Royal Veterinary College
University of London

Summary Minutes: AWERB PPL review meeting

Status: FINAL

Meeting held: 8 February 2023 at 9.30am via MS Teams

Present: 13 plus 1 in attendance, 4 by invitation and 7 apologies

1 NEW PROJECT LICENCE APPLICATION

An application for a new project licence had been received. The purpose of the project was providing a testing platform for developing new medical/surgical devices to improve patient outcomes or deliver against an unmet medical need. Each medical device would be tested in accordance with the ISO10993 guidelines for biological evaluation of medical devices before EU/UK and USA (FDA) approval. This guidance stipulates the testing requirements for the regulatory testing of medical devices. The data obtained would then enable an objective decision to be made regarding whether to progress a novel device or technique through further stages of product development.

For each proposed study received, a protocol would be added to the project licence for review. This would then be assessed by AWERB before being submitted to the Home Office for approval as a project licence amendment.

The first protocol related to a silk-based peripheral nerve repair conduit that would be available off the shelf in a range of lengths. The fibres have proven nerve-regenerating properties that have already been demonstrated to be comparable to autografting. Although classed as a "gold-standard" surgery, autografting as a treatment did have limited success rate, particularly for larger nerve gaps, with a percentage of patients also suffering further complications, such as infection, wound issues and chronic pain from the donor site. It was also a lengthy operation (between 6 to 7 hours) and could only be done by specialist plastic reconstructive surgeons, of which there were not many in the country, so patients could end up waiting months for surgery.

The aim was to replace this autografting technique. As the nerve repair conduit would be available off the shelf, it meant it could be implanted immediately with no donor site risks. This meant that if during a general surgery, a nerve injury was seen, the general surgeon could repair the nerve injury straight away through using this conduit as no complex surgery would be required. This was beneficial to the patient, as they would have the opportunity to recover sooner, as they did not have to wait for surgery. This was important, as the sooner muscles were resupplied with their "electrical" supply, the better. If repairs were delayed, then the patient outcome was not as good.

The use of large animal trials was necessary to accurately test the regenerative properties of the conduits and to assess whether the introduction of luminal silk technology could enhance the regenerative capabilities of the hollow tubes on the market.

The following questions were raised:

- **Were there updated figures in relation to the global market for peripheral nerves repair as the figures in the licence referred to the period 2013 to 2022?**
  It was confirmed that it was still a massive market. Recent market analysis indicated that the market was anticipated to get towards 10 billion by 2025.

- **Two wound gaps were mentioned in the protocol: three and six cm. Which length would it actually be?**
  Initially it would be 3cm gaps, however flexibility was needed to allow up to a maximum of 6cm, so that if the initial trial was successful, it would provide opportunity in the future to demonstrate a bigger gap.

- **Pilot studies: how long would these be for?**
  They would be for about two to three weeks to check that the implants stayed in situ. The plan was then to go to about 5 months for efficacy and possibly up to one year though that would not be known until regulatory guidance had been received.

- **Why were single sex sheep being used in the large animal device testing models**?
  It was explained that this was primarily due to availability. Male sheep were generally not available as they were sold for slaughter at a young age. They were also generally more aggressive and more difficult to handle.

- **Was it possible for AWERB to see a copy of the ISO 10993 regulatory guidelines?**
  It was explained that the project licence holder only had a single user licence, so it was not possible for anyone else to view their copy of the ISO guidelines. If an ISO publication was required for multiple users then ISO would need to be contacted to explore the options.

- **Had this device already been tested in human patients?**
  Yes, an overseas collaborator had done this. They worked in a country that allowed compassionate use trials, which were treatment options that allowed the use of unauthorised medicine. Under strict conditions, products that were in development, could be made available to patients that had life-threatening, long lasting or seriously debilitating illnesses which could not be satisfactorily treated with any currently authorised medicine. The collaborators had been able to trial a form of this device in several patients. The results had been exciting, including a patient that previously had a completely dead arm, but was now able to move it.

- **As silk was being used, were the required moths a sustainable source? What would happen if the source of moth was no longer available – could different types of silk be used?**
  The moth that was used was not a threatened species so should be sustainable. A single moth generally produced a cocoon of roughly 4 km worth of silk. They were also developing Bombyx Mori, which was a domesticated silk moth and was the source of most silk and was now classed as an agricultural animal. Sericulture was an important industry that was unlikely to disappear.

- **The licence mentioned that the sheep would only be weighed if their visual condition deteriorated.** AWERB recommended that the sheep be weighed at least a weekly basis during post-op recovery. The weighing would help detect earlier any problems, rather than waiting for a drop in body condition. The sheep were not undergoing surgical operations that would cause a risk being weighed post-surgery.

- **Could there be any adverse events seen after the implants had been in place for a while?**
  Evidence showed that it was not possible to make a permanent tube that existed forever, as the tubes would stiffen up, resulting in the nerve getting constricted by the implant. Implants were therefore designed to be dissolvable. With regards to the luminal silk, it was designed to mimic the natural process that happened. With previous studies undertaken, the silk had dissolved after 10 months. The silk tubes did last a bit longer but still broke down by hydrolysis. They would then integrate into the human tissues. Histology would show some expected

inflammatory changes – as with any absorbable device – but it was important to assess that this process does not block nerve regeneration.

- **There was a statement in the PPL that peripheral nerve fibres were the same everywhere in the body – the connective tissue, the blood vessels, the mixed fibre types – were they all expected to build together? Would they all link in and repair together and maintain its vascularity?**
  Yes, the peripheral nerves were the same structure wherever they were. There was a huge body of evidence in humans which has shown that with fascicle to fascicle repairs, where nerves have been stitched back together, that it made no difference clinically whether the outer layer was stitched together or the fascicles lined up inside.

The project licence holder was thanked for attending the meeting. Due to shortage of meeting time, it was agreed that further discussions about the remaining sections of the project licence would be held outside the meeting, with a revised project licence then coming back to AWERB for further review.

2 PROPOSED WORK WITH CHINA

A RVC researcher was welcomed to the meeting. He explained that his group was involved in a overseas consortium study. As part of that, a study would be taking place in China which would involve two groups of pigs being challenged with enterotoxigenic Escherichia coli (ETEC). As the work was taking place in China a Home Office project licence was not required, however AWERB needed to review the proposed work to see if it was ethically acceptable.

The aim was to find alternatives for the use of colistin and zinc in dealing with diarrhoea in piglets, as that was one of the largest areas of usage of antibiotics in animal health. An initial challenge model had been carried out in a European country and although the results had initially been considered to be good, it had turned out that the pen holding the control group of pigs had been contaminated which had basically ruined the experiment. They now had opportunity to do another challenge study in China.

The following queries were raised by AWERB:

- **What control group was being used?**
  The researcher explained that a sham treatment would be undertaken.

- **What reassurances could be provided to AWERB about the conditions that the animals would be housed under and the standards of animal welfare the Chinese University would provide**?
  Images were shared of the different pens that were available in the facility. Their initial view was to have between two to three pigs in each pen, separated by plexiglass, so the pigs were separated but were still able to have some social interaction. The pigs needed to be separated so their faeces was sampled and scored separately to gain maximum information from the study.

- **The protocol made reference to piglets being housed in metabolic cages. How long would they be housed for? Did they need to be in these cages for the whole duration of collecting the faecal samples? Could the samples be collected from the pens?**
  This was all being discussed, and the current thinking was to have pens that were separated by plexiglass as a compromise. The advantage of metabolic cages meant that it was known which piglet the faecal sample was from, however individual containment of the piglets was definitely problematic from a welfare point of view. They had also considered using both metabolic cages and pens and transferring the piglets between them but there had been concerns about the stress that this would cause to the piglets, which might also have an impact on the quality of the data.

- **What was the expected mortality rate from this study?**
  It was anticipated to be very low – potentially one or two from the power calculation.

- **What would happen to the piglets after the experiment had finished?**
  They would be euthanised.

- **What schedule 1 methods were permitted in China**
  The scientists would use the methods that best fit UK regulations.

- **How would contamination between groups be prevented as that had been a problem with the first study? Were the pens from different treatments in the same room or were they in different rooms. What barriers would be used to make sure that there was not contamination?**
  Clarification would be sought on this.

- **Why was the work being done in China?**
  The scientists involved were very experienced and accomplished in this type of work and had also helped with advice ahead of the first study.

- **It was very difficult for an AWERB to review the ethical aspects of this study because the reason behind reviewing PPLs was to carry out a harm benefit analysis. The study mentioned that piglets would be monitored daily for general health and those in poor condition would be euthanised. What would be considered as poor health that would result in euthanasia? More information needed to be added about what they would be looking for and at what point would action be taken.**
  It was confirmed that this had been raised with the Chinese collaborators who had indicated they were happy to follow our guidelines and that this would be added to the next version of the document.

- **Did China have the same equivalent of NACWOs? What role and influence did the animal technicians have in the care of the animals and when they should be euthanised if they were suffering? It was important that the people making the decisions on when humane end points have been reached should not have a vested interest in the experimental results**
  Information would be obtained about the legislation that the Chinese collaborators worked under.

- **Would the facilities in China be visited before the study started?**
  It had not been possible to visit the facilities yet, but this would be looked into to see if it was an option particularly as it would also help firm up the scientific interaction between the groups.

- **Where were the piglets being sourced from? What checks were being done to make sure they were healthy?**
  The sourcing procedure would be checked.

- **What would happen to the study if China had to go into another lockdown?**
  This would need to be covered in the contract.

The researcher was thanked for attending the meeting. A copy of the revised protocol would be provided to AWERB for another review.

After the researcher had left the meeting, AWERB discussed how feasible it would be to ensure that the UK's standards for welfare of animals were implemented in this study. The scientists seemed like they were open to suggestions which was encouraging. Also if a contract had not yet been signed,

the protocol could be appended to the contract setting out that this was what was expected to be delivered. This suggestion would be fed back to the researchers.

3 MINUTES OF PREVIOUS MEETINGS

The minutes of the meeting held on 11 January 2023 were confirmed as an accurate record.

4 ANY OTHER BUSINESS

4.1 Petition debate in Parliament – 16 January 2023

AWERB's attention was drawn to a petition debate that had taken place in Parliament about the increase in numbers of scientific procedures that were conducted on animals (in particular dogs, cats, horses and monkeys) and a request that the Home Office share any data they had collected on the reasons for that. The debate had been very one sided with no consideration that the returns included animal work that was done for the benefit of the animals; that the numbers did not necessarily reflect the numbers of animals that have died or even suffered as it would include procedures such as blood samples.

AWERB were advised that similar concerns had been raised by Understanding Animal Research (UAR) who had subsequently written to the MPs involved in the debate pointing out the errors and incorrect assumptions that had been made.

5 DATES OF NEXT MEETINGS

These were scheduled as:

- 22 February: standing agenda items meeting
- 8 March: PPL review meeting

Secretary
16 February 2023