CONFIDENTIAL MATERIAL

THE UNIVERSITY OF BIRMINGHAM

BIOMEDICAL ETHICAL REVIEW SUB-COMMITTEE (BERSC)

14th April 2016

MINUTES

Present:

16/04-01 Apologies

16/04-02 Minutes

The minutes of the meeting held on 3rd March 2016 were considered by the Committee and were approved subject to amendments.

16/04-03 Matters Arising

Regarding the use of saphenous vein blood sampling as a refinement, it was reported that the NC3Rs has produced a guide on the technique and it was suggested that it would be helpful if Birmingham could contribute video footage as a learning aid. It was agreed that BMSU would be happy to do this.

16/04-04 Chairperson's Items

There were no Chairperson's items for discussion.

16/04-05 Verbal Reports from the Director of BMSU and Named Persons

Report from the Director of BMSU:

- An FOI request has been received from Animal Justice Project, seeking information about the number of animals used at Birmingham and the minutes from the meetings of BERSC. All of this information is available on the University's webpages, to which Animal Justice Project has been directed.

- Understanding Animal Research is hoping to run a training day in the Midlands to engage school speakers and outreach workers. Birmingham is happy to be involved in this and possible dates are being considered. BMSU has also agreed to host an 'open labs' session for pupils. The importance of forming links with Schools and providing information to the public on animal research was emphasised.

- A recent BMSU Users' Forum was well attended and benefitted from the presence of the Home Office Inspector. Users' Forums will continue to be held on a termly basis.

- An incident recently occurred within BMSU relating to the cage docking system. The Home Office Inspector has been working with BMSU to ensure that appropriate measures are in place to prevent this happening again.

- The Home Office Inspector will shortly be holding a clinic for BMSU project licence applicants.

- In consultation with the Establishment Licence Holder and the Academic Lead, it has been agreed that two half-day workshops will be held for Project Licence Holders. These will be based on the fourth 'R', i.e. individual Project Licence Holders' responsibilities. It is anticipated that these will take place May-June 2016 and they will be run by Red Kite Veterinary Consultants Ltd. All Project Licence Holders will be required to attend one of the two sessions.

Report from the Named Veterinary Surgeon:

No further items to report.

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No further items to report.

16/04-06 Report from the Fast Track Procedure

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

16/04-07-1 Application Ref TBA – Myocardial Infarction

The objectives of this project are to investigate the underlying mechanism of a heart attack (myocardial infarction) and to assess novel drug targets to protect the heart and vascular function following myocardial infarction.

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

It was clarified that in some experiments, drugs will be given to animals prior to the removal of the heart under non-recovery anaesthesia. The purpose of this is to assess whether the administration of the drug prior to myocardial infarction helps to reduce reperfusion injury. Drugs will be administered no more than once per animal prior to surgery.

It was queried whether it would be possible to cull the animal first and then remove its heart, rather than removing the heart under non-recovery anaesthesia. The PI explained that this would not be possible for the intended experiments as the heart needs to come from a live animal.

The number of animals required will be minimised where possible by taking both the heart and required blood vessels from each animal.

If there will be a need to breed genetically altered animals with high blood pressure or other health conditions, it may be necessary to increase the severity of the licence to moderate. The Committee advised that this should be removed from the licence as it is not yet clear whether it will be needed; if it becomes necessary as the work progresses, an amendment should be submitted.

The Committee queried whether the anaesthesia used will have any effects on the heart which may impact upon the proposed experiments. The PI stated that based on previous experience, this should not be a problem.

The proposed usage of novel drugs prompted the Committee to query whether sufficient information on dose ranging is included in the application. It was explained that these drugs have already been tested in vitro; where necessary, the licence application will be clarified.

The PI confirmed that a named statistician has been identified and is providing advice on the project.

Both rats and mice may be used in this work, depending upon the nature of the experiment. For work on blood vessels, rats are preferred because of their larger size. The majority of the experiments will involve mice and this will be clarified in the application.

Some data may be commercially sensitive (for example, in the case of work with a drug company to develop a new drug) and because of this the publication of some findings may need to be delayed. All publications will abide by the NC3Rs ARRIVE guidelines and this will be stated in the application.

It is stated in the application that animals' intake of food and water will be monitored and if this falls to less than 85% of that of age-matched untreated animals, this will be considered a humane endpoint. The PI was asked to revisit this and revise the application as appropriate, because it will not be possible to monitor food and water intake accurately unless the animals are singly housed.

It is mistakenly stated in protocol 3 that drugs may be given under anaesthesia - this has been included in error and should be deleted.

The references to osmotic mini-pumps should be removed, as they will not be used.

References to appendix one should be removed, as this is a cut and paste error.

It is stated in the Non-Technical Summary that 'either mice or rats' will be used – this should be changed to 'both mice and rats'.

The stated number of animals to be used should be amended to incorporate the number required for breeding.

It was felt that where possible, the likely level of severity of the stated adverse effects should be explained in the application.

The section on refinements should be revised, as refinements are currently discussed within the application but they are not explicitly stated as such.

It was felt that it should be made clearer that the myocardial infarction will occur in the heart after it has been removed and not in the live animal.

After the PI left the meeting the Committee agreed that there were no further issues for discussion.

Resolved that:

The revisions discussed above will be made. 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.

16/04-07-2 Application Ref TBA – The role of genes and environment in rodents

The objectives of this project are to determine the interplay between genetics and environment and to understand how this leads to diabetes.

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

It was clarified that in the rare event that an animal develops peritonitis, in order to minimise any welfare issues it would be euthanized rather than treated. This should be amended in the application form.

Polyuria which does not resolve within 60 days or which causes skin problems will be a humane endpoint. The application will be amended to reflect this, as '>60 days' is currently stated. It was explained that polyuria can be easily identified by monitoring the wetness of the animals' bedding. It should be noted that in previous similar experiments polyuria has not been a significant issue.

The application (particularly the Non-Technical Summary) should be amended to emphasise that the animals will be humanely killed at a point before the majority of the listed adverse effects of diabetes are likely to occur; these effects are listed in the application as they are theoretically possible but are unlikely to happen given the design of the study.

It was explained that those animals fed a high fat diet are likely to gain weight and may develop diabetes. The high fat diet can cause skin irritation, particularly if the food comes into contact with the skin; the high fat diet will therefore be placed on the floor of the animals' cages to avoid skin contact. The PI is considering the use of a high sucrose diet rather than a high fat diet, as a refinement.

It was highlighted that that the proposed gene deletion does not usually cause an animal to display frank diabetes, hence why this model is considered to be of mild severity. However, analysis of the tissue and insulin secretion of such animals will still provide useful information.

Regarding the need for multiple glucose tolerance tests, it was queried whether implantable telemetry had been considered as a refinement. The PI explained that the IPGTT (the form of testing described in the application) is the standard for this type of research and it is likely that it would be difficult to publish the results if telemetry were used instead. However, it is hoped that as the value of telemetry will be proven over time and that it will become more accepted. It was suggested that this should be mentioned in the licence.

Although the use of osmotic mini-pumps is unlikely, they may be used if it is necessary to provide treatment for diabetes over a significant length of time. This should be explained in the application.

The frequency of the proposed glucose tolerance testing should be explained consistently throughout the application.

It is anticipated that 100% of the animals in protocol 3 will provide islets. Islets from human donors will also be studied. It was queried whether pseudo-islets could be used as an alternative and the PI explained that these only contain certain beta cells, which is a problem for anything beyond initial pilot studies.

It was agreed that 6 rather than 16 hours fasting prior to the glucose tolerance testing would be preferable from a welfare perspective, and would be acceptable from a scientific point of view as long as the same period of fasting is used consistently throughout the experiments.

In protocol 1 it should be stated that animals will be transferred to protocol 2.

The Committee queried the maximum number of days over which injections will be given to the animals. It was clarified that if the number of injections will exceed 30 days, an osmotic mini-pump will be considered as an alternative. The maximum number of injections an animal is likely to receive is 2 per day over a period of 30 days. The majority of animals will receive 2 injections per day over a much shorter period.

The surgeries which will be carried out under non-recovery anaesthesia are likely to be short in duration. LASA guidance is that any such surgery which exceeds an hour in length should be carried out under aseptic conditions, and researchers are encouraged to use suitably sterile technique for even short periods of non-recovery surgery.

Both rats and mice may be used under this licence, and it was explained that rats may be used when higher quantities of tissue are required, as a rat is likely to yield 600-800 islets rather than the 100-200 obtained from a mouse. Rats have not been used in the PI's previous work in this area; it is more likely that they will be used if appropriate transgenic strains become available.

The Committee observed that a number of models of type II diabetes are included in the application and it was explained that all of the models used are useful in different ways, with some taking place over a longer timeframe than others.

It was felt that the explanation of the humane endpoints in part D of the application should be tightened up.

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

It was agreed that the sections on refinement and replacement in the Non-Technical Summary should be strengthened and made more explicit.

Resolved that:

The revisions discussed above will be made. 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.

16/04-07-3 Application Ref TBA – Antigen-specific immunotherapy

It was explained that this licence is being considered by the Committee because the PI is moving here from another institution, and the work is classified as severe. The application has already been approved by the Home Office.

It was noted that recent work funded by the NC3Rs has used optic neuritis as a marker of Multiple Sclerosis in order to minimise animal welfare issues. This technique will be considered by the PI and the possibility of adopting it will be explored.

The humane endpoints in this application are more severe than those currently in place at this institution. It was agreed that with the NACWOs and the NVS, the PI should consider whether this level of severity is required and if possible it should be reduced.

16/04-08 Publication lists from end of licences

When a Project Licence expires, a list of the publications arising from it will be included on the shared Collaborate workspace for the Committee's attention.

16/04-09 Any Other Business

BMSU and MDS technology hub have been working together to establish new genome editing technologies in animal models and are pleased to announce the birth of the first CRISPR Cas 9 mice. The use of these technologies makes it possible to breed genetically altered animals in one generation rather than many, which means that a far lower number of animals are required for the purpose of breeding.

16/04-10 Date of Next Meeting

The date of the next meeting is 26th May 2016.

GLOSSARY

ARRIVE	Animal Research: Reporting of In Vivo Experiments (guidance provided by NC3Rs)
BERSC	Biomedical Ethical Review Sub-Committee
BMSU	Biomedical Services Unit
CRISPR Cas 9	A genome editing technique, developed from work on CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) and Cas (CRISPR associated) genes
FOI	Freedom of Information
IPGTT	Intra Peritoneal Glucose Tolerance Test
LASA	Laboratory Animal Science Association
MDS	(College of) Medical and Dental Sciences
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