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THE UNIVERSITY OF BIRMINGHAM

BIOMEDICAL ETHICAL REVIEW SUB-COMMITTEE (BERSC)

17th December 2015

MINUTES

Present:

15/12-01 Apologies

15/12-02 Minutes

The minutes of the meeting held on 12th November 2015 were considered by the Committee and were approved subject to amendments.

15/12-03 Matters Arising

The PI's response to the issues raised by the Committee in minute 15/11-07-1 was circulated to the Committee. This document was considered to be very helpful, and it was agreed that a similar response document should be produced for any future applications which raise substantial issues or concerns.

Application 15/11-07-2 has been redrafted and is now more tightly focused on the recently funded work.

15/12-04 Chairperson's Items

It was reported that a replacement has been found for the outgoing lay member. The new lay member will attend future meetings.

15/12-05 Verbal Reports from the Director of BMSU and Named Persons

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Report from the Director of BMSU:

- Interim reviews will begin in 2016 for all Project Licences which have reached their halfway point.
- The new Home Office Inspector has visited BMSU and is hoping to attend a future BERSC meeting.
- The first electronic Project Licences have been granted. Some 'teething problems' with the system have been experienced and these have been fed back to the Home Office. At the moment researchers are editing their applications as Word documents and then uploading them into the system.
- It was reported that the Animals in Science Committee is organising a system of 'central hubs' and 'spokes' for AWERBs. The Midlands hub will be Leicester, and Birmingham will be a spoke.
- A number of memory sticks containing the latest RSPCA/LASA guidance were handed out to Committee members for information.
- It was reiterated that there is considerable support from Birmingham for the appointment of an NC3Rs Midlands outreach worker, and this matter will shortly be discussed by the BMSU Strategic Board.
- In 2016, a new quarantine room will be made operational within BMSU. This room will be for initial exploratory experiments on animals which have come into the unit from external sources. This will allow such work to be carried out without any risk of infecting the main colonies within BMSU.
- A second IVIS unit, which has been built in-house, has been installed within BMSU. Use of the unit will start in 2016.
- All other matters were reported as being business as usual and running smoothly.

Report from the Named Veterinary Surgeon:

- The NVS discussed some current issues relating to the PhenoMaster system. PhenoMaster is a modular system which allows the measurement of an animal's metabolic rate whilst in its home cage, avoiding the need for a stressful move to an unfamiliar cage. The system therefore represents a refinement.

CONFIDENTIAL MATERIAL

However, a couple of difficulties are being experienced in relation to the system, as follows:

- Animals must be singly housed for around 5-7 days when using the system. It is very unlikely that such animals (particularly if aged) will be able to rejoin a group. Consideration is being given to how best to mitigate the welfare issues of single housing via environmental enrichment, infertile companion animals and the possibility of acclimatising groups rather than individual animals.
- The drinking and feeding systems for the animals are different to those that they are used to. A longer than anticipated period of acclimatisation is required, and this may necessitate applying for an amendment to the project Licence. It is possible that additional food and water may be placed in the cage for those animals that will not use the main feeding and drinking systems.

Helpful input on the above has been obtained from external institutions and efforts are being made to resolve the problems within BMSU.

- The new batch of *Xenopus* frogs (see minute 15/11-05) has now arrived at BMSU. It was reported that the frogs are very large and so far they seem to be of good quality.

15/12-06

Report from the Fast Track Procedure

The fast track procedure is up-to-date, and there are no outstanding issues.

15/12-07-1

Application Ref TBA – Explore the mechanisms of persistence of Tertiary Lymphoid Organs (TLOs) and the relationship with secondary lymphoid organs

The objectives of this project are to investigate the mechanisms of persistence of TLOs and to consider whether stromal cells are involved in the persistence of TLOs and/or whether the drainage system from the inflamed tissue is defective. The project will also seek to establish whether the TLOs would disappear, and with them the disease, if these problems were corrected.

The Home Office Inspector has not yet commented on this application.

CONFIDENTIAL MATERIAL

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

It was explained that injectable anaesthesia will be used rather than isoflurane because of the need to keep the animals' jaws open for salivary gland cannulation. In the non-technical summary it is stated that analgesia will be provided prior to anaesthesia; the NVS noted that analgesia would usually be given both before and after, and this should be explained consistently. The reference to NSAIDS has been included in error and should be removed.

The processes in place for training should be fully explained in the application. The Committee asked for further information about the experience of the research team in carrying out multiple cannulations. The PI explained that a specific researcher has carried out this technique on around ten separate occasions.

The Committee was informed that the proposed procedure for cannulating the salivary gland represents a considerable refinement over previous methods as it is very quick and has a high success rate.

It was noted that replacement is a focus of the broader work of this research group, particularly work on co-culture systems using both stromal cells and lymphocytes. It is hoped that this will grow to be a larger part of the current study. It should be made clearer within the application where co-cultures may be possible, and the limits of this technique should be explicitly stated.

Whilst every effort is made to use human cells where possible, it was explained that it would be almost impossible to carry out some of the proposed work using human cells. This should be made clear in the application.

In relation to the diphtheria toxin model, it was explained that it is possible to give diphtheria toxin to mice as they do not have the diphtheria toxin receptor. There have been some difficulties with this model as the mice tend to lose weight and can seem generally unwell; a small number of animals in previous such experiments had to be culled. It has been established that allowing a rest period between the required injections improves the condition of the mice and this should be considered a refinement. In this model, mice will be given pain relief if they appear unwell (not all mice are expected to require this). Mice which are given diphtheria toxin will not be subject to multiple cannulations.

The PI was advised to amend the application to include more information about the 3Rs and to provide specific examples of them in the context of this project.

CONFIDENTIAL MATERIAL

The descriptions of humane endpoints in the application should be revisited to ensure that they are consistent. It should also be clarified whether intermittent hunched posture is an endpoint or a trigger for increased monitoring.

Whilst some mice will experience dryness of the eyes and mouth, it is not anticipated that this will be enough to require lubrication.

It was felt that discussion of the proposed pilot studies should be strengthened within the application.

A number of funding awards have been secured by this research group. The group includes postdoctoral researchers and medical students who will be, or who are already, appropriately trained.

Part D of the application should be revisited to make it clear that the work will involve some testing of repurposed compounds with therapeutic potential, rather than just being pure basic research. The testing of compounds should be stated as a separate objective within the application and the study should be identified as translational in the relevant section.

In discussion with a statistician, it has been established that for some biological studies, two salivary glands can be used from one animal thus reducing the number of animals required. This is considered a refinement. When testing compounds it will only be possible to cannulate one salivary gland per animal.

The splenectomy model may carry an increased risk of infection and the researcher team will visit other institutions where this model is already being used to learn from best practice.

It was noted that the number of animals required for this work is large; it was clarified that the number includes those animals required for breeding and it is based upon the predicted expansion of the research group. The numbers stated in the non-technical summary should be checked as they are not consistent with numbers given elsewhere.

Information about the incidence of TLO disorders in human patients and about the impact of these disorders on quality of life should be included in the application.

The PI explained that tamoxifen diet has been trialled as a refinement, but has not been successful for this work so far. It is still included in the licence application as it is hoped that future work may make its use more viable.

CONFIDENTIAL MATERIAL

Rather than taking tail vein blood samples, the researcher will adopt saphenous vein blood sampling as a refinement.

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

Regarding amendments required to the non-technical summary, in addition to those already discussed the PI should ensure that all technical terms are explained or reworded.

It was reiterated that part D of the application should be amended to be explicit about the proposed testing of compounds which may eventually progress to clinical trials.

It was suggested that information should be added to the application on the arrangements for training the research team in the techniques required for the splenectomy model as, although they are simple techniques, they are not currently carried out at Birmingham.

It was emphasised that cannulation of salivary glands will only be undertaken by experts in this technique, who have demonstrated the required dexterity in work with cadavers.

The Committee discussed the proposed use of anaesthesia, and it was noted that if sedation were used instead the animals would take just as long to come round. It was considered better from a welfare perspective to use anaesthesia than sedation.

The PI should revisit the total number of animals stated in the application to ensure that it is accurate and encompasses both the animals required for the biological studies and for the testing of compounds. When discussing the number of animals required, expressions such as 'only' and 'not more than' should be avoided.

Resolved that:

The revisions discussed above will be made and feedback will be sought 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.

15/12-08

Any Other Business

It was reported that the University of Birmingham had 18 Project Licences granted during 2015.

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It was suggested that when Committee members are contacted about forthcoming BERSC meetings, a link to the relevant papers on Collaborate should be included each time for convenience.

15/12-09

Date of Next Meeting

The date of the next meeting is 21st January 2016.

GLOSSARY

3Rs	Reduction, Refinement and Replacement
AWERB	Animal Welfare and Ethical Review Body
BERSC	Biomedical Ethical Review Sub-Committee
BMSU	Biomedical Services Unit
IVIS	In Vivo Imaging System
NC3Rs	A UK-based scientific organisation dedicated to replacing, refining and reducing the use of animals in research and testing
NSAID	Non-Steroidal Anti Inflammatory Drugs
NVS	Named Veterinary Surgeon
PI	Principal Investigator
PPL	Project Licence
RSPCA	Royal Society for the Prevention of Cruelty to Animals
TBA	To Be Announced
TLO	Tertiary Lymphoid Organ