

CONFIDENTIAL MATERIAL

THE UNIVERSITY OF BIRMINGHAM
BIOMEDICAL ETHICAL REVIEW SUB-COMMITTEE (BERSC)

5th June 2014

MINUTES

4/06-01 Apologies

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14/06-02 Minutes

The minutes of the meeting held on 17th April 2014 were considered by the Committee and were approved subject to minor amendments.

14/06-03

Matters Arising

General concern about 'replacement' element of the 3Rs

Regarding the difficulties which some applicants seem to have in addressing 'replacement' in their licence applications, it was noted that a representative from the NC3Rs will soon be joining the Committee as an external member, and that the new member's contribution to this issue will be sought.

14/06-04

Chairperson's Items

No Chairperson's items were reported.

14/06-05

Verbal Report from the Director of BMSU

Member of the NC3Rs to join BERSC

As recommended by the Animals in Science Committee, a new member with no prior connections to the University has been invited to join BERSC. As discussed above, this new member is from the NC3Rs, and it is anticipated that their knowledge and experience will be valuable to the Committee.

Monthly induction session for new personal licence holders

A monthly induction session has been set up for new personal licence holders, where they will meet with the Chair of BERSC, the Director of BMSU and the NACWOs, and will learn about the processes within BMSU.

Home Office roadshow on retrospective severity

The recent Home Office roadshow on retrospective severity and the conditions of licences was well-received, but it was noted that the number of more senior project licence holders in attendance was disappointing.

Increased level of security within BMSU

The Committee was informed of an increased level of security within BMSU at the current time.

Compliance advice from the Home Office

The Committee was informed that the University is in discussion with the Home Office on a matter of compliance advice. The Committee will be kept informed.

Update on recent upgrading within BMSU

An update was provided on the progress of recent work to upgrade BMSU. It was reported that the theatres have been upgraded as planned, and three procedure rooms are being upgraded; one is being refurbished to give four workstations. The post-mortem room will gain additional workstations. It is hoped that this work will alleviate some of the space pressures within BMSU.

Clarification on BMSU's responsibility for education

Clarification was requested on BMSU's responsibility for education. It was explained that BMSU does have a responsibility for education and training, and that it now has named Training and Competency Officers, who are responsible for training and competency on behalf of the Establishment Licence Holder and who must report to BERSC. BERSC is also responsible for taking appropriate opportunities to educate its own members and Licence Holders.

Situation regarding Home Office delays

It was noted that the earlier Home Office backlog has now been cleared and the situation is now much improved.

Problems booking rooms for BERSC meetings

The Committee was informed about recent difficulties in booking rooms in the College of Medical and Dental Sciences, both for future BERSC meetings, and for the Home Office training course to be held in October. The Chair agreed that every effort should be made to ensure that rooms are made available for these essential courses and meetings.

14/06-06

Report from the Fast Track Procedure

A report from the fast track procedure was tabled.

14/06-07

Project Licence Proposals

14/06-07-1 Application Ref TBA – Characterising and inhibiting vascular disturbances

This application is for the renewal of an existing licence, and it has not yet been seen by the Home Office Inspector. It will be a project-specific licence rather than a service licence as has been the case in the past.

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

In relation to protocol 2, it was suggested that the PI may at some stage wish to administer inhibitory as an alternative to stimulatory agents prior to the administration of anaesthesia, and this will not be possible as the application is currently drafted. It was agreed that such work would largely be covered by an additional licence application. However, it was also agreed that pre-treatment with stimulatory and/or therapeutic agents should be added to the current application.

Protocol 2 will be amended to clarify that all injections will take place within BMSU. It was highlighted that the duration of the part of the experiment that is carried out under terminal anaesthesia must not go beyond the working day, as no overnight holding is possible in the room which will be used. Once anaesthesia has been administered, the longest experiments are likely to last approximately six hours.

Whilst reduction was addressed in the researcher's presentation, less information was provided about refinement or replacement. It was explained that replacement is not possible here as the effects of this work in a live animal cannot be fully mimicked *in vitro* (e.g. via techniques such as 'lung on a chip'), although the work will be guided by previous *in vitro* experiments, for example on the choice of therapeutic, stimulatory agents. Regarding refinement, every effort will be made to refine the methods used as the research progresses.

In the 'adverse effects' section of each protocol, it is currently stated that any animals shipped from an external source will be used on the same day. This is an error, and will be corrected to state that there will be an acclimatisation period, usually of seven days, before using such animals. Also in the 'adverse effects' section, the penultimate sentence in point three should be amended to clarify that the motivation for humanely killing any animals experiencing distress will be the welfare of the animal.

The lay summary should be amended to correct typographical errors.

The Committee queried whether the proposed anaesthesia will affect the animal's microcirculation. It was explained that the anaesthesia

will influence microcirculation, but that it is not possible or desirable to carry out the work without anaesthesia, and that the effect can be accounted for as anaesthesia has been used in all other similar experiments. It was also noted that some types of reperfusion injury naturally occur under anaesthesia. The Committee considered whether it would be valuable to try to mimic the type of anaesthesia used in surgery, but it was agreed that this would be outside the scope of the current research.

At the request of the Committee, the PI explained that the rationale for the use of immunodeficient mice was that certain studies would use human stem cells, and that immunodeficient animals would be required for these.

A severity level of moderate is incorrectly stated for Protocol 2 in the application, and should be corrected to state the severity of the proposed work as non-recovery (Protocol 1) or mild (Protocol 2).

The Committee advised the researcher to expand the justification for the research in section D of the application.

In protocol 2, 'administration of substances' should be amended to 'administration of cells or substances, to allow stem cells to be given'.

In section D, under 'project plan', it is currently stated that, '....blood pressure, heart rate and ventricular pressure may be monitored'. Some members of the Committee felt that such monitoring of blood pressure would be advisable during all terminal anaesthesia experiments in which intravital microscopy is performed, rather than being optional, as this may help to determine whether 'top up' anaesthesia is required and whether physiological variables that affect the behaviour of microcirculation are at appropriate levels. The researcher explained that the animal's pedal reflex will be tested every ten minutes to ensure that it does not wake up unexpectedly (this should be stated in the 'adverse effects' sections). It was noted that the research is basic science and is not seeking to evaluate effects of the anaesthetic used.

The fact that some animals (less than 10%) may die whilst under terminal anaesthesia should be stated in the application, as although this does not impact upon animal welfare, if it is not explicitly stated any such deaths will require additional notification to the Home Office.

It was explained that the number of experiments per day will depend upon the size of the research group. There will be two experimental 'stations', and both will be used daily for at least one experiment. It was noted that the numbers may be required adjustment as the Home Office will consider whether the stated number of experiments per day is realistic, given the resources available.

The Committee requested further information about the statistical support available to the researcher. It was explained that the person who usually provides statistical support has now left the University, but other resources are available. The researcher was advised to identify an appropriate source of statistical support for this work going forward.

A separate meeting will take place between the PI, Director of BMSU, NACWOs and the NVS to resolve minor issues prior to the submission of the licence application.

The Committee discussed the application further after the applicant left the meeting, raising the following points:

- (i) It was agreed that further work is required on section D of the application, including some rewording and additional justification.
- (ii) The non-technical summary is clearly written, but includes a number of technical terms which should be explained or reworded. The statement that 'Experiments are not conducted with any financial profit in mind' should be removed, as this is assumed. Also in the non-technical summary, what will happen to the animals whilst under terminal anaesthesia should be more clearly stated.
- (iii) Certain members of the Committee felt strongly that blood pressure should be monitored during terminal anaesthesia in which intravital microscopy of tissue microcirculation is performed, and it was suggested that pulse oximetry could be considered as an alternative.
- (iv) The number of animals stated in the application is incorrect, and should be amended.

Resolved that:

A revised draft of the application will be circulated for the Committee's attention. Once the Committee is happy with the revised draft, the Chair will recommend that the Establishment Licence Holder submits the application to the Home Office.

14/06-07-2 Application Ref TBA – Breeding and maintaining genetically altered animals

This application is to renew the existing BMSU service licence for breeding both genetically altered mice, and limited strains of genetically altered rats. Animals are often moved from this licence to other, individual licences.

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

The non-technical summary was missing from the application, but will be forwarded on to the Committee.

It was agreed that BMSU's cryopreserved strains are an incredibly important resource, reducing the number of animals which have to be imported. A web-based database, ARMIS, allows staff full access to this resource. Regarding cryopreservation, the Committee queried whether each strain will be stored at more than one location to reduce the risk of accidental destruction. It was agreed that this would be ideal, but it is a College resourcing issue and is currently under discussion.

It was explained that the difference in severity between protocols four and five (protocol four is of mild severity, protocol five is moderate) is because protocol five includes animals displaying an adverse phenotype.

The total numbers of animals stated in the application include all those used to breed the animals required for experimentation. Some crosses may require a considerable number of animals for breeding, in order to obtain the desired experimental animal. Overall, it is estimated that approximately 50% of the animals will be directly used in experiments.

Non-surgical embryo transfer is mentioned in the application, and the Committee requested further information about this. The technique is carried out vaginally, avoiding the need for laparotomy; however, as it has not proved very successful to date, it has not yet been used within BMSU.

Regarding refinement and reduction, researchers within BMSU have begun to archive tissue from wild strains of mice and it is hoped that this will continue.

In the licence application, one of the expected benefits is stated to be reduced transport time. The PI explained that there are less welfare issues associated with the transport of embryos than there are with the transport of mice. It was suggested that the wording on this within the application should be clarified.

The Committee discussed the application further after the applicant left the meeting, raising the following points:

- (i) This licence is very dependent upon holders of other, individual project licences to control the colonies of animals which fall within the remit of the service licence.

- (ii) Carrying out a large proportion of the breeding required within BMSU under one service licence gives a considerable amount of central control, which would be more difficult to achieve if all breeding was included within individual project licences.
- (iii) Whereas previously, all breeding occurred under the service licence, changes in Home Office requirements have meant that the breeding of project-specific animals is now included within those individual project licences.
- (iv) It was noted that the numbers stated on this licence are high, although it is understood that many animals are often required to breed a particular animal required for experimentation. It was explained that efforts are made to make the best use of the animals and to avoid wastage. The ARMIS database helps to give oversight of the breeding carried out, and to monitor for overbreeding.
- (v) It was agreed that the Committee's concerns centred on any unnecessary wastage, rather than on those animals required for breeding but not ultimately used in experiments. In other words, the Committee felt that it was important to minimise the number of animals bred for experiments but then not used. It was anticipated that the number of such animals would not be high, given financial pressures on researchers and the efforts of the NACWOs to avoid overbreeding. It was also pointed out that there may be negative consequences of breeding too few animals, for example the loss of a particular strain or having to use animals known to be poor breeders.
- (vi) The 'remote' nature of ARMIS may mean that researchers feel detached from the reality of disposing of animals which are no longer required.
- (vii) There are established benefits of breeding in big centrally-held colonies, rather than having many separate small colonies.
- (viii) The Head of the College of Medical and Dental Sciences has agreed to share the costs of a new cryopreservation store, but technical issues are still to be resolved before this can go ahead.

Resolved that:

Minor amendments will be made to the licence application as discussed above, and the non-technical summary will be circulated. Once the Committee has had opportunity to comment on this, the Chair

will recommend that the Establishment Licence Holder submits the application to the Home Office.

14/06-08

Any Other Business

Report from named persons

In line with best practice, it was agreed that at future meetings of BERSC, reports from the named persons will be tabled.

Shared drive for BERSC documents

It was agreed that a secure, shared drive should be set up to hold documentation relevant to members of BERSC.

14/06-09

Date of Next Meeting

The date of the next meeting is 14th August 2014.

GLOSSARY

3Rs	Reduction, Refinement and Replacement
ARMIS	Automated biological service unit management system
BERSC	Biomedical Ethical Review Sub-Committee
BMSU	Biomedical Services Unit
NC3Rs	National Centre for the Replacement, Refinement & Reduction of Animals in Research
NACWO	Named Animal Care and Welfare Officer
NVS	Named Veterinary Surgeon
PI	Principal Investigator
TBA	To Be Announced