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CONFIDENTIAL MATERIAL

THE UNIVERSITY OF BIRMINGHAM

BIOMEDICAL ETHICAL REVIEW SUB-COMMITTEE (BERSC)

7th July 2016

MINUTES

Present:

16/07-01 Apologies

16/07-02 Minutes

The minutes of the meeting held on 26th May 2016 were considered by the Committee and were approved subject to amendments.

16/07-03 Matters Arising

NC3Rs outreach worker

In relation to the discussion of an NC3Rs outreach worker in minute 16/05-05, it was reported that the post has been offered to a Research Fellow at the University of Leicester. They will be starting on 26th September 2016 and will spend one day per week at each University (Birmingham, Nottingham and Leicester) and the remainder of their time working from the NC3Rs offices or from home. The Committee was asked to consider whether there are any specific issues they would like the new post-holder to address. The following ideas were suggested, with any further ideas to be emailed to the Committee's NC3Rs representative:

- An audit of the work of BMSU and BERSC with the intention of sharing best practice and identifying areas for improvement.
- To explore the link between the 3Rs and the wider research and knowledge transfer context, and the link between the 3Rs and University Research Co-ordinators.

- An event at which researchers from the Universities of Leicester, Birmingham and Nottingham get together to share short research presentations and poster sessions.
- To work closely with grant applicants.
- Attendance at some AWERB meetings.

NC3Rs presentation

There will be a presentation on the work of the NC3Rs at the next BMSU Users' Forum meeting.

Minute 16/05-07-1 – Modulation of murine lung injury by hormones, cells and growth factors

This application is still awaiting comments from the Home Office Inspector. It will be redrafted once these have been received and will be recirculated to the Committee.

16/07-04 Chairperson's Items

There were no Chairperson's items to report.

16/07-05 Verbal Reports from the Director of BMSU and Named Persons

Report from the Director of BMSU:

- The Unit is operating smoothly and matters are 'business as usual'. Animal numbers are currently steady, training is up to date and there is a minimal waiting list.

- The new quarantine room for initial exploratory experiments on animals from external sources is now operational. It was noted that no breeding will take place in this room and each application to use it will be reviewed by BMSU staff and the NVS.

- The Home Office Inspector will be visiting BMSU on 8/7/16 to hold another surgery and to address a recent non-compliance issue. It was noted that surgeries are very helpful as they allow applicants to speak to the Inspector before drafting their licence applications.

- No further information is available at this stage on the progress of the West Midlands regional hub for AWERBs.

- There is still a backlog of licence applications which the Inspector is working through. Amendments are now being submitted via the electronic form as it is more convenient for the Inspector. It was noted that 3 new Inspectors have recently been appointed.

Report from the Named Veterinary Surgeon:

- In relation to the recent outbreak of pinworm within BMSU, treatment on the top floor is now complete and monitoring is ongoing. Live animals are not being exported from BMSU until it can be proved that all pinworm has been eradicated.

- The NVS and a NACWO recently attended a useful meeting about sterile technique.

Report from the Named Animal Care and Welfare Officers:

No further items to report.

16/07-06 Report from the Fast Track Procedure

The fast track procedure is up-to-date.

16/07-07-1 Application Ref TBA – MYB proteins and myeloid disease susceptability

The objective of this project is to investigate how the balance of MYB proteins ensures that stem cells in the bone marrow are maintained in sufficient numbers and that they correctly produce blood cells when necessary. The researchers will explore how, when this balance is incorrect, lower levels of MYB proteins can lead to diseases in the blood cell system.

The PI gave a presentation explaining the application to the Committee. It was explained that the application is for the renewal of part of an existing licence – the original licence is being split into two going forwards.

It was highlighted that irradiation will be carried out via two lower doses, which give the same required effect as one larger dose but are better in terms of animal welfare. Given this, it was queried why the option for one single dose was included within the licence. The PI explained that this was included in case it was necessary, but the intention is to use split doses wherever possible.

The Committee queried why the application states that humane endpoints 'will be determined', given the researchers' extensive prior experience in the field. It was explained that whilst the researchers do have a clear idea of the appropriate endpoints, they are also aware of the need to monitor for the unexpected and to modify endpoints as required. Previous work carried out by this group on blood monitoring allowed new endpoints to be developed – animals are now humanely killed at an earlier point and welfare issues have therefore been reduced. The Committee felt that further detail on likely endpoints should be included within the application, and any inconsistencies clarified. It was agreed that it would be difficult to administer treatments to mitigate adverse effects as these may confound the experiments. The research team has a close working relationship with BMSU and every effort will be made to ensure that welfare concerns are minimised. It was agreed that this should be better explained in the licence.

Humane endpoints are currently given for blood sampling, and it was queried whether these were necessary. It was agreed that they should be included in the application given the small chance of an adverse event, particularly in an animal which is developing leukaemia.

The Committee was reassured that there is much experience within BMSU in the husbandry of aged mice and that appropriate adaptations will be made (e.g. extra bedding, long drinking spouts, a softer diet, etc). With reference to aged mice, it was explained that blood sampling will be carried out as the mice age and there are certain blood sample pointers which would indicate that an animal should be monitored more closely or humanely killed.

Both BMSU and the research team have extensive experience in transplantation and this should be explained in the application.

In relation to protocol 3, the Committee queried the likelihood of an animal losing more than 20% of its body weight. The PI explained that this is only likely in a small proportion of animals as the monitoring of blood values will enable the researchers to avoid such weight loss in most cases.

In the application it is stated that pain relief will be used in some circumstances; it was emphasised that pain relief must be used when necessary and this should be reworded in the application.

It was clarified that the mention of 'isolation' in the application refers to the use of IVC housing, rather than the isolation of individual animals.

The reference to animals becoming 'accustomed to' handling prior to blood sampling should be omitted, as the animals will be handled in the usual way (i.e. there will be no additional action taken to accustom the animals to handling).

Further justification is required in the application for repeated bone marrow sampling. Analgesia will be given when taking bone marrow samples. Samples will be taken a month apart. It was explained that the technique seems to be well-tolerated by the animals and does not usually cause any lameness or inflammation.

Adverse effects should be added to the section on femoral sampling.

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

It was felt that more attention should be given to the explanation of the 3Rs within the application.

In the non-technical summary, it should be stated that the application is of moderate severity.

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.

16/07-07-2 Application Ref TBA – Regulation of platelets by CD148 and G6b-B

The objective of this project is to understand how proteins on the surface of platelets, such as CD148 and G6b-B, control platelet function and change the way platelets regulate the balance between excessive blood clotting and bleeding.

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

In relation to humane endpoints, it is stated in the application that if certain adverse effects 'cannot be rectified by minor interventions….within 2-3 hours, animals will be killed by a Schedule 1 method'. The NVS noted that animals would be humanely killed immediately upon the discovery of some of the stated adverse effects and this should be amended within the application. Similarly the

statement that animals will be humanely killed, 'if any of these signs are observed constantly for over 24 hours' should be removed.

Though it is mentioned as an adverse effect, it was clarified that dyspnoea is not considered likely; however, it is always a possibility if new drugs are used. On this basis it was agreed that it should be removed from the application.

The reduction of the volumes of blood and bone marrow required is a refinement as it means that fewer animals are used. Previously, when using mice with very low platelet counts, the blood of 10 mice may have been necessary to get the required number of platelets; new techniques now mean that between a half and a quarter of the previous amount of blood is required. It is also now possible to downsize certain protocols – for example, the use of smaller cell culturing dishes means that fewer mice are required.

The Committee asked whether the PI had obtained advice on the statistics used within the application. It was explained that the same techniques have been used for some time and the statistics are based upon discussions with colleagues with appropriate expertise and the use of statistical software. It was suggested that the PI should provide a clearer breakdown of animal numbers between the various types of experiment within the application.

The PI explained that one healthy adult mouse usually provides enough blood for three experiments; for those mice with lower platelet counts, more blood is required and therefore the use of more animals may be necessary.

It was suggested that a number of the best practice techniques employed by the researchers should be identified within the application as refinements.

It was clarified that retro-orbital bleeding would only be carried out under terminal anaesthesia – a cut and paste error relating to this will be corrected.

In relation to protocol 3, signs of adverse effects are anticipated from 6 weeks of age. The animals will either be used before any such symptoms develop, or will be used as soon as an adverse phenotype is observed. The Committee queried how this will be managed by the research team, and the PI explained that they will be on standby to ensure that mice are humanely killed as soon as necessary, after which their tissues will be harvested for use in the project. It was clarified that even though animals showing symptoms will already have activated platelets, their tissue is still valuable and useful to the project.

It was agreed that the PI was right to classify this as 'basic research', as the project is still some way from the treatment stage.

Figure one (page 16 of the application) is missing and should be included.

A member of the Committee noted that another research group has been using probes to examine thrombotic activity. It was explained that whilst this is a less invasive methodology, it does not yield such a wealth of data as is seen when using the proposed techniques and does not allow the insertion of markers to track changes of interest.

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

It was felt that the explanation of the statistics should be strengthened and it should be explained that an in-group statistician has been involved. The value of power calculations for this study was questioned – it was felt that whilst they are useful for blinded endpoints, experience may be equally useful in cases such as this with a familiar model and known endpoints. It was acknowledged that the statistics would also have been considered by the funding body before the funding was awarded.

More generally, it was noted that it would be helpful to recruit a statistician to serve as a member of the Committee, particularly given the increased scrutiny of statistics by funding bodies and journals. This will be added to the agenda for consideration by the Committee at the next meeting.

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.

16/07-08 Any Other Business

- A member of the Committee has been invited by Understanding Animal Research to take part in a forthcoming event at the Science Media Centre.
- An FOI request has been received from Cruelty Free International and the University has provided as much of the requested information as it is able.

- The Animal Justice Project has recently reposted old information about a University of Birmingham project on its webpages.
- Volunteers have now come forward for the sub-group which will undertake retrospective reviews, and this will be taken forwards.

16/07-10 Date of Next Meeting

The date of the next meeting is 18th August 2016.

GLOSSARY

3Rs	Replacement, Reduction and Refinement
AWERB	Animal Welfare and Ethical Review Body
BERSC	Biomedical Ethical Review Sub-Committee
BMSU	Biomedical Services Unit
CD148	A protein on the surface of platelets
FOI	Freedom of Information
G6b-B	A protein on the surface of platelets
IVC	Individual Ventilated Cages
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
NVS	Named Veterinary Surgeon
PI	Principal Investigator
RSPCA	Royal Society for the Protection of Cruelty to Animals
TBA	To Be Announced