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THE UNIVERSITY OF BIRMINGHAM

BIOMEDICAL ETHICAL REVIEW SUB-COMMITTEE (BERSC)

13th April 2017

MINUTES

Present:

17/04-01 Apologies

17/04-02 Minutes

The minutes of the meeting held on 2nd March 2017 were considered by the Committee and were approved subject to minor amendments.

17/04-03 Matters Arising

Matters arising in relation to the new intravital suite will be addressed in the Chair of BMSU's verbal report.

17/04-04 Chairperson's Items

There were no Chairperson's items to report.

17/04-05 Verbal Reports from the Director of BMSU and Named Persons

Report from the Director of BMSU:

- The users of the surgery and imaging suites were thanked for their patience during the work to upgrade the changing facilities. The new facilities are a significant improvement and were made possible by support from the central University.

- It is hoped that a bid to fund a small animal micro CT scanner will soon be successful. Whilst the funding relates to a particular project, the scanner will also be available to other users of BMSU. It is expected to be extremely useful and will

allow longitudinal analysis within the same rat or mouse, which will represent a 'reduction' in terms of the 3Rs.

- The new intravital suite is almost finished and as soon as the CCTV system is operational the necessary paperwork will be submitted to the Home Office for sign off. The individual who will be responsible for the suite is working with the NVS to draw up SOPs. The suite will only be accessible via a card access system and only those carrying out work within the suite will be given access. Up to 5 experiments will be possible within the suite at once, with one animal per microscope.

- The Chief Home Office Inspector is retiring and her replacement is yet to be confirmed.

- It is anticipated that the group Birmingham Animal Action will be visiting campus to distribute leaflets on 19th and 29th April 2017.

- Regarding animal health and numbers within BMSU, business is operating as usual.

- An upgrade to ARMIS earlier this week did not go to plan and since this it has not been possible to process disposals; when this issue has been resolved users will be credited for any additional charges incurred in the meantime.

Report from the Named Veterinary Surgeon (NVS):

- The NVS expressed his confidence in the individual who will be responsible for the new intravital suite. It was noted that both the NVS and the Director of BMSU will be on hand to provide support when the suite becomes operational.

Report from the Named Animal Care and Welfare Officers:

No items to report.

17/04-06 Report from the Fast Track Procedure

The fast track procedure is up-to-date.

17/04-07-1 Application Ref TBA – Targeted therapies to modulate inflammation in alcohol-induced injury

The overall aim of this project is to understand whether it is possible to target the processes of inflammation in order to treat alcohol-induced liver disease.

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

It was noted that NRF2 deficient mice will be used initially, but it is hoped that the work will also extend to include other strains.

In human patients, anti-platelet therapy improves liver-related clinical outcomes. This work will use mice deficient in platelet receptors to investigate whether existing drugs can be repurposed to treat liver damage in patients. A grant has recently been submitted for the humanisation of certain antibodies, which is an example of how previous mouse work by this research group has been translated into a human model.

The PI explained that the experiments will take place over 14 days. Each animal may be given several doses of antibody, but the majority will receive only one or two doses. The animals usually recover quickly after the last dose; within 24 to 48 hours after the last dose the animal is humanely killed.

It was explained that the models used in this application mimic the acute inflammatory effects of alcohol damage in human patients, rather than the longer term fibrosis associated with cirrhosis of the liver. It was highlighted that patients do present with acute inflammation such as this in a clinical setting. Current treatments for such patients are limited to corticosteroids, the treatment of bleeds and systemic support

and approximately half of such patients do not recover. It was also noted that the model parallels the effects of acute 'binge drinking' in humans rather than those of longer-term steady drinking. Given the likely severity of any model of longer term alcohol-related liver damage, it would probably not be possible to undertake such work in the UK.

The Committee queried whether the pathology in the mouse is likely to be similar to that in the equivalent human condition. The PI explained that it is similar but the effects are not as devastating in the mouse as in human cases.

Both male and female mice may be used, but the former are preferable as the effects are more reproducible in male mice.

It was queried whether there is any difference in alcohol tolerance between different strains of mouse. The PI explained that there is variability between strains, even accounting for differences in the amount imbibed, which mimics the reactions seen in humans.

Gavage may be used in addition to allowing the animals to self-imbibe, as the latter shows considerable variability and the addition of the former allows more consistent reproducibility. Without the use of gavage the number of animals without sufficient liver injury for use in the study would be too high. The number of doses of alcohol given by gavage will be dependent upon an animal's response. To administer the gavage the animal is 'scruffed' and a flexible gavage needle is used. The process takes approximately 30 seconds and is tolerated well by the animals. An appropriate recovery interval will be allowed between gavages.

The PI was asked whether any of the alcohol is likely to be excreted rather than being absorbed; it was explained that this would be very difficult to measure and is not likely to be significant.

After being given the alcohol the animals may be unsteady and appropriate measures will be taken to ensure they can access food and water. Their usual water supply will be supplemented with water gel pouches.

It was felt that the humane endpoints of the model require further work and rewording. The fact that the work will be classified as 'severe' needs to be reflected in the endpoints.

It was noted that the application was very well-written. Tables 1 and 2 were omitted and these should be included in the application.

Depending on the feedback received from the Home Office Inspector, it was suggested that the stated aims and objectives of the study should be made more specific.

The application should be amended to clarify that anaesthesia is not required for the injections of hematopoietic cells. Also, the reference to treatment with cell depleting or function blocking reagents on up to ten occasions should be amended, as the number of treatment occasions will be less than stated.

The PI was asked to include further information about the sources of statistical support for the study.

The anticipated weight loss percentage stated in the NTS differs from that stated elsewhere in the application and this should be amended for consistency.

The Committee was informed that the model used in this application was originally developed by a different PI but there is confidence that the current PI will carry it forward appropriately.

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

Whilst this is a severe model, it was felt that it has been refined as much as is possible and the NACWOs are satisfied with its current form.

It was suggested that it would be helpful to strengthen the references to the development of the model under a previous licence and to explain that the model is fully established within BMSU.

Further work should be done to tighten up the humane endpoints.

Whilst the number of mice to be used is small, this is appropriate given the severity of the model. An amendment may be necessary in the future if there is justification for the use of additional mice.

It should be clarified in the application that the PI holds a Personal Licence.

Resolved that:

The revisions discussed above will be made and feedback will be obtained 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.

17/04-07-2 Application Ref TBA – Production of polyclonal and monoclonal antibodies

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The overall aim of this application is to develop novel antibodies for research and the tissues and antibodies produced from the animals used in this licence will enable a wide range of *in vitro* or *ex vivo* studies to be undertaken.

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

This is a renewal of a service licence for the in-house production of polyclonal and monoclonal antibodies.

The reference to the production of materials for commercial use should be removed from the application as the only external users will be collaborators with the University of Birmingham.

In the section on 'refinements' in part D, the stated blood sample volumes should be converted to millilitres per kilo.

The reference to the removal under terminal anaesthesia of tissues and organs should be removed as this will not be required.

Whilst the application refers to injections into the footpad, in reality they will be closer to the ankle and the wording relating to this will be checked with the Home Office Inspector and amended as necessary.

This application does not include cell rescue, something which was part of the previous Service Licence. An amendment to include this may be submitted at a future date.

It was explained that all injections will be carried out by staff within BMSU.

The reference to nicking the ear vein should be removed as this will not happen.

No adverse effects are anticipated in relation to the involvement of GA mice.

Regarding the use of Complete Freund's Adjuvant, it was explained that animals can usually tolerate its use once, but no more than that. Tolerance to Complete Freund's Adjuvant varies between strains of mice and the more tolerant strains will be used.

Animals will not be aged beyond 12 months.

It was explained that if no effects are seen in a mouse after 3-4 injections, that particular mouse will not be suitable for use. Animals will often be immunised twice in one week and then a booster administered after another 2-3 months.

Regarding the non-technical summary, it was suggested that the terms monoclonal and polyclonal antibodies should be explained and that the requirements of schedule 1 should be explained in lay terms.

No further issues were raised after the PI left the room.

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.

17/04-07-3 Application Ref TBA – Preclinical model of haematological malignancies

The aim of this project is to use mouse models of human blood cancers of different subtypes or with specific targets including precancerous biomarkers to study disease progression and to evaluation novel therapy.

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

The application should be amended to clarify which of the various routes for injection will involve anaesthesia and which will not.

Staff within BMSU are extremely familiar with these models, which have been running successfully for some time.

Statistical support is provided by a mathematician within the research group. It was commented that use of group means will reduce power and also that parametric analysis cannot be used with percentages. These points will be clarified with the statistician.

As a refinement, blood samples will be taken from the saphenous vein rather than the tail vein (in line with other studies within BMSU).

In relation to the dose-finding protocol, it was noted that limits should be stated for the number of weeks of treatment and for the number of repeated doses.

The humane endpoints in protocol 2 should be tightened up.

The adverse effects for the subcutaneous tumour model should be clarified and made more specific.

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

It was explained that the Home Office Inspector had originally requested toxicology studies, but this was a misunderstanding and is not the focus of the study.

In protocol 1 it is not necessary to state that the anaesthetic equipment will be in 'good working order' – this is already assumed by the Home Office.

Minor errors and repetitions in the NTS should be amended and 'Schedule 1' should be explained.

Regarding the injection of cells intrafemorally, it was felt that the wording about the possibility of a broken femur should be revisited and clarified. It was noted that a broken femur has not occurred in previous such work with live animals, but it has occurred when working with cadavers.

The dose of radiation stated in the application is incorrect and should be amended and maximum doses should be stated.

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.

17/04-08 Interim review of PPL Number P53408D2E – Investigating a novel treatment for heart failure

The Committee was informed that this is the first formal interim report to be made to the Home Office and that such reports are now a requirement for severe Project Licences. The report will be accompanied by a summary of the issues raised during the AWERB review.

In relation to unexpected complications (section 6) it was suggested that the wording of the second point should be made clearer. In relation to the first point in this section, it was clarified that the anaesthetic equipment had been assembled incorrectly and that this was a training issue which was immediately addressed. The animals were anaesthetised at the time so there were no welfare issues. The circumstances of this and the steps taken to address it should be explained more fully in the interim report.

The Committee was reminded that this is a difficult model with 25% failure rate written into the Project Licence and to date this percentage has not been exceeded.

The model is still very much in development. The results so far are not as expected, in that the animals are not yet exhibiting signs of clinical heart failure. However, from related experience and considering the data obtained so far it is felt that the work is progressing in the right direction. At the moment the data is still blinded so it is not possible to tell which animals are in the treatment group; once the data is unblinded the PI will have a clearer idea of whether the model has been successful in terms of generating the required scientific effects. It may be that the model is working successfully but that the animals are being humanely killed at stage prior to the development of any clinical symptoms.

More generally, it was agreed that the interim review form is fit for purpose. It was suggested that section 5 ('Have any severity limits been exceeded?') should be followed by a question asking for details if work has gone beyond the stated severity limits, though it was noted that this wouldn't apply in the current case as the Licence is already severe and cannot exceed this. Another suggestion was to amend the question to ask whether any humane endpoints have been exceeded, rather than focusing upon severity.

17/04-09 Matters relating to the 3Rs

Joint 3Rs day

A joint 3Rs symposium between the Universities of Birmingham, Leicester and Nottingham will be held on 19th September 2017. There are up to 30 places available for researchers from the University of Birmingham. 2 places were offered to guests from the University of Keele. Several speakers from Birmingham will be showcasing our work on the 3Rs. There will be a poster session with a £75 prize. Researchers are encouraged to support this event, which will be held at the University of Nottingham's conference centre.

3Rs working group to develop a benchmarking tool

The Director of BMSU and another member of BERSC are part of a working group to develop a self-assessment tool to allow establishments to benchmark themselves in relation to the 3Rs. The questions which will be included in the tool are challenging, with some relating to the establishment and some to individual researchers. The benchmarking questions will be circulated to the Committee for information.

One idea which arose from this exercise was the identification within research groups of 3Rs 'champions', who meet periodically to share and disseminate best practice. The Committee noted that such champions would need to have sufficient influence and that there may

be practical difficulties in implementing such a scheme. The Committee will consider this and it will be discussed again at the next BERSC meeting. As an alternative, it was felt that it may be preferable to identify one individual who provides input when applicants are writing Project Licences and/or to organise the sharing of clinical score sheets between research groups.

NVSs meet to discuss how to avoiding the single housing of rodents

The NVS will be meeting with the NVSs from 3 other establishments to discuss best practice in avoiding the single housing of rodents.

17/04-10 Any Other Business

The Director of BMSU will be updating the standard text to be included in licence applications about commonly used methods such as blood sampling and injections. This will be submitted to the Home Office Inspector for approval.

17/04-11 Date of Next Meeting

The date of the next meeting is 25th May 2017.

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GLOSSARY

3Rs	Replacement, Reduction and Refinement
ARMIS	Automated biological service unit management system
AWERB	Animal Welfare and Ethical Review Body
BERSC	Biomedical Ethical Review Sub-Committee
BMSU	Biomedical Services Unit
CCTV	Closed-Circuit Television
CT	Computed Tomography
GA	Genetically Altered
NACWO	Named Animal Care and Welfare Officer
NRF2	A transcription factor which is a key mediator of the body's antioxidant response
NTS	Non-Technical Summary
NVS	Named Veterinary Surgeon
PI	Principal Investigator
SOP	Standard Operating Procedure
TBA	To Be Announced
UK	United Kingdom