DRAFT

CONFIDENTIAL MATERIAL

THE UNIVERSITY OF BIRMINGHAM

BIOMEDICAL ETHICAL REVIEW SUB-COMMITTEE (BERSC)

28th September 2017

MINUTES

Present:

17/09-01 Apologies

17/09-02 Minutes

The minutes of the meeting held on 17th August 2017 were considered by the Committee and were approved subject to minor amendments.

17/09-03 Matters Arising

Filming was recently carried out within BMSU by the Journal of Visualized Experiments (JoVE) and it was felt that this went very well. More generally, it is hoped that a bank of filmed experimental techniques can be established for internal use.

17/09-04 Chairperson's Items

There were no Chairperson's items to report.

17/09-05 Verbal Reports from the Director of BMSU and Named Persons

Report from the Director of BMSU:

- The disruption caused by the building work on the ground floor of BMSU is now hopefully coming to an end. The autoclave is in the building and is being installed and commissioned. This work represents a significant improvement that will make the service area more functional. Efforts are ongoing to get the new bedding disposal system up and running.

- Several new Birmingham Fellows will soon start to work within BMSU. Linked to this, the aquatics facility will be expanded and there will be some resourcing implications in terms of the level of staffing required.

- A new research group has recently joined the University and will be bringing a number of strains of mice over from Australia.

- BMSU is currently running at approximately 80% capacity. If there is a need for greater capacity it could be achieved by rearranging the layout of some rooms. It was emphasised that there is no possibility of work with larger animals being undertaken within BMSU.

- There is now only one Home Office Inspector assigned to the University. The Inspector is very efficient and it is hoped that

applications will continue to move through the system smoothly.

- Work on the new Project Licence application form is ongoing. It is likely to look quite different and as there will be a tendering process involved for the electronic platform, will probably take some time to develop.

- A new teaching project has been proposed which initially required two rats; the plan was subsequently changed to use mice rather than rats and instead of sourcing animals specifically for the project, tissue will be used from animals which were already due to be humanely killed. More widely, the sharing of tissue from animals used in experiments is already ongoing, is strongly encouraged and is co-ordinated within BMSU.

- BMSU has again hosted the Universities Training Group, which includes all providers of the Home Office courses.

- Existing BMSU animals were used for training on handling, rather than sourcing animals specifically for this purpose.

Report from the Named Veterinary Surgeon (NVS):

- Earlier concerns about the possible impact of the BMSU building work upon breeding performance have so far been unfounded.

- Difficulties continue in relation to BMSU's Xenopus frog colony, as the frogs are still producing a proportion of immature eggs. The NVS and the NACWOs have been in touch with a number of experts and apparently this is a rare problem. Factors which have been adjusted so far, to no effect, include diet, temperature and hormone dosage. It may eventually be necessary to replace the animals if the quality of their eggs does not improve. New frogs are being bred in-house and will be used as replacements if needed. The NVS will be attending an NC3Rs amphibian workshop and will seek further advice there.

Report from the Named Animal Care and Welfare Officers:

No items to report.

17/09-06 Report from the Fast Track Procedure

The fast track procedure is up-to-date and a record of matters discussed is stored on the Committee's Collaborate pages.

17/09-07-1 Application Ref TBA – Targeting of B cells in rheumatoid arthritis

The researchers have identified a population of B cells in the joints of patients with rheumatoid arthritis, which contribute to inflammation and disability. They express a surface protein which is unique to this type of cells. The researchers have produced human recombinant antibodies specific for this protein and have tested and selected them for their ability to deplete these B cells in vitro. As the next step towards development of a new drug the researchers now need to test whether these antibodies deplete B cells expressing this marker protein in vivo in an animal model.

It was explained that the researcher who will hold the Project Licence is actually a Co-I, but has more experience with animal research than the PI and it is therefore more appropriate that they oversee the Project Licence. Both the PI and the Co-I gave a presentation explaining the application to the Committee.

The Committee queried the funding status of the proposed work and it was explained that it is funded by a current grant. The researchers have also been asked to resubmit a funding application very shortly to the MRC.

The 3Rs section of the NTS is quite vague and lacks detail. Some refinements are already in the application but have been included in the sections on adverse events and should therefore be moved.

It was felt that some of the language used within the application is euphemistic, e.g. 'a bit unsettling', and as this is a moderate severity licence the impact upon the animals should be more clearly stated.

In the section on 'Replacement', it is stated that this in vivo work is 'required by law' and it was felt that this should be amended as the work is more 'proof of principle', although it was noted that the MHRA have emphasised the need for this work.

The researchers will meet with the NC3Rs Midlands Programme Manager to obtain further guidance on the 3Rs.

An explanation of how the data will be blinded should be included in the application. The NC3Rs' EDA was used when planning the study and this should be stated in the application and the EDA printout should be included as an attachment. It was felt that the study statistics

are difficult to understand without a description of the parameters being tested and more detail should be included on this.

Objective 2 of the project plan should be reworded as cardiac puncture under deep terminal anaesthesia is not a method of culling.

Regarding the dose volumes, 200ml per kilo is an error and should be corrected.

The Committee asked for clarification about the purpose of the proposed pilot testing. It was explained that the purpose of the pilot is to titrate the dose of cell transfer needed. Also, it is hoped that it will be possible to carry out IVIS imaging at an earlier point than in previous experiments (representing a refinement) but the researcher first need to test the sensitivity of the scanner.

The Committee queried how many times each animal is likely to be anaesthetised to allow IVIS scanning to take place. It was explained that within a 12 day period an animal would have a maximum of 6 episodes of anaesthesia and that this would still fall within the moderate severity banding (albeit at the upper end).

Regarding the title of the study, the Committee noted that this is not actually a rheumatoid arthritis model, but is instead about developing a drug for the treatment of rheumatoid arthritis.

After the PI left the meeting, the Committee continued its discussions.

It was reiterated that the proposed work is 'proof of principle' and is a necessary element of a project which has already received MRC funding.

The NTS should be revised to ensure that it is understandable by a lay person.

Regarding the 3Rs, it was suggested that the proposed use of IVIS could be presented as either a reduction or a refinement. In general the 3Rs section of the application should be strengthened and the input of the NC3Rs Midlands Programme Manager should be incorporated.

Resolved that:

The revisions discussed above will be made and feedback will be obtained from the Home Office Inspector and incorporated into the application. Once the Chair is happy with the changes, a recommendation will be made that the Establishment Licence Holder submits the application to the Home Office.

17/09-07-2 Application Ref TBA – Mechanisms of memory destabilisation to facilitate reconsolidation impairment

The overall aim of this application is to explore whether disruption of a retrieved memory can effectively reduce the expression of fearful behaviour and reward-seeking behaviour. The researchers also aim to determine the mechanisms by which retrieval leads to this opportunity for memory impairment, opening the possibility to enhance the disruptive potential.

The PI gave a presentation explaining the application to the Committee.

The Committee asked why foot shocks will be used, as they aren't part of the normal experience of the animal – it was queried whether a more naturalistic stimulus, such as sight or smell could be used to represent a danger. It was explained that the use of the most obvious naturalistic alternative, a synthetic analogue of fox urine, poses significant technical difficulties as it is hard to link it to a specific, temporary and resolved experience. Also, it would represent a more severe experience for the animal than the use of foot shocks, as would the use of the other alternative of a 'social intruder' model. It was noted that foot shock experiments have very good predictive validity.

The Committee queried how much pain the animal is likely to experience as a result of a foot shock and the PI clarified that it is similar to an intense static shock. Regarding the number of shocks to be administered, the majority of animals will experience 1 or 2 shocks, with the maximum number being 15 in one day followed by 2 further shocks later on. The shocks create anxiety, which affect future experience.

Based on work carried out to date, it was confirmed that the number of animals stated in the application is a sensible estimate.

Some concerns were expressed about the use of foot shocks to induce fear and anxiety, particularly as it is not clear that the benefits outweigh the harms in a basic science study which is not immediately translational. It was noted that the Home Office Inspector has recently visited BMSU to observe some foot shock experiments and members of BERSC are invited to do the same if they would find it helpful. It is generally agreed that the experience of an animal undergoing a foot shock is relatively minor and is much milder than one would assume when hearing the experiment described. The NVS felt that the surgery represents more of a potential welfare issue than do the foot shocks.

After experiencing a foot shock, the animals generally display fear by 'freezing' (not moving) in approximately 40-50% of cases. Shocks are usually cued rather than being unpredictable and it was noted that unpredictable shocks would create a more generalised level of anxiety than do cued shocks.

The Committee queried whether the proposed work is trying to model PTSD and addiction. The PI responded that the work is modelling aspects of both of these conditions, but not the conditions in their entirety. It was explained that there are already ongoing clinical studies being carried out in this area with human participants, using beta blockers and targeting memory reconsolidation. However, it is not clear whether such work is either safe or effective – the proposed animal work is effectively 'catching up' and informing the translational work which is already happening.

It was explained that the duration of the foot shocks is usually between 1 and 1.5 seconds. The duration and strength of the foot shocks will be clarified in the application.

The Committee asked whether there is any evidence that the memory mechanisms tested in the proposed work are the same in rats as in humans. The PI responded that there is already very similar translational work being undertaken and so far, there is nothing to suggest that the model is not predictively reliable.

Regarding the surgical procedures, considerable effort has been made to refine the techniques used. Animals are now only housed singly for 7 days and are jointly housed at all other times. Antibiotics are given before and after the procedure and analgesia is provided as required. It was suggested that the PI should amend the application to better explain these refinements.

The animals are usually at approximately 90% on normal growth charts and any concerns about their growth are rapidly identified and addressed. The application should be amended as the figure stated in relation to percentage of normal growth is currently 85%.

The need for intracranial surgery should be made clearer in the NTS.

It was noted that in protocol 1, all steps are currently optional apart from schedule 1 killing. This should be corrected to indicate that the behavioural experiments are not optional steps.

After the PI left the meeting, the Committee continued its discussions.

It was explained that because of the use of cocaine and nicotine this application will be assessed by a special sub-group of Home Office

Inspectors, to ensure consistency of review across such projects involving addictive drugs.

It was explained that whilst it is not technically necessary to kill the animals after protocol 1, it would not be possible to suitably rehome such a large number of animals. It was emphasised that the tissue of the animals is put to as much use as possible in other studies.

It was suggested that the references to translational work should be removed from the application as it is essentially a basic science study. However, on the other hand it was felt that the references to translational work provide important context.

It was agreed that this is not a model of PTSD, but that the work will have implications for the condition.

Resolved that:

The revisions discussed above will be made and feedback will be obtained from the Home Office Inspector and incorporated into the application. Once the Chair is happy with the changes, a recommendation will be made that the Establishment Licence Holder submits the application to the Home Office.

17/09-07-3 Application Ref TBA – Impact of chronic intermittent hypoxia on atrial electrical stability

The aims of this application are to characterise a new mechanism showing how repetitive exposure of the heart to low oxygen causes atrial fibrillation and to evaluate whether the detrimental electrical changes can be protected against by specific anti-oxidant drug therapies or genetic manipulation.

The PI gave a presentation explaining the application to the Committee.

It was noted that the Home Office Inspector has commended this application as one of the most well-written she has seen in some time.

The Committee asked for further information about the nature of and concerns relating to oxidative stress. The PI explained that when cells do not have enough oxygen to create energy in the usual way, they start to produce energy via alternative means which creates free radicals. Oxidative stress induces a protective mechanism within cells, a reaction which reduces their acute function but which protects against cell death.

The short pulsed changes at 5% oxygen result in short-term physiological responses which reverse as soon as the oxygen content rises. It is very unlikely that symptoms such as hyperventilation will be seen during the experiments, given the proposed combination of duration and oxygen levels.

It was confirmed that this work mimics what a sleep apnoea sufferer will experience and that it is an accepted and established model.

During the experiments the entire home cage is placed within the apparatus and the animals remain with their cage mates.

It was explained that the equipment for ECG measurement has 4 electrically sensitive pads which allow an ECG reading to be taken when the animal's feet are in contact with the pads. There is no need for direct restraint as the animal is contained within a tube.

It was felt that the plan of work currently suggests that most animals will experience all of the possible interventions and the PI clarified that this is not the case and will be explained more clearly.

It was noted that the best technique for assessing structural change is the measurement of atrial size. Work is ongoing to develop a system for 3D data acquisition for the future.

Some of the information within the refinement section will be moved to the section on reduction.

Whilst the ARRIVE guidelines relate to the reporting of findings, they also have wider implications for good scientific practice and the PI emphasised the importance of these guidelines in his approach to research.

Any potential adverse events relating to the use of the plethysmography chamber should be explained in the application (e.g. reductions in activity, alteration of breathing patterns).

The Committee queried whether intraperitoneal injections will be required and it was clarified that they will, as some drugs are not suitable for delivery via mini-pump.

After the PI left the meeting, the Committee continued its discussions.

Discussion about the 3Rs needs to be strengthened within the application and comments from the NC3Rs Midlands Programme Manager will be passed on to the PI.

Resolved that:

The revisions discussed above will be made and feedback will be obtained from the Home Office Inspector and incorporated into the application. Once the Chair is happy with the changes, a recommendation will be made that the Establishment Licence Holder submits the application to the Home Office.

17/09-08 Matters relating to the 3Rs

Joint 3Rs day

This event has recently taken place and was well-received. Of the 150 places in total, only 10% of the attendees were from the University of Birmingham; however, Birmingham was well-represented in terms of posters. The University of Birmingham has volunteered to host the event next year and it is hoped that this change of location will increase attendance from Birmingham.

NC3Rs Summer School

A number of Birmingham researchers recently attended the NC3Rs Summer School and feedback about the event was very positive.

Work of the NC3Rs Midlands Programme Manager

The NC3Rs Midlands Programme Manager reported that over recent weeks, their work has included communicating with students, attending departmental meetings and sharing best practice. Establishing contact with researchers has been proving a challenge and ideas from BERSC on how to do this were welcomed. It was suggested that one of the main issues is the location of events, as holding events on-site is more likely to encourage good attendance.

17/09-09 Any Other Business

There was no other business to discuss.

17/09-11 Date of Next Meeting

The date of the next meeting is 9th November 2017.

GLOSSARY

3Rs	Replacement, Reduction and Refinement
ARRIVE	Animal Research: Reporting of In Vivo Experiments
B cells	B lymphocytes, a type of white blood cell
BERSC	Biomedical Ethical Review Sub-Committee
BMSU	Biomedical Services Unit
Co-I	Co-Investigator
ECG	Electrocardiogram
EDA	Experimental Design Assistant
IVIS	In Vivo Imaging System
JoVE	Journal of Visualized Experiments
MHRA	Medicines and Healthcare products Regulatory Agency
MRC	Medical Research Council
NACWO	Named Animal Care and Welfare Officer
NC3Rs	National Centre for the Replacement, Refinement and Reduction of Animals in Research
NTS	Non-Technical Summary
NVS	Named Veterinary Surgeon
PI	Principal Investigator
PTSD	Post-Traumatic Stress Disorder
TBA	To Be Announced