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THE UNIVERSITY OF BIRMINGHAM

ANIMAL WELFARE AND ETHICAL REVIEW BODY (AWERB)

14th June 2018

MINUTES

Present:

18/06-01 Apologies

18/06-02 Minutes

The minutes of the meeting held on 19th April 2018 were considered by the Committee and were approved subject to minor amendments.

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18/06-03 Matters Arising

Feedback on the recent NC3Rs workshop entitled 'Improving peer review of in vivo research proposals' will be carried forward to a future meeting.

18/06-04 Chairperson's Items

- There were no Chairperson's items to report.

18/06-05 Verbal Reports from the Director of BMSU and Named Persons

Report from the Director of BMSU:

- Activities within BMSU are running smoothly with nothing major to report.

- As previously discussed, statistics on the problems (e.g. hydrocephalus or overgrown teeth) which can arise when inbreeding with C57 as a background rather than buying in wild-type mice are being monitored. A dedicated summary from the database is being developed to avoid having to compile these statistics manually.

- The Home Office Inspector has recently held a surgery with new applicants. The Inspector is working through applications very quickly and is providing high quality responses. It is anticipated that there will be a considerable number of new applications coming through soon, due to the recruitment of new Birmingham Fellows.

- Birmingham is heavily involved in the development of the ASPeL system. The Inspector has asked the University to nominate a new applicant and a more experienced Project Licence holder, both of whom will be submitting applications, in order to help to test the new form. Workshops about the development of the new form continue and there will be another meeting on 28th June 2018. It is understood that initially, the form will look similar to the current version, but there are likely to be more changes once the system is up and running. It is hoped that the new form will be easier for applicants to use and as each applicant will have their own profile, some of the preliminary information will autofill which will save time. There may still be some challenges to be faced in extracting the existing data from the current system.

- Regarding staffing within BMSU, one member of staff has recently gone on long-term leave and her post has already been covered. Another member of staff is likely to be leaving soon and a candidate for their role has already been identified. More generally, efforts are being made to ensure that competencies within BMSU are spread across a larger group of people than previously. A new Assistant Director will shortly be appointed, who will focus on transgenic research and will be funded centrally.

- There has recently been a meeting of the BMSU Strategic Group, at which no concerns were raised. A piece of horizon-scanning work will be carried out to look at future imaging capabilities and needs within BMSU.

- The Academic Lead will change in the new academic year.

- A working group has been set up to consider the issues relating to recharges for research animals. It was agreed that it would be helpful to have academic input into the group.

- Birmingham is now leading the regional AWERB hub and work on this is progressing.

Report from the Named Veterinary Surgeon:

- Xenopus frogs are now being bred within BMSU. The intention is to maintain a self-sufficient supply of frogs, but in the short-term any shortfall may still have to be met by obtaining frogs from external suppliers.

Report from the Named Animal Care and Welfare Officers:

- The Establishment Licence Holder will be meeting with the named people later in June 2018.

18/06-06 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.

18/06-07-1 Application Ref TBA – Mechanisms for the development and treatment of ATM-/- lymphomas

The overall aim of this project is to identify the main pathways which co-operate with ATM loss in tumour development. These analyses will provide important information for treating patients whose tumours have impaired DNA damage responses.

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

It was noted that the application is at an early stage and has not yet been seen by the NVS, the NACWOs or the NC3Rs Midlands Programme Manager. Further meetings will be scheduled in order to get their input.

The PI was asked why NSG mice will be transferred in, rather than using wild type mice. It was explained that NSG mice will be needed to grow tumour tissue.

It was queried whether biophotonic imaging will be used and it was noted that no anaesthesia is detailed in the protocols. The PI explained that biophotonic imaging will be used to monitor tumour reduction and anaesthesia will be used. This should be explained within the application.

In the application, the wording 'Whether the dose is tolerated by the animal' is used and the PI was advised to clarify what is meant by 'tolerated', i.e. whether or not the animals show signs of illness.

The mouse grimace scale is mentioned in the NTS but its use is not really appropriate to these cancer models, which do not in normal circumstances give rise to pain.

Inconsistences between protocols in the weight loss related humane endpoints should be corrected. It was also flagged that as some of the animals' weight will be tumour tissue, the endpoints should also encompass body condition scoring. The NVS and the NAWCOs will work with the PI to revise the humane endpoints.

The PI clarified that the use of oral gavage is necessary, and that no problems have been experienced when using it to date.

Regarding sample size calculation, the effect size has been set to 25% difference; the Committee queried what the primary outcome measure will be in relation to this, and the PI explained that it would be reduction in tumour size.

It was felt that the first sentence in the second paragraph of the NTS should be revised to ensure it will be understood by a lay audience. The typo in that paragraph should also be amended.

In the 'adverse effects' section, adverse effects that are not in the protocols are listed; these should also be added to the protocols. Some of the wording under adverse effects might be better included in the 3Rs section.

For the longer-term studies, it explained that the extra sensory enrichment will involve different cage stimulation, different layouts, etc.

It was felt that the NTS was too technical overall and it should be amended to rectify this.

The application refers to 'regular' blood sampling, and the meaning of 'regular' should be explained.

It was confirmed that the mice to be used will be radiosensitive.

In the 'replacement' section, it should be explained clearly why animal work is necessary.

It was confirmed that the stated endpoints in the plan for objective one are correct.

It was clarified that femurs will be taken post-mortem in order to obtain bone marrow.

Regarding the number of animals to be used, the discrepancy between the total stated in the NTS and the numbers stated in the protocols should be rectified.

The PI explained that the findings of the study will hopefully be of value to cancer research more widely, rather than just to the study of ataxia-telangiectasia.

Further detail should be included in the 'benefits' section of the application (e.g. short, medium and long-term benefits).

The humane endpoint relating to the increasing number of circulating B cells is confusing and should be amended.

The PI reassured the Committee that there will be no toxic effects from the removal of T cells.

All of the drugs to be used at this stage will be drugs already used in clinic.

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

No further issues were raised.

Resolved that:

The revisions discussed above will be made and incorporated into the application. Once this has been done, a recommendation will be made

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

18/06-07-2 Application Ref TBA – Mechanisms behind T-cell function and regulation

Using a newly developed tool to temporarily label T cells, the overall aim of this project is to reveal how T cells behave under normal healthy conditions, as well as in diseases such as allergy, infection and autoimmunity. In addition, the researchers will look to understand how drugs may alter the function of T cells in autoimmune disease.

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

For the severe model, it was queried how many people within the research group will have the experience to carry out the necessary techniques. Currently, only the PI has this experience; however, they intend to initiate collaborations with others. BMSU currently has no experience in undertaking the models to the level required.

Clarification was requested about the stages that the animals will reach before being humanely killed in the severe protocol. 90% of the mice will only experience up to level 3. 10% may transiently progress to stages 4 or 5, but then may quickly return to stage 3 or less. Once an animal has reached stage 3 it will be subject to more frequent monitoring.

It was explained that unless the model is allowed to progress to severe, it would be necessary to use more mice overall to get the necessary data. By stage 4, most of the activation of T cells will have already happened but the inflammation may not have yet peaked, so there is scientific value in allowing the model to progress to the later stages.

The Committee noted that the application covers a lot of ground, when only one researcher will be working on it initially. The researcher will focus on the basic science work first, with the more severe treatment models coming approximately 2 years later. It was agreed that the best approach would be to submit the initial work as a moderate severity application, and to then amend it in the future to include the more severe work once scientific evidence is in place.

It will be necessary to allow additional time for the training of BMSU staff in the new models, for the establishment of the models within BMSU and for pilot work to take place.

Another research group that the PI hopes to work with is using a relapsing model, whereas this is an acute model. Whilst there are clear differences between the work of the two groups, it is believed that there will still be considerable value in this collaboration.

The NC3Rs Midlands Programme Manager will provide comments on the 3Rs aspects of the study via email.

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

It was reiterated that the initial work should be submitted as a moderate severity application and then amended later to add in the severe protocols. The Home Office Inspector will want the PI to focus on what is achievable with the resources available over the next 2 years.

The NTS was considered to be very well-written and clear. The reference to severe symptoms will need to be removed as these will now not be part of the initial application. Also, it should be clarified that the use of fewer mice is a reduction, rather than a refinement.

A general point was made that it would have been helpful during both this and the previous presentation to have seen a diagram showing the order and timing of the various procedures.

After further discussion about the potential use of the mouse grimace scale, it was felt that the scale would be of limited value in this project as pain will very rarely be an issue and the animals will be humanely killed if anything likely to cause pain occurs.

It was clarified that this research is of potential benefit to 0.5% of the population (i.e. a considerable number) although it is acknowledged that it is of more direct relevance to a smaller group of approximately 200 people.

Resolved that:

The revisions discussed above will be made and incorporated into the application. Once this has been done, a recommendation will be made that the Establishment Licence Holder submits the application to the Home Office.

18/06-07-3 Application Ref TBA – Provisional Fast track Brazil

This proposal was originally considered by the fast track committee. The fast track committee referred it on to the full committee because of the potential ethical and reputational risks which may arise from carrying out the proposed work in Brazil rather than in the UK.

It was clarified that the remit of the AWERB is to ethically review the proposed study on behalf of the University, and that this remit extends to overseas work as well as to UK Project Licences.

The researcher gave a presentation explaining the proposed work to the Committee.

It was explained that a Newton Award from the Global Development Assistance Fund is in place and that it had funded the initial work already carried out.

The policy of the Research Councils is that if animal work will be carried out overseas, it has to be done to an equivalent standard to that required within the UK. The NC3Rs checks on this and advises on how to deal with any discrepancies in standards, but it doesn't routinely carry out these checks for rodent studies. It was therefore suggested that the PI should work through the NC3Rs' checklist of UK standards to confirm that the Brazilian standards will be equivalent.

Photographic evidence for the tibia model was provided in the researcher's presentation. The Committee queried whether similar evidence is available for the skin model and the researcher explained that whilst work on the skin model has not yet started, the Brazilian collaborator has carried out similar work previously and pictures of this were provided to the Committee.

The skin model will involve a 15mm diameter full thickness wound on the back of the animal, which will then be filled with the experimental 'cotton wool' like material which is being tested.

The Committee expressed concerns about the large size of the wound and the proposed method of generating it, and queried whether it would be possible to have a smaller wound, possibly via punch biopsy. The researcher felt that this would not be suitable because of the toughness of the animals' skin, but the Committee noted that a similar approach has been successfully used in other similar studies. In these other studies, the wounds used have been just 4-5mm and it was queried why a wound of 15mm is necessary; in response, the researcher expressed doubts that a smaller wound would allow a proper assessment of the effect of the experimental material on the rate at which the wounds close.

The experimental material will be secured in the wound via the application of transparent foam.

The wounds will normally heal fully within 14 days and will have partially healed by day 7.

The Committee queried what form of analgesia will be used and it was clarified that paracetamol will be given in drinking water after surgery. The NVS emphasised that if the work were being carried out in the UK, then opiate-based, more powerful analgesia would be required.

The researcher had no information about humane endpoints and this will be required in order to properly assess the proposed work.

On the basis of the photographs provided, the NVS expressed concerns about the lack of sterile technique for the tibia procedure and the fact that it would be unacceptable if the work were to be carried out in the UK because of the high chance of infection. Whilst it is understood that during previous work on the tibia model, of 30 animals only 1 died, there is still a risk of sub-clinical infection that could cause pain and affect the outcomes of the study.

The researcher has so far not seen any of the work first hand and has no experience in carrying out research with animals.

It was queried whether it would be possible to carry out the skin model here at Birmingham, rather than in Brazil. The researcher emphasised that he would like to progress the proposed collaboration with Brazil and that he has been previously advised when applying for the scholarship that some of the work must be carried out in a country with the relevant clinical challenges. It is anticipated that the work will have accelerated impact if it is carried out in Brazil.

There is currently no funding in place for the skin model and an MRC grant application will be submitted. If this is successful the main part of the work would be carried out in the UK. The current application is to carry out some preliminary work on the skin model in Brazil, in order to inform the MRC application. It was suggested that the pilot experiments could perhaps be carried out in the UK rather than Brazil, and the samples sent to Brazil for analysis.

In the future, the researcher intends to progress to work with pigs at another research institution in the UK. However, the relevant institution currently uses pigs because they are a very good model for burn injuries, whereas they are likely to be considered a less justifiable model for other types of wound.

The Committee concluded that on the basis of the evidence so far provided, the work carried out in Brazil is not of the standard that would be required in the UK. It was agreed that further information is required from the Brazilian collaborator, including translations of material the Committee has not yet had sight of.

The work already carried out in Brazil on the tibia model is now at analysis stage and no live animals are now involved.

The researcher left the room and Committee's discussions continued.

Although it is understood that work on the tibia model is now complete, there is some reputational risk if it is now to be associated

with the University of Birmingham. Clarity is needed on whether any further work on the tibia model is still to be carried out.

The Committee debated whether the University should provide financial support for the researcher to carry out the skin model here rather than in Brazil. However, it was noted that this consideration is outside the remit of the AWERB, which is in place to consider animal welfare issues.

Further dialogue and information is required about past and future work to be carried out in Brazil. AWERB will need to consider future work for ethical approval. It was suggested that a Skype discussion with the Brazilian collaborator and veterinary surgeon would be helpful.

It would be very difficult for the researcher to carry out the work here as a project licence would be needed, which would be problematic for someone with no experience of animal work.

The researcher will be asked to work through the NC3Rs checklist of UK standards.

18/06-08 Matters relating to the 3Rs

Report from the NC3Rs representative

Activities undertaken recently:

- The recent workshop on the 3Rs in research using fish resulted in a number of useful suggestions for improvements, which the University of Leicester has tested for preference and signs of anxiety. The suggestions will now be taken to the Universities of Nottingham and Birmingham. A suggestion has also arisen from the University of Manchester.

- A meeting has recently taken place with the University's Press Office and the outcome is that there will be a news item on recent NC3Rs funding and some 3Rs examples will be included on the website.

- The speakers are now finalised for the Midlands 3Rs symposium, to be held at Birmingham on 19th September 2018. Members of the Committee were invited to suggest potential poster presenters.

- The NC3Rs Midlands Programme Manager has recently attended a 3D cell culture symposium and a Charles River meeting on genetic drift in different models of disease.

- The NC3Rs Midlands Programme Manager has been in discussion with a researcher about funding ideas – both a project grant and an NC3Rs CRACK IT Challenge. She has also been working with another academic on a big multicentre funding application.

Upcoming activities will include:

- The group work activities recently carried out as part of the NC3Rs' meeting on peer review will be repeated at a forthcoming event for University staff.

- The NC3Rs Midlands Programme Manager is due to speak at a Research Support all staff meeting, to inform support staff about the 3Rs and the funding available.

- The NC3Rs Midlands Programme Manager will be sitting in on the forthcoming Home Office meeting about the development of the new licence application form.

- The NC3Rs Midlands Programme Manager will be speaking at the University of Warwick to share best practice on the 3Rs.

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18/06-09 Any Other Business

There were no additional issues to report.

18/06-11 Date of Next Meeting

The date of the next meeting will be 19th July 2018.

GLOSSARY

3D	3 dimensional
3Rs	Replacement, Reduction and Refinement
ASPeL	Animals Scientific Procedures e-licensing system
ATM	Ataxia telangiectasia-mutated
AWERB	Animal Welfare and Ethical Review Body
BMSU	Biomedical Services Unit
C57	Strain of laboratory mouse
CRACK IT	NC3Rs open innovation programme
MRC	Medical Research Council
NACWO	Named Animal Care and Welfare Officer
NC3Rs	National Centre for the Replacement, Refinement and Reduction of Animals in Research
NSG	NOD scid gamma mice (a brand of immunodeficient laboratory mice)
NTS	Non-Technical Summary
NVS	Named Veterinary Surgeon
PI	Principal Investigator
T cells	A type of lymphocyte (a subtype of white blood cell)
TBA	To Be Announced
UK	United Kingdom