The University of Manchester

ANIMAL WELFARE AND ETHICAL REVIEW BODY

Minutes of the meeting held on 30 January 2025

Present: [redacted]

Apologies: [redacted]

In attendance: [redacted]

1. **Minutes**

Agreed: That the minutes of the meeting held on 12 December 2024 were approved.

2. **Applications for New Project Licences**

2.1. [redacted], Improving Phage Therapy to Combat Multidrug-Resistant Infections Understanding How Bacteria, Bacteriophages & the Immune System Interact.

Considered: A completed AWERB form, PPL application and presentation.

Interviewed: [redacted]

Committee discussion:

- The applicant is an experienced researcher who has recently moved to the UK, therefore this is their first licence application under ASPA.
- Members discussed and were satisfied with implementation of the 3Rs, HEPs and the rationale underpinning the 'harm benefit' analysis.
- The original draft provided to committee contained errors in that the researcher had answered 'yes' to the question 'Will your experimental design be determined by a regulatory guideline' which meant that all the experimental design questions had not been answered. The committee discussed in the general the process for applicants getting feedback from [redacted] and if this is happening in a timely manner. An updated form had to be circulated committee for this application which increased the workload for AWERB members and the Secretariat. The process will be discussed in a future meeting.

Discussed with applicant:

- The Chair explored with the researcher if in their experience there were welfare burdens on germ-free animals. The researcher explained that they have not noticed any differences, but in general you can have health issues with germ-free mice as the immune system doesn't develop as usual as the animals don't encounter any germs.
- [redacted] raised a number of points of clarification making suggestions for improvements that the applicant was keen to consider (particularly adjustments to reduce risk of stress and improve the quality of blood drawn).
- [redacted] and [redacted] raised questions of clarification on the experimental design that were satisfactorily explained with revisions agreed.
- The NVS and Chair questioned the researcher about why oral gavage is being used when there are alternatives available. The researcher explained that dosing with a syringe is not a technique they are currently trained in but they would be open to learning it. In addition, the techniques listed in the draft licence, including oral gavage, have been used by the researcher at a previous institution successfully and they wish to keep the experiments the same while they establish the model at the University of Manchester. The applicant committed to working with the NVS to refine this technique where possible.

Feedback to applicant: The page numbers provided below are based on the draft dated 07/01/2025 which was circulated to committee. That version was missing information on experimental design and an updated draft (dated 26/01/2025) was provided to committee however many comments had already been submitted by the committee by that point. We hope the numbers aid in you making your revisions.

[redacted], a lay member on the committee and also the University's lead on animal research communications would be happy to promote the results of the Phase 2 trials to the media is this is possible and when the trial is completed. If you would be interested in this, then please do get in touch with [redacted] directly ([redacted]).

Revisions: It was explained to the applicant that the committee had provided comments to the Secretariat prior to the meeting and while some would be discussed in the meeting, the list below includes all the comments whether they were raised in the meeting or not.

- There are some minor typographical errors which will need correcting before submission.
- The revised draft must be sent to [redacted] who will advise you on refinement of your experiment design sections. [redacted] must give approval as statistician on behalf of AWERB before you can submit the revised draft licence. Please copy in myself and [redacted] when you contact [redacted])
- Page 11 - The response to the question as to whether the work has been peer-reviewed should be improved and clarified. As it is currently written, it may be read as implying that the feasibility of the proposed work is in question. AWERB would not support such an application. However, AWERB was reassured in discussion that this was a question of presentation and could be resolved by revising the prose.
- Page 12 - The science background might not clearly support the stated objectives, at least for a non-expert in this field; it feels there's some disconnect. Additionally, Objective 2 could be improved for clarity.
- Page 13 - does host always refer to the mammal or sometimes the bacteria?
- Page 14 - what does interacting mean - infection? And, what does validation mean? Some clarification would be useful.
- Page 14 – Objective 3 - I don't think is necessary to set a timeline, especially for ex vivo work. Also, one might ask if such a milestone should not have already been achieved before this proposal.
- Page 15 - What is meant by "simplified and complex microbiome settings in vivo"? Consider clarifying this.
- Page 15 - the aim to use and explore computational modelling is not as explicit as it may be in NTS. You may wish to briefly mention this in the appropriate previous section.
- Page 29 - "Persistent diarrhoea (>48 hours) unresponsive to fluid and nutrient treatment." How is diarrhoea treated? Consider clarifying, as it seems to suggest that fluid and food supplementation might improve diarrhoea, but I am not sure that is the case.
- Page 30 - Do you expect any adverse reaction due to oral gavage itself (e.g. dyspnoea)? This is mentioned in later protocols (e.g. page 35).
- Page 34 - Technically, DT ablates target cells expressing the target gene rather than switching off a gene.
- Page 35 – As discussed in the meeting, you may want to consider using 4OH-tamoxifen. [redacted] on the committee would be happy to discuss this with you.
- Page 35 – Please seek advice from the Named Persons on the collection of blood and if AB would be more appropriate.
- Page 37 - Q. protocol 2 - typical cumulative experience is typically 2-3 procedures (short period of moderate suffering) usually temporary and not overlap; but 20% animals have 5-6 protocols; how can we be

confident these experiences of repeated moderate suffering do not venture into severe? What is the recovery time and checks between?

- Page 45 - Mice will be monitored frequently (every 2 days) during administration to check for development of moderate weight loss and diarrhoea.' I recommend putting at least every 2 days and increasing as appropriate. As written, this appears that the mice will only be weighed every 2 days when weight loss and diarrhoea for 48 hours are the HEPs. We note that 'or daily during peak inflammation' was added to step on page 49 which better reflects what will take place.
- Protocol 3 - The colitis protocol has both a bacterial infection and a colitis induction as mandatory steps. Please check this with the Named Persons.
- A number of comments were made regarding your Non-Technical Summary which are listed below. Please update your NTS based on the comments and send it to the following lay members for their review ([redacted])
    - Page 2 – "Understand how the immune system affects phage therapy from effectively killing bacteria resistant to antibiotics, to ultimately improve the use of phage therapy" is a bit of a clunky sentence that is hard to read. Something like "To ultimately improve the therapeutic use of phages by better understanding how the immune system interacts with the phage's ability to kill bacteria resistant to antibiotics" might be clearer? You may also want to define what a phage is here as opposed to the next question as it is first used here.
    - Page 2 - "we should" - could? or better "could develop that have potential to....."
    - Page 3 - Might it be good to list the groups in some kind or order and provide context so that the reader understands what the main benefactors as well as whether the benefits are anticipated to occur in short, medium or long (past end of license) term?
    - Page 3 – 'How will you look to maximise the outputs of this work?'. Is I appropriate or we? Most scientific work is collaborative, and team based? Later on you use we.
    - On collaboration this reads as aspirational - do you have collaborators? And could you concisely indicate that you have collaborators in the clinical world - how is the translation to patient benefits that are listed first in your list of outcomes likely to occur?
    - Page 4 - The section on "Typical Experience" needs a syntax check.
    - Page 4 - Perhaps under what will be done on P4 add that the mice will be kept in a germ-free environment with an explanation as to why? Also perhaps add that injections are given and blood samples are taken?
    - Page 4 – AWERB are keen for researchers to use alternatives to oral gavage where possible. As discussed in the meeting, AWERB encourage you not to limit yourself to techniques you may learn and want to use in the future, for example giving substances to animals from a syringe. Please discuss with the NVS how this can be included in the licence for potential future

use and how you can learn the technique should you wish to use it.

- Page 4 – As discussed in the meeting, some brief information on why you are using different methods to induce colitis would be beneficial in the NTS.
- Page 4 – it may be useful if you can expand on how or in what form the negative results will be published, as AWERB understand that it can be difficult for researchers to publish so-called 'negative' results.
- Page 4 - "phage therapy understanding" - phage therapy by OR by better understanding
- Page 4 - "lab-based systems" - in vitro or some other words? A lay reader may assume animal based research is lab based.
- Page 5 – In the sections of the licence that will be public, i.e. the NTS, please express more than, approximately in words rather than using symbols.
- Page 5 - Consider rephrasing the first paragraph, as most people may not regard "1-3 weeks" as an 'acute' phase response.
- Page 5 - *Citrobacter rodentium* is expected to cause only minor inflammation in immunocompetent mice however you have listed this as 'a moderate acute infection'. Please can you clarify this.
- Page 5 - presentation of severity and proportion of animals in each severity is somewhat unclear and open to misreading; particularly "10% of animals might suffer greater symptoms" which may mean greater than moderate severity - if it does, then you should clearly state severe but I do not think this is your meaning? This section could be clarified.
- Page 6 - I'm not sure the public will understand what "fermenters " are. Can you explain in the NTS?
- Page 6 - unsure why " model of choice" is mentioned. Please can you clarify this.
- Page 7 – As discussed in the meeting, please seek advice from [redacted] on the type of designs you are using. Crossover design does not seem appropriate for the studies you have outlined.
- Page 8 - The sentence "We can hypothesize from our previous studies that the use of phages as a treatment minimizes the need for additional pharmacological interventions that may exacerbate side effects or cause harm" seems unnecessary and may trigger additional questions regarding the control group — would pharmacological intervention be required for mice not receiving the phage?

Outcome: The study was given provisional approval based on the applicant making the changes/clarifications listed above to the satisfaction of the Chair/AWERB along with [redacted].

3. Report on licences processed from 25/11/2024 to 15/01/2025

The following amendments were approved by the executive committee.

3.1. Amendments to Project Licences

[redacted], Immune Cross-Talk Between the Oral & Distant Mucosal Barriers [redacted]., Immune Regulation of Health & Disease in Mucosal Barrier Tissues

3.2. Applications for Category C work

[redacted], Understanding the Role of KANK1 in ALS

4. Update on applications outstanding from previous meetings and upcoming Project Licence applications

4.1. The committee were provided with a document showing the status of applications considered previously and those pencilled in for future meetings.

5. NVS report

5.1. The Chair welcomed the new NVS.

5.2. The NVS stated that she has not seen any patterns or things of concern from the NVS reports that were provided to the committee by the previous NVS since she has started in the role.

5.3. An external facility reported [redacted] that animals sent to them had tested positive for Mouse Kidney Parvovirus (MKPV), so the [redacted] building was tested and found to be positive for MKPV and mouse parvovirus (MPV). [redacted] has communicated with researchers about the matter, and work underway to limit impacts and learn from this experience to better mitigate future recurrence. All the processes are being reevaluated but early signs indicate that risk prevention measures operated very well to limit impact. The virus was found in a mouse that was undergoing rederivation (transferring embryos from one mouse to another to produce pathogen-free mice) but the biosecurity that was in place picked up the virus before the pups were released which the NVS believes will have helped to contain the virus. The Chair raised a number of questions and was reassured that everything had been done that could be and processes were being reevaluated to mitigate risk of future instances.

6. 3Rs AWERB subgroup report

6.1. The Chair of the subgroup reported to the committee what one member who was not in attendance had raised regarding publishing negative data. The committee discussed the difficulties faced by researchers when trying to publish negative data, and agreed this topic should be on the agenda of an away day where it could be explored more. AWERB would like to understand from researchers the issues they face but also from those licence holders who have been able to publish negative data, and how they went out this. It was noted the research area may have a bearing on what is possible.

6.2. The Chair agreed with point 4.3 of the 3Rs subgroup minutes from the meeting on 11 December 2024 that it should be explored how reviews of work being carried out on service licences held by [redacted] staff can be done.

6.3. The Chair noted an interesting 3Rs project by [redacted] and wished him luck with the submission to the NC3Rs for a large programme grant to develop in vitro models with a network of bladder researchers.

6.4. The Chair thanked the subgroup Chair and organising committee for leading on an amazing 3Rs symposium with many highlights and for all the work that went in to arranging it.

7. Home Office and ASC

7.1. The Home Office has asked the Animals in Science Committee's (ASC) to undertake to projects which may mean AWERB will be asked for feedback.
Commission on leading practice in the animals in science sector
Commission on non-technical summaries and retrospective assessments

8. Topics and Speakers for future away days

8.1. The Chair invited and encouraged members to raise topics for future away days. Topics suggested included oral gavage, and translation and reproducibility. In terms of oral gavage, members would like to know more about the alternative of syringe feeding including where this may not be possible for use, e.g. dosing of parasites. The NVS reported that where this is used in other facilities there has been a positive impact on both animal staff and the animals. In terms of translation and reproducibility, the Chair mentioned [redacted] suggested [redacted] could be invited to talk about this matter as someone that does translational work and had an interest in research integrity.

8.2. It was agreed that [redacted] would be invited to the April 2025 meeting to discuss new methods of measuring light.

9. Minor administrative matter(s)

9.1. The Chair asked if AWERB members would wish to re-review an application that is not submitted to ASRU in a timely manner after receiving AWERB approval. It was agreed that should a licence not be submitted within 12 months, AWERB would want assurance from the prospective licence holder that they had checked there were no changes to the model or advice on Humane End Points.

Action: The Secretary will add a line into the feedback letter stating this requirement.

10. Any other business

10.1. [redacted]

The next meeting will be on 26 February 2025 at 10am-12.30pm.

Dates of meetings for the 2024/2025 academic year are:
30 January 2025
27 February 2025
27 March 2025
24 April 2025
29 May 2025
26 June 2025
31 July 2025
August break

Dates of meetings for the 2025/2026 academic year are:
25 September 2025
23 October 2025
20 November 2025
18 December 2025
29 January 2026
26 February 2026
26 March 2026
30 April 2026
28 May 2026
25 June 2026
30 July 2026

Dates of meetings for the 2026/2027 academic year are:
24 September 2026
22 October 2026
19 November 2026
17 December 2026
28 January 2027
25 February 2027
25 March 2027
29 April 2027
27 May 2027

24 June 2027
29 July 2027