CONFIDENTIAL MATERIAL

THE UNIVERSITY OF BIRMINGHAM

BIOMEDICAL ETHICAL REVIEW SUB-COMMITTEE (BERSC)

23rd April 2015

MINUTES

Present:

15/04-01 Apologies

15/04-02 Minutes

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

15/04-03 Matters Arising

Minute 15/03-05 – Condition 18 notification relating to unexpected, unexplained hind limb paralysis

The Committee was informed that since the reported incidence of unexpected, unexplained hind limb paralysis, no similar issues have arisen when using a new batch of animals. Nothing untoward was found during post mortem examination of the affected animals. This therefore seems to have been an unfortunate but isolated occurrence with no obvious cause.

Minute 15/03-05 – Issues relating to xenopus frog colony

Another supplier of captive-bred xenopus frogs has been found and will now be used.

Minute 15/03-07-2 – Protecting and repairing injured retinal ganglion cells

Feedback from the last BERSC meeting has been discussed with the researcher and has been incorporated into this application, along with additional comments from the NVS. The amended version of the application has been included on BERSC's SharePoint site for information, and is now with the Home Office Inspector.

The Committee again noted the need for additional researchers to be trained in the relevant techniques, and for these researchers to then carry out the techniques (thus relying less upon one researcher for all procedures), and it was agreed that an action plan should be formulated with realistic timeframes for this. The Director of BMSU and the NVS will take this forward with the research team.

15/04-04 Chairperson's Items

No Chairperson's items were reported.

15/04-05 Verbal Reports from the Director of BMSU and Named Persons

Report from Director of BMSU:

Key issues reported were:

- The Committee was informed that a recent news article made reference to animal experiments carried out at Birmingham, specifically those using an animal model of brain trauma. The Home Office Inspector visited in response to this, consulted

with the NVS and considered all the relevant facts along with BERSC minutes. The Inspector was entirely satisfied with the approach and procedures followed by BERSC, and it was noted that this application had been reviewed on two separate occasions by the Committee.

- The cryo facility is now back up and running after temporary problems.
- MPV has now almost been eradicated within BMSU.
- A senior Home Office Inspector has visited BMSU to provide useful help and advice to a researcher on matters of experimental design.
- Researchers' training records are being updated, and this will be done periodically going forwards.
- A BMSU Users' Forum, attended by the Home Office Inspector, will be held on 24/4/15.
- The creation of an animal biobank will be proposed to the BMSU Strategic Group. This should be cost neutral in the short term, but in the longer term may require additional space.

Report from the NVS:

No additional items were reported.

15/04-06 Report from the Fast Track Procedure

It was reported that the fast track procedure is up-to-date, and there are no outstanding issues.

15/04-07 Project Licence Proposals

15/04-07-1 Application Ref TBA – The physiological role of B3 vitamins in energy metabolism

The aim of this project is to better understand and accurately measure B3 vitamin effects on metabolism and muscle mitochondrial energy production during ageing and exercise to understand normal physiological processes and age-related disorders and test the interaction with exercise.

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

The Committee queried the likely age of the youngest mice to be used, and the PI clarified that they would probably be 6-7 weeks of age.

There are a large number of optional steps included in the stated procedures, and the PI was asked whether any animals would undergo all of the options. The PI explained that a typical animal experiencing the 'maximum' combination of options would likely undergo aging, endurance exercise, various methods for assessing energy expenditure and the administration of supplemental vitamins.

The researcher was advised to state the prospective severity of the study as moderate, even though when retrospective severity is assessed it is anticipated that a proportion of the procedures will be classified as mild. However, if the prospective severity were to be stated as mild at the outset, this would place considerable restraints on the work and could mean that experiments would have to be halted at a crucial point. It will be explained to the Home Office Inspector that while the cumulative experience of the animals may be moderate, it is more likely to be mild.

The Committee queried whether it would be possible to carry out the proposed work with humans, rather than animals. The researcher explained that as the experiments require aged subjects, animal models are more feasible than human models in terms of duration. If, in an attempt to reduce the length of time required, human subjects of various ages were used rather than aging individual subjects during the study, the inherent variability would mean that a huge number of participants would be needed to power the experiments. Also, the availability of genetically altered mice provides valuable opportunities to study particular metabolic pathways. Finally, it is easier to control for healthy subjects, similar genetics, etc when using an animal model than when working with human beings. The Committee felt that the application should be amended to strengthen the justifications given for using an animal model.

The Committee queried the anticipated attrition rate in an aged mouse population. The PI explained that data for the strains of mice used puts survivorship at 85% at 24 months.

It was clarified that if an animal is found dead, its retrospective severity must be classified as severe, even if the cause of death is natural causes (unless the researcher can prove that the animal did not suffer). The Committee discussed the implications of this for aging studies, and it was explained that if an animal is found dead, a condition 18 notification must be submitted to the Home Office. In the current application, it is anticipated that less than 5% of animals will be found dead, and this should be stated in the licence application.

The Committee queried whether the PI's main focus was to increase longevity, or to increase quality of life/healthiness in old age. The PI

explained that the focus is to make old age as healthy as possible, until an individual reaches their natural age of death. It was acknowledged that increasing longevity may be a side effect of this.

The PI was asked whether both sexes of mice will be aged, and it was clarified that only aged males will be used. This research unit has traditionally worked with aged males rather than females, and to change this now would introduce confounding factors. However, the Committee noted that greater welfare concerns are often encountered when aging males rather than females. Because of this, aged males cannot be obtained from commercial breeders. It was queried whether the stated 85% survivorship is for both males and females, as if it is, and if only males will be used in the planned experiments, the correct percentage may be lower. The PI will look into this, as it may impact upon the number of animals needed.

The Committee discussed the possibility of providing enrichment in the cages of aging mice, such as a voluntary running wheel. This is possible, but it may interact with the planned exercise protocols. BMSU is able to monitor the activity of animals using such wheels, so basal activity levels could be monitored, and it was clarified that no separate protocol would be required in order to incorporate this into the study.

It was noted that on a high-fat diet, wild type mice will show few changes over a period of just 10 weeks. There are other diets available which would give rise to greater changes during the same time period; however, the PI explained that the high-fat diet does result in the changes required for his experiments, with minimal impact upon the welfare of the animals. The PI was advised to revise the application to allow for the use of a variety of diets, so as to avoid limiting the experiments unnecessarily.

While the researcher plans to use stable isotopes to achieve steady state distribution without anaesthesia, it was suggested that this may not be possible and a non-steady state system may be the best alternative.

The Committee queried whether the PI will determine VO_2 max prior to carrying out the exercise protocols. There is no intention to do this, as it is possible to rely upon existing data and determining VO_2 max would increase the severity, as exercise protocols carried out to exhaustion or near to exhaustion would be classed as severe.

The PI explained that ex vivo analysis will be carried out at the end of the study, and this will help to standardise the data. It was noted that whilst grip test monitoring involves considerable variation, other available methods for measuring skeletal muscle strength would introduce additional welfare issues.

The Committee requested further information about the restraint tube to be used during glucose tolerance testing. It was explained that after injecting glucose, the researchers need to monitor the clearance rate of the glucose. The use of a restraint tube, a dark tube in which the mouse cannot move, allows very quick and efficient tail bleeding with minimum impact upon the animal. This is not a regulated step and therefore does not need to be specified within the application.

In response to a query about the intended approach to habituation, the researcher explained that initially, a mouse will be handled, shown the experimental equipment, and returned to its cage. This will be done a couple of times, then the equipment will be turned on at low speed. The animal will next be encouraged to run on the treadmill and rate and duration will be gradually increased. Habituating the animals in this way should eliminate any confounding effects of stress.

The application should be amended to state that the experiments will be randomised.

Some concerns were voiced that as currently written, this is a very broad project licence with many different elements. It was suggested that the wording of the key outputs should be tightened up to make them more specific.

The PI explained that the PhenoMaster cages to be used are effectively standard home cages, which is a big refinement when compared to the older metabolic cages, and this should be emphasised in the application. Continuous monitoring will not be required, and the cages will be alarmed in relation to gaseous exchange. The researcher will check whether there is a failsafe mechanism to override the gaseous exchange system in the event of a power cut.

It was suggested that a 10° grade for treadmill running was quite strenuous, and that the mice may be unable to run for an hour at 10°. The PI justified this as standard within the literature, but explained that most of the running will be on the flat, and that if an incline is used, it will be increased gradually. The PI will work closely with the NACWOs to ensure that the animals are not put under undue stress.

It was emphasised that the PI should not underestimate the amount of time/people/monitoring required for the proposed work.

The NVS expressed concerns that this is an acute protocol using aged mice. The PI explained that VO_2 max is age-dependent, and that therefore less exercise will be needed to stimulate the required response in older mice. The experiments will be at approximately 60-70% VO_2 max, so the animals are unlikely to reach the specified endpoints. Extensive pilot testing will be carried out prior to the exercise testing.

It was queried whether opportunities for collaboration may arise from this work, particularly in terms of the tissue available once the work is complete. Arrangements are already in place for cardiac tissue to be sent to a collaborator overseas, and further possibilities for storing and the local/external archiving of useful tissue should be explored - this will be followed up at the next meeting of the BMSU Strategic Group.

It is proposed that the animals will be housed singly for up to 2 days, up to once every 3 months. The researcher explained that in the literature, this has not been found to be problematic; however, the Committee felt that there may be problems associated with the single housing of aged male mice and considerable monitoring will be required when the mice are reintroduced to a group. This may raise the severity of the procedures from mild to moderate.

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

It was agreed that considerable work will be required to establish the protocols in this application, but the Committee was reassured that the NACWOs have extensive experience with similar models.

In response to a query about whether the higher likelihood of male mice being 'found dead' would render the work 'severe', it was explained that as long as the anticipated numbers are accurately reflected in the application, and appropriate notifications are made for any animals found dead, then there should not be a problem.

It was agreed that an interim review should be carried out for this work.

Concerns were expressed that providing a running wheel could increase the aggression of aged male mice. Careful consideration by the NACWOs will be needed in respect to this. Advice will also be sought from other institutions with relevant experience, and pilot work will be essential. It was queried whether the provision of a free running wheel could corrupt the data, in relation to variability and power. This will be assessed as the work progresses, and if necessary the wheels will be removed.

Resolved that:

The revisions discussed above will be made, and the revised version of the application will be recirculated to the Committee. Once the Committee is happy with the changes, the Chair will recommend that the Establishment Licence Holder submits the application to the Home Office.

15/04-08 Any Other Business

Educational remit of BERSC

It was agreed that the educational remit and responsibilities of BERSC will be put on the agenda for discussion at a future meeting.

Whilst it is important that AWERB members are kept appropriately informed, it was queried whether there is also still an intention for AWERB to be involved more widely in matters of education on animal research.

Tracking translational benefits of animal research

Many studies claim to offer translational benefits, and the Committee discussed whether the reality of such claims is ever checked as the research progresses. It was felt that this should be considered during interim review, and that if a translational aspect is stated in a licence application, it should be followed up.

An agreed **action point** is that a rolling cycle for interim reviews should be drawn up, and an interim review report form should be designed and tabled for consideration by the Committee. It was proposed that interim reviews will usually be carried out via a light touch procedure that will feed back into the Committee.

It was also suggested that REF outputs could be used to inform the Committee, particularly those 'impact' activities relating to animal work – this will be incorporated into the review report form.

Charles River visit to BMSU

On 14th May 2015 Charles River will give presentations within BMSU. Information about these presentations has been circulated to all licence holders.

Movement of live animal experiments into BMSU

Some concerns have been raised about the movement of all live animal experiments (e.g. intravital microscopy) into BMSU, and a group has been formed to discuss these issues.

It was suggested that the appropriate forum to discuss such matters is the MDS Strategic Group, rather than BERSC; however, in response it was strongly argued that BERSC is the appropriate forum for any ethical or welfare issues.

A paper laying out the concerns will be prepared for initial presentation to BERSC, and then if necessary more political matters can be passed on to the MDS Strategic Group.

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15/04-09 Date of Next Meeting

The date of the next meeting is 4th June 2015.

GLOSSARY

AWERB	Animal Welfare and Ethical Review Body
BERSC	Biomedical Ethical Review Sub-Committee
BMSU	Biomedical Services Unit
MDS	(College of) Medical and Dental Sciences
MPV	Mouse Parvo Virus
NACWO	Named Animal Care and Welfare Officer
NVS	Named Veterinary Surgeon
PI	Principal Investigator
REF	Research Excellence Framework
TBA	To Be Announced
VO_2 max	Maximal oxygen consumption