CONFIDENTIAL MATERIAL

THE UNIVERSITY OF BIRMINGHAM

BIOMEDICAL ETHICAL REVIEW SUB-COMMITTEE (BERSC)

18th August 2016

MINUTES

Present:

16/08-01 Apologies

16/08-02 Minutes

The minutes of the meeting held on 7th July 2016 were considered by the Committee and were approved subject to amendments.

16/08-03 Matters Arising

West Midlands regional hub for AWERBs

There is still no update on the activity of the West Midlands regional hub for AWERBs and no contact has been made by the hub Lead. If there is no progress on this soon it will be followed up by the Director of BMSU. It was noted that all necessary information from the Home Office is still reaching BMSU, just via routes other than the hub and spoke system.

Applications discussed in minutes 16/08-07-1 and 16/08-07-2

Both of these applications discussed at the last meeting of BERSC have been submitted to the Home Office Inspector for comment.

16/08-04 Chairperson's Items

There were no Chairperson's items to report.

16/08-05 Verbal Reports from the Director of BMSU and Named

Persons

Report from the Director of BMSU:

- The NC3Rs outreach worker for the Midlands has now been appointed and will start work in September 2016. The Director of BMSU recently met with counterparts in the animal research units at the Universities of Leicester and Nottingham to draw up a list of issues for the outreach worker to address. It is hoped that this will help to structure and focus the post, particularly during the first few months. The suggested initial matters for the outreach worker's consideration are as follows:

  - The NC3Rs Experimental Design Assistant.
  - Practice relating to single versus group housing of animals.
  - Animals with head-mounted equipment and chronic implants.

  These three areas are of interest to all three Universities involved. The outreach worker will attend meetings of all three AWERBs and will provide assistance to licence applicants on matters relating to the 3Rs (either directly or via University Research Facilitators). The suggestions above will be discussed further with the NC3Rs and any other suggestions are welcomed. The NC3Rs will also carry out assessments of how the 3Rs are embedded within each of the three Universities involved at the beginning and at the end of outreach worker's two year post to measure any changes.

- Regarding the need for statistical support for licence applicants, applicants are now being encouraged by the Home Office to utilise the NC3Rs' Experimental Design Assistant (EDA). This is an online tool which provides statistical guidance. All applicants are now expected to have attempted to use this when preparing their licence applications. As some users may not find the EDA intuitive, a presentation will be given on its use at the BMSU User Forum.

- A number of new staff have recently been recruited to work in BMSU.

- Part of the aquatics area in Biosciences will be refurbished (at no direct cost to BMSU) – a small area has been given up for other uses but the remaining area has been refurbished in such a way as to give the capability for future expansion.

- Schedule one training for new personal licence holders is up-to-date and there is currently no delay in training provision.

- BMSU was recently affected by a major steam leak, due to the failure of a door seal on the autoclave. Although this caused some inconvenience and disruption no animals were harmed. Thanks were given to colleagues from University Estates and Security who dealt with the situation extremely well.

Report from the Named Veterinary Surgeon:

- It is believed that the recent outbreak of pinworm within BMSU has now been eradicated. Export of live mice has been resumed, although from a welfare perspective the export of embryos rather than live animals is being encouraged.

- As a result of the attendance by the NVS and a NACWO at a recent meeting on sterile technique, the procedures for scrubbing up with BMSU are changing and Sterilium disinfectant gel will be used going forwards. Also, sponges will be used as swabs rather than cotton buds – the former are considered preferable as they leave no foreign matter behind.

- It was reported that a researcher who has recently joined the University from another institution has successfully established 9 new lines of mice at Birmingham. There has also been a successful round of IVF within BMSU and that the technology is now in place to carry out IVF going forwards.

Report from the Named Animal Care and Welfare Officers:

No further items to report.

16/08-06 Report from the Fast Track Procedure

The fast track procedure is up-to-date.

Interim reviews will be handled via the fast track procedure and an update on this will be given at the next meeting.

16/08-07-1 Application Ref TBA – Targetting MYB in Myeloid Leukaemia

The overall objective of this project is to determine how MYB is essential in myeloid leukaemia cells and how this knowledge can be used in the development of small molecule inhibitors of MYB as anti-leukaemia agents.

The PI gave a presentation explaining the application to the Committee. The application is for the renewal of one part of an existing licence – the original licence has been split into two going forwards. Due to the diary constraints of the PI, this application was at an earlier stage that would normally be submitted to the Committee; however, a revised version will be circulated electronically to the Committee prior to submission to the Home Office. The PI has recently had a related application reviewed by the Committee, and it is anticipated that many of the required revisions will be the same for both applications.

A non-technical summary should be prepared for submission with the application, as none was included.

The Committee queried whether the xenograft models progress as predictably as the mouse transfer models and the PI explained that whilst the xenograft models are less predictable, they do not usually result in death and so determining endpoints is less of a concern.

There was some confusion in the application relating to protocol numbers. There should be no protocol 4 and this will be amended in the application.

It was queried why the required breeding activity was included within the licence rather than relying upon the BMSU service licence. It was explained that this was appropriate because the required breeding is a significant and logistically intensive element of the proposed project and individual strains specific to this work are required.

The PI explained that the stated number of 4000 mice for mouse cell transfer in protocol 2 is an upper figure; it was considered to be a sensible estimate based upon previous usage in similar work.

It was suggested that it would be helpful to include a specific protocol for dose-finding work. The PI explained that pharmacokinetics may be outsourced.

In section D of the application, lethal irradiation is mentioned whereas only sub-lethal irradiation is included in the protocols. This will be corrected within the application.

In relation to the 'reduction' element of the 3Rs, more information should be provided about the statistics underpinning the work and the proposed group sizes. It was emphasised that there is a balance to be reached between a reduction in the number of animals used (i.e. by obtaining more data from each individual animal) and refinement as related to the welfare and experience of each individual animal.

The Committee queried whether 5000 mice will be sufficient for the proposed breeding programme. The PI explained that breeding will be rationalised, thus minimising the numbers required. Once a stock of the required primary leukemic cells have been built up and frozen, the requirement for live animals will drop considerably.

In relation to adverse effects, the Committee noted that very few specific humane endpoints are described within the application. The PI explained that apart from possible unexpected toxic effects from the drugs being tested, the leukaemia itself should never reach a stage where it causes significant adverse effects because blood markers will be monitored and the animals will be killed before the point at which adverse effects might arise. It was agreed that this should be stated more clearly in the application.

It will be necessary to take blood samples as regularly as possible over quite a small timespan in order to monitor blood markers. The smallest possible samples will be taken. It was noted that the PI may choose to make a case in his application to exceed the LASA blood sampling guidelines where necessary.

The potential adverse effects of intrafemoral injections should be stated within the application. It was clarified that opiate analgesia can be used for these.

In relation to protocol 3, it was queried why two doses of irradiation will be given with a break in between. The PI explained that this is to allow the researchers to observe any recovery which takes place – this will be explained more clearly in section D.

The PI was asked to revisit the large number of optional steps within the protocols to ensure that they are appropriately labelled. It should be made clear how many optional procedures each animal is likely to experience.

The reference to animals becoming ‘accustomed to’ the blood sampling procedure should be removed from the application as standard blood sampling procedure will be followed.

In protocol 3, the reference to cells derived from donor mice should be removed as protocol 3 is the xenograft protocol.

Protocol 3 should be amended to clarify that vehicle controls will be used.

After the PI left the meeting, no further issues were raised by the Committee.

Resolved that:

The revisions discussed above will be made and feedback will be sought from the Home Office Inspector and incorporated into the application. The application will then be circulated electronically to the Committee for comment. 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.

16/08-07-2 Application Ref TBA – Retrieval-relearning to strengthen memories

The objective of this project is to explore whether memory retrieval allows for subsequent relearning to strengthen an existing memory more effectively than other behavioural approaches.

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

The Committee expressed some concerns that all of the researcher's previous work has involved rats, whereas this new application will include work with mice. Though the PI has no personal experience of working with mice, the majority of existing literature in this field of study involves mice and another member of the research group has previously carried out studies involving mice and surgery on mice.

It is not anticipated that genetically altered mice will be required.

The PI explained that he would not initially be pursuing all of the objectives detailed in the application; to start with he would be carrying out pilot studies to obtain the data necessary to secure funding for future work.

It was agreed that as surgery on mice may not be necessary at all, and certainly won't form part of the initial work, it should be removed from the application and if necessary it can be added back in later as an amendment. Surgery may be used in the future to allow the PI to isolate a specific mechanism to an exact part of the brain.

Aged mice will be obtained from the supplier Charles River and the researcher will have access to the score sheets which the supplier uses with such mice.

It was clarified that there will be no restrictive feeding as part of this study.

The aged mice will be singly housed and will be provided with environmental enrichment as is best practice.

The Committee queried the statement in the application that 'mice would be culled if they show signs of abnormal behaviour or activity'. This was a cut and paste error and does not apply to the current application.

It was queried whether all mice are expected to learn in the same way, and whether all mice are likely to be suitable for use in the proposed experiments. The PI explained that he does not foresee a problem as he anticipates that the mice will have a strongly ingrained preference for novelty and he expects their object recognition memories and behaviour to be sufficiently robust.

The Committee requested further information about the nature of the retrieval/relearning model. The PI explained that in the initial learning phase, the animals would initially be exposed to the conditioning stimuli (e.g. a sound) and a shock. When the animal is then re-exposed to the stimuli in the future it will experience a learned fear response. After the initial phase, retrieval experiments will involve re-exposure to just the stimuli, whereas relearning experiments will involve re-exposure to both the stimuli and the shock.

It was noted that a large number of the animals used will act as controls and the experience of the control animals will be very similar to that of the experimental animals; for instance, for the controls the order of the phases of the study may be altered but the nature of the tests will otherwise remain the same.

The Committee queried whether the experiments have to involve a negative reinforcement (i.e. a shock) or whether a positive reinforcement could be used. It was explained that because the direction of this work is towards the memory basis for conditions such as PTSD and phobias, a negative reinforcement is more relevant. However, in the application it is indicated that this is basic science rather than translational work, and the PI acknowledged that if this work were translational there are more advance models of PTSD which could be used. It was felt that this should be better explained within the licence application.

It was queried whether mice of different strains may respond differently to the behavioural tests. It was also queried whether the aged mice to be obtained from Charles River may have had different experiences and may have been exposed to different stimuli during their development, causing them to respond differently to the tests. It was noted that there would need to be some reassurance that all of the aged mice have been raised in the same environment to ensure the

validity of the experiments. As Charles River has a dedicated facility for aged mice it is hoped that this will not be a problem.

The main collaborators for the work are based overseas; however, there are other researchers within the UK carrying out mouse behaviour studies and hopefully the NACWOs will be able to learn from them as necessary.

The reference in protocol 3 to 'long term consequences' relates to the fear response learned by the animals.

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

The Committee reiterated its concerns that the PI has no previous experience in working with mice and it was emphasised that the PI and BMSU will need to liaise closely with other researchers who do have this experience.

It was agreed that the Committee would require feedback on the progress of the research after one year rather than after the usual interim point (which is halfway through a 5 year licence) to ensure that the science underlying the work continues to justify the number of animals used.

As this will be pilot work in its early stages, the research team does not yet have sophisticated equipment for tracking and monitoring the animals' behaviour. This is likely to become necessary as the work continues and funding is obtained.

Regarding the proposed use of rats, the NVS expressed some concerns that the licence needs to better explain exactly what will occur and that better justification should be provided for the use of head mounts.

It was agreed that an appendix should be added to the application which details all of the proposed behavioural tests and their frequency and duration (e.g. maximum number of shocks to be given).

It was suggested that the application should be amended to avoid reference to longer term translational aspirations (e.g. understanding/treating PTSD and phobias) as this is currently a basic science experiment about the reinforcement and enhancement of memories.

It was noted that the NTS should be amended to ensure that it will be understood by a lay reader.

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.

16/08-08 NC3Rs items

- It is proposed that a website be developed to share 3Rs resources across the Universities of Birmingham, Nottingham and Leicester.

- Birmingham's outward-facing animal research webpages will be personalised with local examples and activities relating to the 3Rs.

16/08-08 Any Other Business

- The next CPD session for Project Licence Holders will be held on 12th September 2016. This is the second of two identical half-day refresher courses, the first of which was very well received. The sessions are backed by the Establishment Licence Holder, who is keen that all existing licence holders attend.

- Regarding the previously discussed need for statistical support for applicants, the progress of the EDA will be monitored and it may still be appropriate to identify a statistician to join BERSC.

- The Home Office Inspector, who sat in on this meeting, commended the Committee on its level of questioning of applicants and its discussion of the issues arising from the applications under review.

- Annual animal usage statistics have been published on Collaborate (the University's document sharing platform).

- It was reported that UAR are currently undertaking proactive work on the number of animals used in research and the University is developing a communications plan related to this.

16/08-10 Date of Next Meeting

The date of the next meeting is 29th September 2016.

GLOSSARY

3Rs	Replacement, Reduction and Refinement
AWERB	Animal Welfare and Ethical Review Body
BERSC	Biomedical Ethical Review Sub-Committee
BMSU	Biomedical Services Unit
CPD	Continuing Professional Development
EDA	NC3Rs Experimental Design Assistant
IVF	In Vitro Fertilisation
LASA	Laboratory Animals Science Association
MYB	MYeloBlastosis family of proteins relevant to the development of diseases of white blood cells
NC3Rs	National Centre for the Replacement, Refinement & Reduction of Animals in Research
NACWO	Named Animal Care and Welfare Officer
NTS	Non-Technical Summary
NVS	Named Veterinary Surgeon
PI	Principal Investigator
PTSD	Post-Traumatic Stress Disorder
TBA	To Be Announced
UAR	Understanding Animal Research
UK	United Kingdom