CONFIDENTIAL MATERIAL

THE UNIVERSITY OF BIRMINGHAM

BIOMEDICAL ETHICAL REVIEW SUB-COMMITTEE (BERSC)

14th December 2017

MINUTES

Present:

17/12-01 Apologies and welcomes

A representative from the University's Press Office was welcomed as a new member of BERSC.

17/12-02 Minutes

The minutes of the meeting held on 9th November 2017 were considered by the Committee and were approved subject to minor amendments.

17/12-03 Matters Arising

In relation to the licence application discussed in minute 17/11-07-1, it was noted that the Named Persons met with the PI after the meeting and comments from the NC3Rs Midlands Programme Manager were also resent to the PI. Work on this application is still in progress.

It is understood that the application discussed in minute 17/11-07-2 has still to be finalised.

17/12-04 Chairperson's Items

The Chairperson reported that they recently attended the RSPCA Lay Members Forum and found it very useful. A summary of the matters discussed will be presented to the Committee in the New Year.

17/12-05 Verbal Reports from the Director of BMSU and Named Persons

Report from the Director of BMSU:

A report from the Director of BMSU was provided by the NVS, in the Director's absence. The key points were as follows:

- The Home Office Inspector has held a surgery with Project Licence applicants this week.
- It is understood that the number of times Project Licences are 'bounced back' from the Home Office can vary considerably, and the Home Office is emphasising that well-written Project Licence applications are likely to be approved more quickly. The quality of applications from the University of Birmingham is considered to be generally good.
- The Home Office Inspector recently attended the annual risk meeting with the Establishment Licence Holder. The feedback provided from the Inspector was extremely positive and the risk rating continues to remain as low as it possibly can be for our establishment.
- There will potentially be disruption to BMSU in January 2018 as work is carried out in the car park to remove the old steam boilers. This is likely to involve drilling and some resulting vibration.
- BMSU's charge-out rate will increase in the New Year. This reflects the increasing FEC rate and going forwards the

increased rate will have to be used in new grant applications. The rate is likely to continue to increase annually. It was noted that only current costs may be used in grant applications (i.e. not anticipated future costs) and any increase in the cost per animal which occurs after the award of a grant will be covered by the College.

- The Home Office training course which was scheduled for this week was cancelled due to adverse weather conditions. This course will be rescheduled for January 2018.

- In light of this week's adverse weather conditions, BMSU staff were thanked for making every effort to get into work and there has been no negative impact upon animal welfare.

Report from the Named Veterinary Surgeon:

- BMSU is currently quiet but is likely to get busy again early in the New Year.

Report from the Named Animal Care and Welfare Officers:

- No items to report.

17/12-06 Report from the Fast Track Procedure

The fast track procedure is up-to-date and a record of matters discussed is stored on the Committee's Collaborate pages.

17/12-07-1 Application Ref TBA – Regulation of DNA replication and damage by small protein modifiers

The overall aim of this project is to understand the regulation of DNA replication by small protein modifiers (e.g. ubiquitin and SUMO). The project will especially focus on understanding how the final stages of DNA replication are executed. Ultimately, the researchers would like to use knowledge generated from the project to inform research on potential targets for cancer therapy.

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

It was explained that the animals will be injected a maximum of every 3-4 months. The number of times that each animal will be reused has not been specified, but there will be a point beyond which the quality of an animal's eggs deteriorates and it will then be humanely killed.

At least 3-4 months is allowed between injections to allow an appropriate rest period which reflects the number of breeding periods per year for Xenopus laevis frogs in the wild. The NVS highlighted that in the work carried out by the PI to date, most animals have only been injected once or twice per year as this has been sufficient to meet requirements – excess materials are frozen for future use when needed. It was emphasised that each time an animal is reused this has to be carefully considered and signed off by the NVS.

The Committee queried the total number of animals to be used under this Project Licence. It was noted that the numbers stated in the application are quite high, but these are actually the numbers of procedures (i.e. the number of incidences of reuse) rather than the number of animals involved. Currently, the PI has approximately 90 animals which supply the necessary quantity of material for experiments. The number required for future work is likely to be slightly higher, and some of these may need to be replaced during the lifetime of the Project Licence. It was agreed that the application should be revised to clearly differentiate between the total number of animals required versus the number of procedures (i.e. incidents of reuse).

The procedures to be carried out are considered very mild and not likely to cause stress to the animals; in fact, given the animals' aversion to vibration (e.g. from being transported) it is considered better from a welfare perspective to reuse them instead of obtaining new animals to use in each experiment.

Advice on the application was provided by the NC3Rs Midlands Programme Manager. It was suggested that in the section on replacements, it should be explained that the alternative model of budding yeast has been considered and why it is deemed inappropriate for this work. In 'refinements', examples of how the approaches have been 'refined and optimised' should be stated. In 'reduction', the PI should explain that the total number of animals proposed is based upon previous experience of how much extract the research group requires. They should however state that they will only generate as much extract as is needed.

The Committee queried how the animals' welfare is maximised in terms of tank enrichment, etc. The PI explained that piping/housing is used in the tanks, the density of stocking of the tanks is well within the relevant guidelines and appropriate tank lighting is used. Other forms of enrichment have been trialled at various points or are being considered. It is difficult to measure the animals' reactions, as they are not very responsive – the primary way of telling if they are stressed or content is via the quality of their eggs. Regarding the animals' food, a foodstuff based on animal protein was recently replaced with one

based on plant protein; however, this was detrimental to the quality of the eggs and so the animal protein-based food has been reinstated.

It was suggested that the PI should amend the application to provide justification for the use of 2 injections per procedure.

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

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.

17/12-07-2 Application Ref TBA – The effect of H. pylori infection on colitis

The overall aim of this application is to study how H. pylori infection in the stomach affects the diversity of bacterial species in the intestine (by analysing faeces) and intestinal inflammation during colitis to understand the mechanisms underlying the epidemiological link between H. pylori infection and protection against IBD.

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

The PI was advised to amend the application to clarify the weight loss thresholds at which animals will be humanely killed. It was noted that weight loss will be measured as a percentage of the animal's last known weight and that the animals will be at full adult weight at the time (i.e. they will have stopped growing).

A score sheet already established by another researcher doing related work will be used to help determine humane endpoints.

The NC3Rs Midlands Programme Manager provided feedback on the application. It was emphasised that there was much useful information (including details of the application of the 3Rs) in the presentation which was not in the application, and the application should therefore be amended to include this. Regarding reduction, the data underlying the power calculations should be provided and information should be included about randomisation and blinding. With reference to refinements, any relevant refinements and details of the PI's previous experience/learning should be included. Any limitations on dosages taken from the relevant guidance should be stated.

It was queried whether there will be any negative effects associated with the rectal route of administration in the TNBS model. The PI explained that the ethanol in the solution will affect the microbiome but this will be controlled for within the experiment. The PI did not know whether the ethanol is likely to have any negative effects on welfare and will discuss this with colleagues at other institutions who are already using the model. This model is common within the literature and the PI will work closely with the NACWOs and other colleagues to minimise any negative effects.

The PI will clarify whether the TNBS model requires overnight fasting, and if this is needed it will be included in the application.

Further information was requested about the possible need to use GA mice. The PI explained that these will be 'reporter' animals which will experience no adverse effects. No knockout mice will be used. Any potential impact of the genetic alteration on the severity of colitis will be considered during the pilot stage.

It was felt that the NTS should be amended as it is currently too technical and may not be understood by a lay person.

The Committee queried how the PI will study the resolution of inflammation. It was explained that this will be done by studying T cells or changes in Tregs.

The DSS model is reported to result in colitis in 60-70% of animals and it was queried how the PI will establish whether or not an animal actually has colitis. It was explained that this will be established at the end of the experiment, via differences in the T cells, rather than via scoring during the experiment.

The use of immortalised cell lines (as described in the presentation) should be included in the 3Rs section of the application as a replacement.

As positive results for H. pylori sometimes come up during routine health screening within BMSU, it was queried whether this would be a problem in the control group. It was explained that it will be possible to tell whether or not an animal has H. pylori at the end of each experiment. It was noted that in all previous work, the PI has never encountered a control animal with H. pylori.

The PI was unsure whether the oral administration of DSS will affect H. pylori in the stomach and will test for this in vitro prior to the experiments.

The Committee queried how relevant these models are to the equivalent human diseases. The PI explained that whilst they are

chemical rather than T cell models (the latter will be used at a later stage) they are simpler and more reproducible and act as good models for IBD in human patients. The appropriateness of the models should be explained in the application.

The NVS noted that the reference to placebo doses when training staff to perform oral gavage should be removed.

After the PI left the meeting, the Committee continued to discuss the application. The Home Office Inspector has provided comments and whilst they have been incorporated into the presentation, they are not yet reflected in the licence application.

Resolved that:

The revisions discussed above will be made and the feedback from the Home Office Inspector will be incorporated into the application. The NVS will go through the new draft and provide comment. Once the Chair is happy with the changes made, a recommendation will be made that the Establishment Licence Holder submits the application to the Home Office.

17/12-08 Matters relating to the 3Rs

Report from the NC3Rs Midlands Programme Manager

- A University of Birmingham PhD student who attended the last NC3Rs Summer School has now been awarded an NC3Rs Training Fellowship.

- The NC3Rs Midlands Programme Manager met with the Research Support Team within the Medical School and going forwards, will be working closely with them and contributing to discussions as appropriate.

- The NC3Rs Midlands Programme Manager has also recently met with staff within the Institute of Inflammation and Ageing and will be meeting with members of other Institutes over forthcoming weeks.

17/12-09 Any Other Business

There were no further items for discussion.

It was agreed that if there are no Project Licence applications for review at the next meeting, the meeting should go ahead anyway and mid-term reviews should be included on the agenda.

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17/12-11 Date of Next Meeting

The date of the next meeting will be 25th January 2018.

GLOSSARY

3Rs	Replacement, Reduction and Refinement
BERSC	Biomedical Ethical Review Sub-Committee
BMSU	Biomedical Services Unit
DNA	Deoxyribonucleic Acid
DSS	Dextran Sulfate Sodium
FEC	Full Economic Cost
GA	Genetically Altered
H. pylori	Helicobacter pylori
IBD	Inflammatory Bowel Disease
NACWO	Named Animal Care and Welfare Officer
NC3Rs	National Centre for the Replacement, Refinement and Reduction of Animals in Research
NTS	Non-Technical Summary
NVS	Named Veterinary Surgeon
PhD	Doctor of Philosophy
PI	Principal Investigator
RSPCA	Royal Society for the Prevention of Cruelty to Animals
SUMO	Small Ubiquitin-like MOdifier
T cells	T lymphocyte cells
TBA	To Be Announced
TNBS	Trinitrobenzenesulfonic acid
Tregs	Regulatory T Cells