Royal Veterinary College
University of London

Summary Minutes: AWERB PPLs meeting

Status: FINAL

Meeting held: 11 July 2023 at 10am via MS Teams and CEEED Seminar Room, Hawkshead

Present: 14, plus 1 in attendance, 7 by invitation and 11 apologies

1 PPL AMENDMENT

The PPL Holder and three colleagues were welcomed to the meeting. It was explained they were seeking to make several changes to one of the protocols in the licence that had secondary availability at the RVC.

A summary of the requested amendments and why they were required was provided including:

- There had been a typographic error in the licence in relation to gestation age and when the ratio of food to animals should be changed. This needed to be corrected.
- One of the steps in the protocol did not include details about the expected miscarriage/pregnancy loss rate of the animals. This needed to be added.
- It was proposed to change determining whether an animal was pregnant to earlier than 30 days gestation, so that if the animal was not pregnant it would reduce the amount of time that she was on the study.
- For the ultrasounds, it was proposed to increase the time limit of the general anaesthetic. The current time limit was turning out to be too short to determine the viability of all the foetuses.
- There would be a new option step to determine the effect of prenatal intervention on the glucose tolerance of the pregnant animals. This step was necessary to confirm whether the animal models closely replicate the human disease state and so are appropriate for testing mechanisms and therapeutic interventions.

The following queries were raised by AWERB:

- **The amendment involved mice being fasted for 18 hours. Why so long?**
  It was explained that 18 hours had been suggested to allow the flexibility to do the fasting overnight, so producing the most stable basal blood glucose levels in the mice. However following AWERB's request it was agreed that this would be reduced to 12 hours. Although AWERB asked whether it was possible for the fasting to be done during the day (so would have less impact on the mice), it was explained that it had to be done overnight in order for it to be "true fasting" as mice were nocturnal animals.
- **Were there any possible adverse effects associated with the glucose administration and the withdrawal of food to the pregnant mice, such as increased risk of miscarriage or significant tissue damage?**
  There might be a mild discomfort from the injection but there should be no other potential adverse effects. However another review of the literature would be done to double check this.

- **The licence mentioned that if there was evidence of foetal loss then the guinea pigs would be euthanised. However if miscarriage was a natural occurrence, why was it necessary to euthanise them?**
  This was because the mother would have been on a nutrient restricted diet and she was now no longer pregnant.

- **Could any of the guinea pigs be rehomed, if their miscarriages had occurred before surgery had taken place?**
  This had not been considered so would be looked in to and the breeders of the guinea pigs consulted with.

A query was raised with AWERB whether the process of getting a guinea pig pregnant should be included as a procedure in the licence. It was explained that it depended on the phenotype of the guineapigs and whether there were any harmful effects from the breeding of those animals apart from the natural loss. It was agreed that this needed further discussion separate to the meeting and potentially advice sought from the Home Office.

The researchers were thanked for attending the meeting. Once the requested changes had been made to the project licence, it would be circulated for a final check.

2 PPL AMENDMENT:

A representative of the PPL Holder was welcomed to the meeting. She explained that she was presenting the amendment as she was responsible for running the in vivo studies. The main change was the addition of a new protocol to permit the use of a ligand induced model of immune activation. The addition of this model was to reflect the development of their therapeutic strategy and identification of potential new targets that required readouts not provided by the models that were currently in the licence. By including an inflammatory model, they would be able to model some aspects of inflammation to see how their therapeutics could potentially alter the pathology of inflammation.

AWERB asked for the following changes:

- The licence needed to be amended to clarify how many intramuscular injections there would be and for how many days. The PPL Holder confirmed that the injections were not planned as routine administration.
- Provision of enrichment such as more nesting material, bedding, toys and treats etc to make the animals more comfortable whilst they were undergoing their procedures would be looked into.

The representative was thanked for attending the meeting. She would make the required changes and the project licence would then be recirculated for a final review.

3 NEW PPL – REQUEST FOR SECONDARY AVAILABLITY AT THE RVC

The PPL Holder was welcomed to the meeting. It was explained that the PPL Holder was in the process of applying for a new project licence to replace one that was due to expire in December 2023. Her current project licence was primarily focused on rodent work but for this new licence she was aiming to add pig work to the licence and would be doing that work at the RVC. Her research was focused on the causes of inherited blindness, particularly developmental and conditions that affected children. More recently they had expanded into underlying conditions that lead to hearing loss as well. Through their research they were developing a better understanding of the genetic pathways that regulated eye development.

The reason for using a pig model was that its eyesight was similar to human eyes, so they would be able to evaluate interventions prior to going into a clinical treatment.

The following queries were raised:

What non-animal alternatives had been considered? There were publications available on in vitro model systems that studied development of the eye. Could animal cells be used to generate these models, so requiring fewer animals for the experiments? Where possible in vitro models were used. However, it was not yet possible to study sight or hearing using in vitro model systems as they needed to study the effect on the immune system and the effect on the host tissues and organ physiology, which could only be done in vivo. This explanation would be added to the licence.

- **Instead of using mini pigs, which can have inherent issues associated with them, could young standard pigs be used, as they would be smaller than mini pigs and maybe mimic children better as they would grow?**
  The PPL Holder wanted the flexibility to be able to use both pigs and mini pigs, particularly if this work progressed towards a clinical trial. Mini pigs had the following advantages: their small size; genetics; background data; health status; similarity to humans and their availability in uniform groups.

  AWERB were also advised that as pigs grew very quickly, between 5 to 8 kilos a week, there was uncertainty in relation to what happened to eye size relative to the growth of their head and the rest of their body. Over the duration of the work, the genetic background and immune suppressing on an intentionally genetic pathogen free mini pig might be something that the PPL Holder would need to use. Also the immunosuppression drugs for the pigs would likely be very expensive (as the amount to be given was generally pro rata per kg weight of the pig) and difficult to administer on a daily basis to 150kg animals.

- **How would it be decided which reagents or cells would be injected?**
  The PPL Holder explained the process that would be used. They would mainly use substances that had been administered previously with pilot studies undertaken where applicable. Checks would be carried out on potential toxicity for novel test substances.

  This information would be added to the project licence to explain how the materials to be injected would be chosen. The adverse effects section would also be amended to include an explanation about the possible adverse effects and that some of it would be unknown.

It was decided that as the licence required further work, a separate meeting would be held in order to provide guidance and finalise the details. The licence would then be circulated to AWERB for a final check. The PPL Holder reminded AWERB that her current licence expired in December and asked for reassurance that the RVC AWERB process would be completed as quickly as possible. Although AWERB were sympathetic to the timelines, it was necessary to review the licence carefully to ensure that they were comfortable with the work proposed.

4 ANY URGENT ITEMS TO RAISE?

4.1 Project Licence

It was reported by the NVS that issues had been experienced with work being carried out under one of the project licences, which had resulted in three birds exceeding the severity of the licence. A condition 18 report had been submitted and work paused whilst advice was sought and options explored such as modifying the anaesthesia protocol or moving to different birds that were generally more robust and tolerable of anaesthesia.

4.2 Mice

There was a recurrent issue of some mice having sensitive skin. There were also a few with broken nails. Reasons why this could be happening was being looked into, including contacting the suppliers to see if they had any listed events for skin or nail issues.

5 MINUTES

The minutes of the meeting held on 28 June 2023 were approved subject to several suggested changes being made.

6 DATE OF NEXT MEETING

This was scheduled for 2nd August 2023. It would be a PPL review meeting.

Secretary
21 August 2023