during the study including venous blood and skin. Cattle may be

vaccinated and challenged. Blood-feeding insects may be allowed to feed on the skin. The typical duration of experiments will be 21-28 days.

What are the expected impacts and/or adverse effects for the animals during your project?
Cattle may develop lumpy skin disease (LSD). This is characterised by fever, swollen lymph nodes, development of miltuple skin lesions, and mild lethargy. These signs appear between 5 and 14 days post challenge and last for up to 15 days. The animal can develop mild clinical signs, characterised by a small number of lesions and a short fever, or it can develop more extensive signs for example greater than 100 lesions and fever lasting more than 3 days.

Expected severity categories and the proportion of animals in each category, per species.
What are the expected severities and the proportion of animals in each category (per animal type)?
Mild: 80%
Moderate: 18%
Severe: 2%

What will happen to animals at the end of this project?
Killed
Rehomed

A retrospective assessment of these predicted harms will be due by 14 December 2027
The PPL holder will be required to disclose: What harms were caused to the animals, how severe were those harms and how many animals were affected?

Replacement
State what non-animal alternatives are available in this field, which alternatives you have considered and why they cannot be used for this purpose.
Why do you need to use animals to achieve the aim of your project?
It is necessary to use animals because we are studying the complex interactions between the host and virus. It is not possible to replicate these interactions without using animals.

Which non-animal alternatives did you consider for use in this project?
Using non-animal alternatives to cattle has been considered by searching suitable websites (http://www.nc3rs.org.uk/, www.norecopa.no, http://www.frame.org.uk/). The scientific literature directly relating to the work that is being proposed was also searched for replacements for the proposed work (https://www.ncbi.nlm.nih.gov/pubmed/).

A membrane feeding assay was identified as a possible alternative to having insects feed on donor cattle in insect transmission experiments. This has included using thin slices of skin in a membrane feeding system. This area is being developed further. Other potential alternatives such as skin organoids, cutaneous explants and in vitro cell culture systems were also considered, and may be used in some studies.

Why were they not suitable?

The alternatives to animal use that were considered above are not suitable to replacing the work described in this project as they do not replicate the complexity of a systemic infection, as occurs in LSD.

A retrospective assessment of replacement will be due by 14 December 2027
The PPL holder will be required to disclose:
What, if any, non-animal alternatives were used or explored after the project started, and is there anything others can learn from your experience?

Reduction
Explain how the numbers of animals for this project were determined. Describe steps that have been taken to reduce animal numbers, and principles used to design studies. Describe practices that are used throughout the project to minimise numbers consistent with scientific objectives, if any. These may include e.g. pilot studies, computer modelling, sharing of tissue and reuse. How have you estimated the numbers of animals you will use?
The action plan of this PPL was used to plan the experiments likely to be carried out over the five year span of this licence. I then estimated the group sizes needed for each study following advice from an experienced statistician, incorporating the knowledge gained from previous work by ourselves and others with bovine experimental models of LSD.

What steps did you take during the experimental design phase to reduce the number of animals being used in this project?
I used advice from a statistician who is experienced in experimental design. This ensured I was proposing the minimum number of cattle required to obtain reliable and reproducible results. Each individual study will be reviewed by a statistician.

What measures, apart from good experimental design, will you use to optimise the number of animals you plan to use in your project?
We will use the outputs from the research carried out under the previous licence which characterised different models of LSD. This included a large amount of data and archived samples which can inform decisions on the best study design (such as selecting specific time points within the model).

We have close collaborations with other researchers using experimental models of LSD. We will implement the learnings from their studies into our plans, and if possible, combine their studies within our planned experiments, therefore reducing the number of cattle used in LSD research. We also publish our results in a timely fashion in open access journals.

We will maximise the use of tissues from these studies. For example under the previous licence we provided serum samples from LSD inoculated cattle to international agencies. These samples are used for standard setting and as positive controls for diagnostic laboratories around the world. We also donated tissues to a histology slide set which was made available to veterinary schools for use in training vet students and veterinary pathology residents.

A retrospective assessment of reduction will be due by 14 December 2027
The PPL holder will be required to disclose:
How did you minimise the numbers of animals used on your project and is there anything others can learn from your experience?

Refinement

Give examples of the specific measures (e.g., increased monitoring, post-operative care, pain management, training of animals) to be taken, in relation to the procedures, to minimise welfare costs (harms) to the animals. Describe the mechanisms in place to take up emerging refinement techniques during the lifetime of the project.

Which animal models and methods will you use during this project? Explain why these models and methods cause the least pain, suffering, distress, or lasting harm to the animals.

We will use a bovine experimental model of LSD that causes disease similar to that described in the field. Humane endpoints will be used to restrict the severity level to moderate in most studies. However some experiments may require the "severe" LSD seen in the field to be replicated experimentally.

Symptomatic treatment as agreed with a veterinary surgeon will be provided to alleviate suffering whenever possible.

Refinement will continue throughout the lifetime of the programme to eliminate or reduce to the minimum any possible pain, suffering, distress or lasting harm to the animals. Assessment of suffering will include both direct and contingent suffering, and take into account the time over which the suffering occurs.

Why can’t you use animals that are less sentient?

LSDV is very species specific and causes disease only in cattle and water buffalo. A less sentient species cannot be used in experimental animal models that aim to mimic natural disease (objectives 1- 4), or in field studies (objective 5).

How will you refine the procedures you're using to minimise the welfare costs (harms) for the animals?

Housing and husbandry: Cattle will be housed in social groups whenever possible. Cannulated calves may be housed singly so that the cannula is not dislodged, however they are in sight and sound of another animal. Cattle naturally spend a large amount of time each day browsing for food and in social interaction. In order to mimic this in high containment conditions, and therefore minimise contingent suffering, we will provide them with ad-lib hay along with a dry lying area (rubber matting) to aid rumination. Enrichment devices will be supplied such as toys and fruit/vegetables as a reward. Salt licks will be available.

Pre-study meetings involving the NVS, NACWO and animal services staff will be held to discuss any advances in animal care. Meticulous records will be kept of behavioural, physiological, immunological and virological measures in order to identify predictive markers and design humane endpoints for future experiments. Pain and distress scoring sheets specifically designed for LSD will be used. Highly trained animal technicians will monitor these animals throughout the day, ensuring they are comfortable and to maximise their welfare status. We have 24/7 CCTV surveillance which can be used to monitor the animals behaviour over time. All experiments will be followed by a wash-up meeting to discuss all aspects of the study and to ensure lessons are learnt.

What published best practice guidance will you follow to ensure experiments are conducted in the most refined way?

I will follow the PREPARE (Planning Research and Experimental Procedures on Animals: Recommendations for Excellence) guidelines for planning our experiments

(https://www.ncbi.nlm.nih.gov/pubmed/28771074) and ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines for reporting these studies (https://www.nc3rs.org.uk/arrive-guidelines).

How will you stay informed about advances in the 3Rs, and implement these advances effectively, during the project?
I will attend appropriate 3Rs conferences, read the relevant scientific literature including the veterinary literature on pain relief, and undertake regular project licence holder training and refresher courses. I will take advantage of news and information provided by the NTCO. I will also use other sources of information such as: The NC3Rs (AALAS) American Association for Laboratory Animals Science (FELASA) Federation of European Laboratory Animal Science Associations (ICLAS) International Council for Laboratory Animal Sciences

A retrospective assessment of refinement will be due by 14 December 2027
The PPL holder will be required to disclose:
With the knowledge you have now, could the choice of animals or model(s) used be improved for future work of this kind? During the project, how did you minimise harm to the animals