Royal Veterinary College
University of London

AWERB Summary Minutes: AWERB: PPL review meeting

Status: FINAL

Meeting held: Wednesday 15 January 2025 at 10am

Present: 16 plus one in attendance, 4 by invitation and 3 observers; 14 apologies

1 WELCOME

Two new student AWERB members were welcomed to their first meeting. Three observers were also welcomed.

2 MID TERM REVIEW

A Project Licence Holder (PPL Holder) was welcomed. He had recently submitted a mid term review for his project licence and had been invited to attend to discuss the report.

The following questions were raised:

- **Severity: the report identified that there had been animals that had exceeded severity; but later states that no unexpected adverse effects or welfare issues had been encountered. Why was there no mention about the animals that had exceeded severity?**
  Although there had been issues which had resulted in some animals being scheduled 1, this had turned out to be due to the anaesthesia rather than a procedural cause. The anaesthetic regimen had been slowly changed and was now no longer used. This information would be added to the report.

- **Estimated numbers: The estimated numbers of animals required when compared to the actual numbers used so far, when more than halfway through the project life cycle, were vastly different. Would the estimated numbers be decreased, or was the intention to rapidly accelerate the work programme and so the numbers used?**
  Originally, the numbers had been estimated too low, so an amendment was submitted in 2021 to increase the maximum number. Subsequently though activities had to be put on hold for nearly 18 months. Work had now recommenced, and numbers were picking up, but the specified estimated numbers on the licence would not be reached.

- **Scientific results: had there been any efficacy observed in the mouse model used?**
  Different studies had been undertaken over the years to test efficacy with different vectors, doses and concentrations. For the most recent study a couple of blood injections had been carried out in young animals and this had demonstrated that vision loss can be rescued in up to 80% of the normal wild type mice. This information would be added to the report.

- **The licence was due to expire late 2025. For the replacement licence, the condition 18 reports should be reviewed to identify which protocols these applied to and to take this into account when writing it.**

- **For the new licence, developments in the field need to be considered, in particular whether a system was now available to reduce the numbers of animals in terms of screening.**

- **Was it possible to show or infer that a drug is unlikely to be efficacious from an in vitro model? Was screening done before putting a drug into an animal?**
  Screening was regularly done as part of the selection of vectors, as well as measuring the expression of potential. This was done to avoid both wastage of animals and time and money of carrying out a big study when it was not likely to work.

- **In relation to reducing the numbers of animals being used, there had been mention about changing the breeding system. Was this successful?**
  This had been trialled but had not really been successful.

- **For refinement, it was suggested that mention should be made about the work done to improve the anaesthetic regimens which has better welfare consequences for the animals.**

The PPL Holder was thanked for attending the meeting.

3 NEW PROJECT LICENCE

The PPL Holder was welcomed to the meeting. She was applying for a new project licence, to replace a licence that had expired in March 2024. A background to why the licence was required was given, followed by some specifics of the primary experimental methods the team would be using.

The primary focus of the research was inflammation being a modifier for neurodevelopmental diseases and how those things that happen in early life then contribute to disease in later life such as attention deficit hyperactivity disorder; learning disorder; anxiety and depression and disruptive behaviour. These all have some commonality in roots and associations with inflammation and infection. This research would focus on preterm brain injury.

The following queries were raised:

- **Aged mice: protocol 1 indicated that aged mice would be used. Aged mice refers to mice over 15 months so if these were being used then they would need to be on a separate aged mouse breeding and maintenance protocol.**
  It was clarified that this was due to a misunderstanding over the definition of "aged". Mice in this protocol would not be kept over 15 months. This would be removed from the licence.

- **Non-Technical Summary:** this needed to be simplified.

- **Humane Endpoints: one of the humane end points for protocol 2 indicates that if an animal does not move within 15 minutes of being separated from the litter they would be culled?**
  It was clarified that this should say within 15 minutes of being introduced back to the litter after separation. The licence would be amended to make this clear.

- **The mice would be administered a high fat/sugar diet. When they returned to their normal diet though, was there a risk that they would not eat it?**
  Studies have shown that mice that have been on this type of diet during the early postnatal period, do not show a sudden weight loss when switched back to a normal diet. This detail would be added to the licence.

- **The licence mentioned that if there were signs of tissue damage, a topical antiseptic would be used for 24 hours in an attempt to resolve the injury. It was suggested that the use not be**

limited to 24 hours as this could limit the ability to treat animals showing signs of improvement but not fully recovered within 24 hours.
The licence would be amended accordingly.

- **Tattooing of mice: this proposed method for marking the mice was not the most refined. Had the use of permanent markers been considered?**
  Tattooing needed to be used, as an age-appropriate method for identifying and treating pups individually over days was necessary as this was a specific requirement for the grant they had been awarded for this work. Although using a permanent marker would be less invasive, it would not last long enough to allow tracking of animals over a day or multiple days. This explanation would be added to the licence to justify the selected method.

- **Under protocol 1 there was mention that ear notching would be used as identification. Could this be used as an alternative to tattooing?**
  Ear notching would be used for adult mice but was not a suitable method for baby mice.

- **Protocol 2 mentioned that animals would receive up to 9 IP injections over 5 days which seemed a lot. How well do the pups cope with this?**
  The pups cope really well with the injections. Occasionally there was a mild abrasion to the site of injection or bleeding from the abdomen. If that happened, the other side of the abdomen would then be used. As standard they would vary the injection site to avoid repetitive placement of the needle. In relation to what is being injected, generally no major inflammatory effect is seen.

The PPL Holder was thanked for attending the meeting. She would address the comments that had been made and recirculate the project licence for a final review.

4 BRACHYCEPHALIC OBSTRUCTIVE AIRWAY SYNDROME (BOAS) TREATMENT IN DOGS

A request had been received to support a multi-centre clinical trial using their product that would provide relief to BOAS dogs. However AWERB were asked would they be open to this type of work being carried out at the RVC, given the controversial aspects of this breed and the welfare issues that have arisen from their breeding? The dogs are bred with flat faces as owners like the way they look, but in doing so, this has unintentionally led to associated health problems including obstructions to the dogs upper airway causing breathing problems (BOAS); recurring skin infections related to skin folds; eye disease and spine disease and an inability to give birth naturally. An internal expert, who has carried out research into the welfare aspects of Brachycephalic dogs, had been invited to attend for this discussion.

The study would conducted according to Good Clinical Practice guidelines. Based on the study design, it was understood the medication would be delivered under VMD ATC and A(SP)A would be required for blood samples at follow-up visits. Some field and PK data had been provided.

AWERB members were asked did they in principle agree with the concept of this study. The following was considered: if this clinical trial was supported to help combat BOAS, would it encourage breeders to continue breeding these animals without improving breeding practices? The RVC are involved in actively educating breeders of these types of dogs and advocating for improved breeding practices and research to improve the breed health. RVC's focus through the Brachycephalic Working Group was more on prevention of these harms to start with rather than palliating the existing population.

There was concern about what would it look like reputationally to agree to be involved in a clinical trial for a treatment to this problem when the RVC institutionally did not agree with the avoidable man-made formation of the problem in the first place.

There were initial differing thoughts: if the RVC are involved in this trial and are part of a successful treatment, would that undermine progress of trying to stop the breeding of these types of dogs and perpetuate the breeding of dogs that were essentially deformed; with others thinking more that it would be good to be part of something that could help individual animals with their welfare, care and treatment.

The Chair suggested that AWERB members should take some time to absorb the information that had been provided. A discussion would be held at a future meeting to decide whether AWERB were in principle supportive of this concept or not. These views would be fed higher up to senior management due to the potential reputational impact. CRERB and the new Clinical Ethics Board would be approached for their input too, on whether, if this was a new treatment, would they recommend its use.

5 **PPL AMENDMENT**

A PPL Holder was welcomed to the meeting. It was explained that this was an amendment to add a new protocol to their licence to be able to test biocompatibility, stability and/or safety of an Anterior Cruciate Ligament (ACL) reconstruction device. Initially short term pilot studies would be conducted to assess the suitability of the device in an animal model and to inform product design. Chronic longer-term studies would then be conducted to assess the biocompatibility, stability and safety.

The following queries were raised:

- **Was antibiotic prophylaxis required?**

  The issue of surgical site infections is a considerable and complex concern following orthopaedic procedures. Peri-operative antibiosis reduces the potentially high risks associated with infection to prevent future complications.

- **Body weight/condition loss: potentially could an animal have a body condition score of 1/5 and not eat for a further 4 days?**
  It would be clarified in the licence that animals could reach an earlier endpoint as a consequence of inappetence or pain/lameness. An animal would not be left for 4 days.

The PPL Holder was thanked for attending the meeting. There were some points that needed to be addressed. The project licence would then be recirculated for a final review.

6 **MINUTES**

The following minutes were formally approved:

- 20 November 2024
- 04 December 2024

7 ANY URGENT ITEMS TO RAISE?

- **Internal tissue requests**: Issues have been encountered with the internal tissue request system which were being looked into, in order to make the process easier to follow. Discussions were being held with the intention to bring this as an item to a future AWERB meeting.

8 DATE OF NEXT MEETING:

- 21 January 2025.

AWERB Secretary
23 April 2025