Royal Veterinary College
University of London

Summary Minutes: AWERB

Status: Chair approved

Meeting held: 14 December 2021 at 2pm via MS Teams

Present:
Attendees: 9 plus 1 in attendance, 9 by invitation and 7 apologies

1 WELCOME

The students that had applied to be AWERB student representatives were welcomed to the meeting. They had been invited to attend as observers.

2 PROJECT LICENCE

The project licence holder was welcomed to the meeting. He explained that he was in the process of writing a new project licence to replace one that was due to expire in early January. One of his colleagues was wanting to amend an existing protocol that was on the licence, so they had submitted this early for feedback from AWERB on whether they foresaw any problems with it.

A brief introduction to the history of this project licence was provided. It had existed in various formats for a number of years. The licence consisted of individual projects, which were overseen by an experienced licence holder. The individual projects were of direct benefit to treating companion animals. The advantage of how this project licence was set up was that it enabled clinicians to carry out research, without having to be the project licence holder.

An outline of successful research that had happened as a result of this project licence was provided:

- Feline Diabetic Remission clinic: uncovered the recipe for diabetic remission in the cat
- Amoxicillin Clavulanic acid study: population pharmacokinetics of Amoxicillin-Clavulanic acid in critically ill dogs
- Inflammatory Bowel Disease (IBD) study: a study investigating the efficacy of hyaluronic acid, Entero-Chronic + hyaluronic acid in reducing the clinical signs associated with canine IBD
- Olfactory Ensheathing Cells (OEC) Spinal Study: a pilot prospective, interventional, single-arm trial of transplantation of OEC expressing chondroitinase ABC in chronically paraplegic dogs.

There was a current protocol which the clinician wanted to add a sacral neuroprosthesis to. The existing study involved 4 pet dogs who had been paraplegic with no pain sensation for at least 3 months. The owners were keen to improve their pets' lives as they were paraplegic and incontinent. A pilot study had been run to test the safety and feasibility of autologous intraspinal transplantation of mucosal olfactory ensheathing cells transduced to express chondroitinase in these dogs. This work had now finished however they were planning future work to combine intraspinally transplanted OECs expressing ChABC and repeated electrical stimulation of the sacral bladder nerves. The surgical implantation of the neuroprosthesis was the procedure that the researcher wanted to add to his protocol.

In addition to cell transplantation in the spinal cord, recent experiments had confirmed that repeated electrical stimulation of the spinal cord segments below the actual lesion, can change neural

networks controlling bladder function. Clinically, the researchers have shown that electrical stimulation of mixed sensory and motor sacral nerves in dogs, via a canine book electrode like the Brindley system, restores bladder emptying. The Brindley system was already used in humans in the UK through the NHS. The researchers predicted that multiple daily electrical stimulation of sacral nerves should have a 'training' effect on bladder neuronal circuits that could be exploited during nerve regeneration from the OEC transplant, to restore urinary function in severe chronic contusive spinal cord injuries in dogs.

The following queries were raised:

- These two procedures had previously been done separately but the idea was to now combine them together. Was there any evidence or concerns about the interaction between the cells and the electrical stimulation? The clinician advised that it was not known at this stage. There was a possibility that pain might be caused, however the cells that were transplanted were rarely a cause of neuropathic pain. A safety trial would be done first.
- It was noted that it was intended for both surgeries to be done under the same anaesthesia. How long would the total length of time be for the surgery? It was anticipated that it would be 4 hours in total including time to prep, which was a standard time for neurological surgery.
- How soon after implantation would the sacral nerves be stimulated? Usually, it would be a couple of days (48 hours) afterwards. Essentially the cells were implanted and immediately receiving the guidance cues that came from the training.
- A question was asked about the design of the experiment. How many animals would be used and would there be any comparative experiments? They would be starting off with safety trials on a couple of dogs first to make sure that there were no concerns with the concept. No comparative studies were currently planned, but if there were any they would possibly involve some of the dogs with the cell transplants and sacral implants getting stimulation whilst the other implanted dogs didn't. However this would be costly as ideally there would need to be between 15 to 20 dogs per group for any impact to be seen. There was also an ethical dilemma: if an implant was placed but not used, was that ethically right, as using it would have the most useful impact on the dog.
- For dogs that have had spinal cord injuries, what was the impact on their quality of life and what was their survival rate? Who would be making the decision about which dogs would be used in the trial? Also why would owners choose surgery rather than euthanizing the dog, as its quality of life was poor? The clinician advised that there was a lot of discussion about the ethics of keeping a dog alive after this type of injury. The clients' owners were given information about the different options that were open to them including euthanasia. Some decided to try the treatment if their animal was not suffering. The owners were usually very committed to their dogs and determined to improve their quality of life.
- A question was asked about possible interference between the 2 systems – was it possible to look at that *in vitro* at all? The clinician was not aware of this having been done. It was a good suggestion but would need a complex *in vitro* system which would be difficult to replicate, hence why the natural models were so useful.
- A question was asked about the scoring of the motor recovery. For spinal injuries a lot of papers referenced the Olby score to evaluate the extent of spinal cord injury. Would that provide a better comparison? The clinician advised that this had been used previously. It was a clinical score, complex and was quite subjective though and it was felt there were better ones. The Texas spinal cord injury score for example distinguished between the left and right leg. He was using the kinematic gait score which was more of an objective measure and involved the dogs walking on a treadmill which they generally enjoyed.

The project licence holder and clinician were thanked for attending the AWERB and providing a very interesting presentation. They were advised that the protocol needed to set out the potential different options of what could be done on the dog, as the Home Office Inspector would be doing a harm benefit analysis on all of these as well as what was being done as standard.

After they had left the following comments were made:

- The proposed work seemed a logical and reasonable next step to the work and had been well explained.
- As the aim of this project licence was to cover different types of work being done by the clinicians, it was important to be clear about what the ultimate aims and intent of the licence were. It would be very easy to do work that was permissible in a protocol but did not actually match the intent of the licence.

3 PROJECT LICENCE AMENDMENT

The project licence holder was welcomed to the AWERB. He had a proposed amendment to one of his project licences. He worked with external clients who wanted to run *in vivo* models but who did not have either the facilities or expertise to do so, so the studies were run for them. This could range from renting accommodation at the College to studies where everything was done for the client. This particular project licence focused on respiratory pharmacology and was a licence that was offered to external clients to work with them to test their compounds and products.

It was a broad licence based on a service licence. A protocol was written to do a specific study on a specific group of animals which was then reviewed to see if it was in-line with the project licence and whether it was acceptable in the boundaries of the project licence. One of the clients was investigating novel approaches (such as probiotic or microbiome altering compounds) as treatments for respiratory diseases such as asthma and COPD.

The Home Office had asked that the project licence include a list of the current clients who were working on the licence. If new clients were bought in or if a client wanted to expand their area of research, an amendment had to be submitted to justify this. This particular client was expanding their area of research to cover 3 new areas including probiotic or microbiome altering compounds, anti-infective, anti-viral small molecules, kinase inhibitors or steroids as treatments for asthma and COPD. They were using their knowledge on these respiratory diseases to investigate new novel approaches and the next generation of current treatments.

An amendment was therefore being submitted to cover this work. As the models to be run were the same models that had been run before, there would be no additional adverse effects to those that were already listed. Advice had been sought from the Home Office who had recommended that rather than submit a new protocol, changes be made to the aims and objectives of the existing protocols to cover these new three areas.

As part of the subsequent discussion the following queries were raised:

- There were now several different types of treatments that were being added to the project licence. What pre-screening was done in advance of adding these treatments? What would be the cut off (both ethically or morally) that would determine if a study would not be done where it was felt that the science did not support these treatments? It was explained that the client had to provide a package of proof of why they thought the compound was working and a plan of how they would be using this data. Proof was also needed that the company behind the research had the funding to take this on and make use of the results.
- Although different types of treatment were being added, there were no changes to the adverse effects or control points. Did that mean no changes at all in the adverse effects were expected? This was confirmed as a number of the products had been tested so they already knew what the adverse effects were and did not predict them to be any worse than existing treatments. A quick google search on kinase inhibitors adverse effects was carried out during the meeting, which resulted in some coming up, so it was suggested that it might be worth putting assurances in there, as the broad scope of how these compounds worked did raise red flags.
- A check was also needed that the humane end points tallied with the adverse effects such as gut pain, digestive issues and toxicity issues.

- The weight loss humane end points were queried as there were no time scales. How regularly were the animals getting weighed? How quickly were they expected to regain weight? The project licence made reference to the animals being euthanised if there were 3 consecutive measures of more than 12% but did not say over what time period: was it daily or weekly? Clarity was needed. The project licence holder advised that if a weight loss was seen then the animal would be weighed daily, otherwise it would probably only be weighed on a weekly basis. The trigger was the weight loss which was why they had not put a timescale in the licence as they were responding to what they saw. It was pointed out that on other project licences this was generally included and it was recommended that this be clarified if possible with limits and guidance being provided.
- The project licence holder was reminded of the importance of making it clear in the licence that they were doing whatever they could to refine.
- The end points and the adverse effects were very tricky to follow through from an NVS point of view. It was important to go through the licence and make sure the protocol, steps and animal experience all matched up in terms of what it was said would happen and that there were no differences.

The project licence holder was thanked for attending the meeting. He was asked to make the requested changes (in particular the adverse events) and then to resubmit the revised licence for a final review to AWERB.

After the project licence holder had left the following comments were made:

- The way the project licence was currently written was very difficult for an NVS to be able to follow through. It was very generalised. Things needed to be clear cut: a list of what was expected or not expected would be better for the NACWOs and NVS.
- Complex multi study project proposals like this were very hard to evaluate, as it was difficult to work out whether the proposed study was justified and to do a proper harm benefit analysis, as a lot of the answers were often "depends if necessary". For example with the routes of administration: how can this be reviewed? It was recognised that this was a general problem with service licences, as there were so many potential different permutations of what could be done. It was a challenging area. It was suggested that for licences like this, each new type of study that was requested should be approved individually. An outline of a proposed dosing regime for a particular study could be submitted which was then reviewed by AWERB to assess whether there was a clear benefit that outweighed the harm being done to an animal. It would be a way of assuring AWERB about the work being done under this licence and also knowing what was being done.

4 MINUTES

The minutes from the meeting held on 30 November 2021 were confirmed as an accurate record.

5 MATTERS ARISING:

5.1 Item 2.2: ASRU (30 November 2021 meeting)

The SOP for obtaining a PIL had nearly been finalised.

5.2 Item 3: Having more small animals oriented clinicians on AWERB: (30 November 2021 meeting)

A meeting was booked with the Establishment Licence Holder to discuss the options for increasing the number of small animal clinicians on AWERB.

5.3 Item 5: Students attending AWERB meeting on 14 December 2021 (30 November 2021 meeting)

The PPL Holders had been informed that there would be student attendees at the meeting and they were fine with that. An "introduction to AWERB" session had been held on 6 December.

5.4 Item 7: Working group to revamp mid/end of project licence reviews (30 November 2021 meeting)
AWERB members would be contacted to see who would be interested in joining this group.

5.5 Item 8: AWERB Terms of Reference (30 November 2021 meeting)
The Terms of Reference had been amended as requested.

5.6 Item 10: Study Requests received (30 November 2021 meeting)
The person who co-ordinated the tissue sharing programme would be asked to do a presentation to AWERB.

5.7 Item 3.2: Condition 18 training (24 November 2021 meeting)
The updated documents from the Home Office Condition 18 training workshop had not yet been received.

5.8 Item 3.4: ARRIVE compliance report (24 November 2021 meeting)
The aim was to have completed the slides and exercises before the end of January. Once they had been done they would be circulated for comment.

The training would be aligned with the BSU users group meetings that were being arranged, so that this training could be drawn to their attention.

5.9 Item 3.5: AWERB membership (24 November 2021 meeting)
The call for internal lay panel members had been circulated.

5.10 Item 3.7: Schedule 1 register and Assessors list (24 November 2021 meeting)
The review of the Schedule 1 and Assessors list for Hawkshead had been completed.

5.11 Item 3.8: Establishment Licence: updating the room names (24 November 2021 meeting)
This was ongoing. Floor plans were needed that matched with the establishment licence.

5.12 Item 3.9: Air handling units at Camden (24 November 2021 meeting)
A meeting had been scheduled with the BMS specialist to go through his report.

5.13 Item 4.4: Establishment Licence (9 November 2021 meeting)
It was agreed that a copy of the Establishment Licence should be placed on a shared drive.

5.14 Item 4: AWERB membership – external lay panel members (5 October 2021 meeting)
The Establishment Licence Holder needed to speak to the Ethics and Welfare Committee chair about a potential new lay panel member.

6 NACWO REPORT – CAMDEN
It was reported that the large animals had returned to Hawkshead for the Christmas break.

There was a new teaching pony who had been picking on one of the other ponies, when they were walked together at Camden. No issues had been reported since they had returned to Hawkshead. Instead the two ponies were wanting to be together all the time when in the field. They had not been walked together though. If time could be spared, then this would be done to see how they reacted.

7 BSU – COVID OUTBREAK
There had been a COVID-19 outbreak over the weekend with a number of positive cases within the units. It had therefore been decided that for the foreseeable future only essential staff and users could access the units so as to decrease traffic flow through the units, in order to minimise exposure

and risk of infection spread. The priority was to look after the animals whilst protecting the staff and ensure there was enough staff on the ground to look after the animals.

8 THANK YOU

AWERB were thanked for their contribution throughout the year. The student attendees were thanked for their input to the meeting which it was hoped they had found interesting.

9 DATES OF THE NEXT MEETINGS:

- 12 January – standard agenda items meeting
- 25 January – PPL review meeting

Secretary
20 December 2021