Royal Veterinary College
University of London

Summary Minutes: AWERB: PPL review meeting

Status: FINAL

Meeting held: Wednesday 28 August 2024 at 10am

Present: 15 plus 1 in attendance, 5 by invitation, 14 apologies

1 ENVIGO UPDATE

It was noted that senior management has decided RVC will cease trading and collaboration with Envigo US and Labcorp US, as a result of Envigo US's fine for animal welfare and water pollution crimes, and Labcorp US's fine for alleged violations of animal research laws. Envigo UK may still be used as a supplier, but that use should be considered by AWERB. Any work that involves a Contract Research Organisation (CRO) should come to AWERB for initial discussion and consideration. It was suggested that to streamline the process it would be useful to have a template for researchers to complete when wanting to use a CRO. Although each request would be different, a list of standard questions based on UK welfare standards could be used as a starting point.

2 PPL AMENDMENT

The Project Licence Holder (PPLH) was welcomed to the meeting. He was attending as he wanted to make some amendments to his project licence.

The amendments involved:

- Adjusting the wording to a protocol that related to the subcutaneous injections.
- Adding in a protocol from a previous project licence to allow aspects of the natural history of the DMD phenotypes in the dogs be evaluated. Pilot data shows that the hearts have a significantly reduced force of contraction, even though *in vivo* the hearts appear to function normally. The aim was to understand why this was happening.

The following comments were made:

Subcutaneous Injections Protocol

- The protocol mentioned that subcutaneous administration can cause transitory "discomfort": was this the right wording to use as it did not fully reflect the reaction the dogs showed? **Action: this sentence would be amended.**
- The statement that if a dog "develops a *detectable aversion* to the daily treatment identified on 3 or more successive occasions then administrations will be stopped" needs to be defined more specifically: currently there were dogs on the trial that showed daily aversion prior to injection, but then returned to normal until they knew it was the next dosing time. Under this wording they would have to be removed from the trial. **Action: The wording would be revised to indicate that it was referring to continuous or persistent signs of aversion lasting for more than 3 min after the immediate administration of treatment has been done. The proposed re-wording would then be shared with AWERB and the NVSs.**

Natural History protocol

- **Clarity should be added to the project licence about the time gaps between procedures, to provide reassurance that adequate and appropriate rest periods between the procedures was being given.**
- **The severity category for this protocol is estimated as moderate. Would there be any wild type dogs that could potentially be rehomed though, or would each one always have a moderate procedure done to it?**
  It was anticipated that some of the wild type dogs might only undergo imaging (classed as mild severity) and so would be able to be rehomed. The statement that 100% of the animals would experience moderate severity would be amended. It would also be made clear on the licence that some of the Wild Types would only be undergoing GA imaging.

The PPLH was thanked for attending AWERB. The requested changes would be made and then circulated a final check.

AWERB were reminded that it had been reported at the previous meeting that trials would be undertaken with the next cohort of dogs to see if changing the temperature (either through cooling or warming reduced the immediate response to the injections). This had been done as well as desensitising the skin through using ice packs and sprays but none had resulted in any beneficial impact. The decision had therefore been taken to revert back to giving the dosing as quickly as possible so the dogs were stressed for as short a time as possible.

3 NEW PROJECT LICENCE APPLICATION

The Project Licence Holder (PPLH) was welcomed to the meeting. He was in the process of applying for his first project licence. The aim of their project was to develop nanoparticles to deliver therapeutic genes to specific cells to achieve in vivo gene therapy. They would be developing and testing vectors for their ability to achieve *in vivo* gene therapy.

AWERB discussed the licence. The consensus was that a lot of further work was needed on it:

- The scoring system needed to be reviewed to make sure it was consistent, relevant and valid throughout the licence
- More explanation was needed on the tumour growth and how this would be monitored.
- There was also mention of ulcerations: information needed to be included on what the chances were of these tumours ulcerating and what was likely to happen if they did ulcerate? Were they likely to heal? If they were seen, did the animal need to be euthanised?
- One of the protocols mentioned that "unexpected symptoms that do not appear in the scoring table will be discussed with the NACWO and mice will be treated or humanely killed as advised": this needed to be amended for as written, it was too open, as in theory anything could be allowed to happen and so did not enable a harm benefit analysis to be carried out.
- It was queried why any animal that showed deviation from normal health would only be monitored every 24 hours. This was a long time to wait to reassess an animal already showing signs of abnormal health/behaviour. This should be amended and made more frequent for those animals that were showing more signs of discomfort. All the monitoring timelines and regimens in the project licence needed to be reviewed, with consideration given to what the animal would be going through for the different scenarios to ensure that the animals were being monitored on a regular basis in order to look out for the adverse signs that were indicated on the scoring sheet.
- A query was raised about the imaging equipment that would be used. This was not equipment that the RVC currently had: was the intention to bring in this equipment or to use equipment located elsewhere? If the latter, the project licence would need to have secondary availability at

that establishment, so the project licence would need to be reviewed there too. At least six months would need to be allowed for this process.

- Currently it was not clear whether the aim was to have a pilot study, or a toxicity/tolerability study. A tolerability study looks at the safety or toxicity of compounds/drugs/products; a pilot study is used to do a small-scale test of the methods and procedures that are to be used on a larger scale. A tolerability study should be a protocol in itself.
- For determining the group sizes, example calculations should be provided to explain how the numbers had been determined.

A meeting would be held outside of AWERB to go through the licence to provide more advice, in particular to the scoring sheets and endpoints. The licence would then be resubmitted for another review.

4 PROJECT LICENCE AMENDMENT

The Project Licence Holder (PPLH) was welcomed to the meeting. She was wanting to add two new protocols to her licence: one relating to meniscal repair model in sheep and one relating to acute wound model in pigs. These protocols were not interlinked. The backgrounds to the protocols were explained. The first protocol related to testing a deep penetrating wound repair device for stopping deep penetrating wound bleeding enabling patients to be stabilised very quickly. The second protocol related to testing a synthetic total meniscus replacement medical device for surgical implantation. AWERB reviewed the protocols and were supportive of them but requested that several changes be made.

5 ANY OTHER BUSINESS

5.1 Keeping of wild type normal rodents over 15 months for schedule 1: potential policy

It was explained that a new policy was in the process of being written which would detail that no rodents should be kept above 15 months of age without being under a project licence or the jurisdiction of a project licence. This was following a query about using tissues from aged mice and concerns about the mice experiencing adverse effects from ageing. Advice had been sought from the Home Office who had advised that each animal strain should be evaluated and that if any adverse effects were expected then they should be put under a project licence.

AWERB confirmed that they were supportive of the proposed approach detailed in the new policy.

6 DATES OF NEXT MEETINGS:

25 September at 2.30pm: Standing agenda items meeting
9 October at 10am: PPL Review meeting

Secretary
15 November 2024