
Minutes: AWERB summary minutes

Status: Chair approved

Meeting held: 12 May 2020 at 2pm by MS Teams

Present

Attendees: 11 plus 2 in attendance, 3 by invitation and 5 apologies.

1 WELCOME

A new member of the BSU Management team was welcomed to the meeting – she was attending as an observer.

2 PRESENTATION FROM PROJECT LICENCE HOLDER

An application for a new project licence had been received. It was to replace an existing project licence that was due to expire in the summer. One of the scientists that had reviewed the project licence on behalf of AWERB had also been invited to the meeting.

The project licence holder explained that the aim of the project was to improve understanding of the molecular mechanisms underpinning the development of skeletal and vascular disease. There were two sides to the project: using transgenic models for increasing understanding of how things regulate bone cell function/bone homeostasis; and also looking at factors leading to the development of vascular calcification.

The following queries/points were made:

- Protocol 1: A query was raised that as this protocol included harmful mutants, could the protocol be justified as being mild? Either an explanation should be included about the steps that would be taken to avoid the harmful mutants exceeding the mild threshold, or the protocol should be amended to moderate.
- Protocol 1: maximum number of animals to be used: The number provided seemed very high. Was this based on use in the existing project licence? It was explained that the numbers were probably over-estimated the numbers in order to avoid the risk of exceeding the numbers. It was explained that this was not good practice and that the numbers used in the current licence should be reviewed in order to determine what the likely numbers needed should be.
- Protocol 1: Although this was listed as a mild protocol, there was mention that it was unlikely the animals would experience any suffering. This section should be reviewed.
- Protocol 2: there was confusion over the mentioned diets: adenine-enriched diet and a low protein diet. It was explained that on the current licence the adenine-enriched diet had been used and then the low protein diet, however a collaborator, who was an expert on this model had done studies using the low protein diet first and had found that the effects were more consistent, so the “n” number could be reduced slightly. It was recommended that this section be reworded to make it clear what was being asked for, as how it was currently written, meant there were a number of different permutations.

- Protocol 2: It was noted that one of the proposed procedures within this protocol involved intramuscular injections (along with intraperitoneal and intravenous options). It was pointed out that intramuscular injections were very painful and if used could make the severity of the protocol moderate instead of mild. The project licence holder advised that all potential administration routes had been included though it was unlikely all would be used. It was recommended that only the routes of administration that were definitely going to be used should be included, as otherwise it made the project licence more difficult to assess. The project licence holder would check with the co-researchers to make sure there was no intention of using intramuscular or intravenous injections for the initial period of the licence and if there wasn't, they would be removed. If it was found they were needed an amendment would be applied for.
- It was noted that there was a contradiction in the project licence, in that it initially said that both sexes of rodents would be used, but later on advised that generally only males would be used. A query was raised under what circumstances would females be used instead of males or mixed sexes. It was suggested that both sexes should be used as vascular calcification was a significant problem for women as well as men and suffered potentially more in the way of bone disease (osteoporosis). This needed to be clarified in the project licence.
- A query was raised on the blood sampling. The licence mentioned that it would be no more than weekly but did not indicate how much would be collected and via what method.
- There were concerns about the scoring system as it did not seem consistent. The scoring system was there for the technicians and researchers to follow when working on the study to provide guidance in order to help with reviewing and monitoring the animals to ensure they were healthy or to identify if there were problems, but the specifics did not need to be included in the licence.
- Non Technical Summary: this needed to be simplified and made more user friendly. Although the NTS was automatically generated from text provided in the project licence, these sections should be reviewed to make sure that they were understandable.
- There had been a query about the body weight loss within the project licence as it was set at >20% which it had been pointed out was too high for a moderate category. It was clarified that a mistake had been made with this. There was a CRF-independent model where they had observed an average <5% weight loss in animals during the first week, but then had started to gain weight which continued as the study progressed; for the CRF-dependent model this was much more variable as it depended on the extent of the kidney failure. Some animals lost up to 10%, others up to 20%. It was suggested that instead of having these listed together they should be separated out into two different protocols. It was also felt that 20% was too extreme. The data on this should be further reviewed but the committee expected the permitted loss of body weight before the end point was reached to be reduced (15% was suggested as the maximum tolerable level).

The project licence holder was asked to rewrite the project licence to take into account AWERB comments. It would then be re-circulated for another review, when AWERB would then make a decision about the project licence.

3 MID TERM REVIEW

The project licence holder was welcomed to the meeting to present the mid-term review on the DMD dog colony in person and to also discuss how the dog model was progressing.

The project licence had been amended in May 2019 and it was felt that these amendments had worked well. There had been recent discussions about further amendments that were needed to the project licence. The dog model was work in progress as it was very novel. The aims of some of the protocols were to learn more about the model. As more was learnt, then amendments could be made to the licence, to ensure that everything was absolutely right for the model.

AWERB asked for a summary of how the model was working out as a model for DMD in boys and what the potential was. Although AWERB could assess the harms to the animals from the paperwork, what they could not assess very easily was whether there were likely benefits in using this model to test new treatments and how well the model recapitulates what happened in the boys and what the promise was for new treatments coming through. The project licence holder reminded the Committee that there were a lot of models for DMD including mice, rats, rabbits, dogs and pigs. The rodent models were useful biochemical models of the disease so were used to evaluate treatments but were not useful to demonstrate functional improvements as mice failed to display an overt clinical phenotype. Pigs had a severe phenotype so were unable to get further than a few weeks in age. For rabbits it was too early to tell how useful the models were.

For many years scientists had worked with a golden retriever model which was a key translational model for treatments. The model was more severe than the beagle model though: it had a higher perinatal mortality and the dogs were heavier than the beagles. The main difference though related to the mutation - the mutation that the golden retrievers had was in a different part to the dystrophin gene compared to the beagle. There have been thousands of different mutations identified in the dystrophin gene in human patients. One particular region of the dystrophin gene has been identified as most commonly mutated in people. For the beagle model it had been found that the dogs harbour a mutation that corresponds to a mutational “hotspot” in the human DMD gene (exon 50).

There have been a number of different treatments evaluated for DMD. Two of these could only easily be tested in beagles (exon skipping and gene editing). The College had been involved in the first published trial of gene editing in a large animal model for any disease that had been very successful, with scientists being very excited about the results. The trial supported the concept, that with further development, gene editing approaches could prove clinically successful for the treatment of DMD. The work had been regarded by the BBC as one of the 10 most important scientific breakthroughs for 2018 worldwide. It was one of the treatments from that study that was being taken forward for further trials using a greater number of animals in order to demonstrate long term efficacy and safety.

The beagle model was a good model for DMD as it displayed the clinical signs of the disease but was not as severe as the golden retriever model so had distinct welfare advantages.

The future of the research project was discussed including proposed changes and why they were required.

It was noted that AWERB had discussed previously the humane end points and adverse effects of this project licence and this model. The model was still very new and was being developed. It was important to remember though that each dog was an individual and had different clinical signs, with all reacting differently to the disease and how it progressed. When talking about humane end points, it was important to find a balance between the project licence being general enough so that it was possible to account for all different variations in the dogs but also ensure that the project licence was usable by both the named people and the people on the ground.

A traffic light system document had been drafted to provide warning alerts of what should be looked out for in the dogs to provide guidance for the humane end points. However using the traffic light system was not so straightforward as might have initially been thought and would require constant review to make sure it was still relevant. Guidelines and flexibility were needed so that the situation could be approached as required and the NVS and NACWOs and clinical experts could make the right decisions for both the animals and the study.

The project licence holder was informed that AWERB have had discussions in the past about what was a reasonable amount of time to keep a dog institutionalised. What point in time did it come impossible to rehome a normal dog as it had been institutionalised too long? How many litters was it acceptable for a bitch to have? There were due to be discussions over the coming weeks on how the older dogs should be rehomed and also a review of how many litters a dog should have and how long they should be institutionalised.

The project licence holder was thanked for attending. It had been a very helpful discussion. There had also been a lot of conversations and discussions over the past few weeks which had been productive. It was an ongoing project and there would be further discussions at the AWERB. It was recognised that it was challenging to get it right.

AWERB noted after the project licence holder had left that concerns had been raised about the paddocks in the mid-term review, in particular that the dogs no longer had open access to them but had to be let out/in from them. It was reported that the paddocks had been revamped: new fencing had been put up and shelters provided and new toys bought to provide enrichment for the dogs. The project licence holder had suggested additional enrichment and toys but these needed to be evaluated to ensure they were suitable. It was also important to make sure that any enrichment that was provided was safe. The affected males were not as agile, or as fit as the healthy dogs, plus they felt the cold more easily. A query was raised whether the dogs were able to access the paddocks directly or whether they had to be let out into the paddocks. It was explained that the paddocks used to be open access but now that there were more dogs, the dogs needed to be let out into the paddocks. The affected dogs had their own special paddock which was more secluded and had a shelter for them. Advice was also being sought from internal experts for suggestions on appropriate enrichment that could be used for the dogs in a structured way.

4 MINUTES OF PREVIOUS MEETING

The minutes of the meeting held on Wednesday 8th April 2020 were confirmed as an accurate record.

5 ACTION LOG

5.1 Item 2: DMD dogs (February 2020 meeting)

The meeting with the dog reproduction specialist would probably now have to be held virtually.

5.2 Item 4: BSU Virtual tour (October 2019 meeting)

The company was being set up on Agresso so that they could formally be approached for a quote. [Secretary update: since the meeting, it had been identified that the External Relations Team already work with a company that provides virtual tours. By using this contact it would mean that the virtual tour of the unit would be in the same format as other College campus tours that had been set up.]

5.3 Item 8: use of animals for teaching in UK Veterinary Schools (5 November 2019)

It was important to capture where animals were being used for teaching purposes as well as research purposes and reviewing the ethics for that. AWERB were responsible for overseeing the ethics for the teaching animals at Camden. Following the request from the Veterinary Schools Council it had highlighted that documentation should be put together reporting on how the teaching animals were looked after by the BSU. This was being compiled.

5.4 Item 12: ARRIVE guidelines (November 2019 meeting)

It was reported that it was planned for UK Reproducibility Network events to start up across the RVC soon, including journal clubs. These journal clubs would be discussing various issues and could include ARRIVE guidelines and how to discuss these aspects of the experiments to improve people's knowledge.

5.5 **Item 7: Checklist for reviewing project licences (April 2019 meeting)**

The NVS sought clarification of what the aim was for this check list and what need to be achieved. It was explained that the intention was for the check list to have several functions:

- To provide guidance to AWERB reviewers of what things they should consider when reviewing project licences.
- To provide guidance to PPL Holders of areas they needed to consider when completing the mid and end of project reviews, as currently a lot of them were providing only the bare necessities. By having more extensive reviews it would make the system more effective and allow conversations on how work had been progressed and also prompt the project licence holder to consider what 3Rs could be implemented for the animals. The forms needed to be updated to make them more user friendly and also to prompt for details of what happening to the animals.

Once amended, a copy of the revised project review template would be circulated to AWERB.

5.6 **Item 9: Companion animal Query (June 2019 meeting)**

The trial of using mirrors for the singly housed pig was on hold due to the pandemic as there were not the required technicians available to do the monitoring. When the pandemic was over, there would be a number of enrichment projects for the pigs that could be considered.

6 **3RS UPDATE**

Information would be forwarded in relation to the NC3Rs webinar series for circulating to PPL and PIL Holders.

7 **NVS REPORT**

- DMD dogs: two dogs had recently been euthanised as they had approached humane end-points.
- Anatomy pony: Her legs were healing well.
- Electric Fencing: the parts to do the electric fencing had now arrived.
- Ferrets: There was concern about one of the ferrets as it seemed slower but there had been no change in weight. A recheck would be done the next time the NVS was in the unit.

8 **NACWO REPORT**

- The Ferret Group were slowly returning to the unit to continue with their behavioural sessions with the ferrets. They were very good at communicating their whereabouts to the technicians. The technicians were monitoring the ferrets for any hormonal changes and were in discussions with the NVS over any they were worried about.
- The rest of the unit was fine with no major problems.
- Home Office Inspector: The unit was in contact with the Home Office Inspector on a weekly basis either by e-mail or by phone. He was happy with the welfare of the animals.

8.1 **General**

- Staffing: the teams were working on a shift basis (4 days on/4 days off at Hawkshead; 3 days on/3 days off at Camden) – this would continue until there was reassurance that the staff would not be at risk of infecting each other. AWERB expressed their appreciation of the technicians for all of their hard work – they added that as well as being responsible for monitoring animal welfare, they were also there to provide support to the technicians.

9 **FOR INFORMATION ITEMS**

Due to limited time, it was agreed that the “for information items” should be deferred to the June meeting.

10

DATE OF NEXT MEETING

This was scheduled for 16th June 2020.

Secretary
20 May 2020