Retrospective Review of Project Licences

The information you provide in or attached to this document must reflect data generated only from work carried out under the licence under review. A copy of the final agreed version of this document and any advice provided by the University AWERB in relation to this document will be placed on file. Retrospective Reviews may be requested under the Freedom of Information Act. If this is the case, we will contact you.

1. General Information:

Project licence holder to complete if information provided is incorrect

Name:	Chaeyeon Lee	
Contact details: Address & tel.	5 London Road, Harston Cambridge Cambridgeshire CB227QQ	07762387477
Project number	PP4428667	
Project title	Development of an implantable device for the treatment of brain tumours	
Project purpose	To develop and test an implantable device, which has been designed to deliver chemotherapeutic drugs for the treatment of brain tumours.	

Date licence was granted	17th November 2021
Date Retrospective Review was sent to the PPLh	20th August 2025

Please tick one of the options below:

A	√	My licence is due to expire in 12 to 15 months' time and I have no plans to write a new licence
B		My licence is due to expire in 12 to 15 months' time and I plan to write a new project licence to continue my research
C		I plan to request the revocation of my licence before its natural expiry date
D		I will no longer be the project licence holder but, another person will continue to hold the licence. The name of the new licence holder will be:
E		The AWERB Committee has asked for this Retrospective Review.

2. Animal Welfare/Recorded Harms:

2.1 Using the table below please provide the information requested.
How to complete this table: Return of procedures count animal numbers from 1st January to 31st December. In the table below if your licence was granted part way through the year count year one as the time from when the licence was granted to the 31st December of that year. Year two will be from January to December etc. until the final year for which the report is requested and count from 1st January to the requested report

date. Please insert rows for additional protocols as necessary. For any animals that experienced a higher level of severity than that of the protocol please highlight these figures in **bold.**

Protocol No.	Species	Protocol severity category	Total number	Actual number used	Actual severity recorded					
					Non-recovery	Sub Threshold	Mild	Moderate	Severe	Totals
1	Mice	Moderate	200	1st year				15		15
				2nd year				0		0
				3rd year				0		0
				4th year				0		0
				Total				15		15
2	Mice	Moderate	300	1st year				24		24
				2nd year				34		34
				3rd year				12		12
				4th year				0		0
				Total				70		70
3	Mice	Moderate	100	1st year				22		22
				2nd year				0		0
				3rd year				15		15
				4th year				0		0
				Total				37		37
									Whole Total	122

*If actual severity data has not been formally assigned at the point the Retrospective Review is undertaken, the columns can be used to indicate the estimated severity for each of the categories.

2.2 Does the information provided in the table reflect the projected incidence of harm provided in the adverse effects for each protocol? If not, please indicate where this was not the case and whether the projected level of suffering was more or less than you anticipated when you first wrote the licence. If the severity category for a protocol was amended during the tenure of the licence, please include this information in the reasons box.

Protocol number	Severity higher/ same/ lower than anticipated	Reason
N/A		

Describe any unexpected adverse effects and include the percentage and the number of animals affected. How were these episodes managed and recorded? If any of these resulted in a Project Licence Standard Condition 18 report, please indicate which were reported under Condition 18 and the date (also see Section 5.2).

2.3

Unexpected adverse effects: Weight Loss Death (Side effect from analgesia)
The percentage: 33% of the study plan
The number: 4 out of 12
Species: Athymic Nude Mice
Brief Explanation: Four nude mice were humanely euthanised (Schedule 1) due to significant weight loss. My colleague and I requested a veterinary pathological examination for those animals later, and the submitted samples identified acute tubular necrosis, tubular epithelial simplification (cuboidal epithelial cells), and renal papillary necrosis. A review of the case determined that the analgesic dose administered exceeded the appropriate dosage for the animals. At the time of the incident, the analgesic injection schedule and dosage had been recently revised, and animal technicians were involved in the administration. Hence, a meeting was held with the NACWO and NVS to review the incident, identify contributory factors, and assess procedural compliance. Following discussion, a future action plan was agreed, including further refinement of analgesic dosing, consideration of alternative administration volumes, and evaluation of alternative analgesic agents for subsequent studies to prevent recurrence. None of the animals were reported because they were humanely culled before reaching the minimum weights.

- Project Licence Standard Condition 18 repot

The submission date of sc18: 2nd December 2024
The numbers of animal affected: 1 out of 12
Species: Athymic Nude Mice
Brief explanation: The animal was found moribund the day after surgery. The procedure involved the subcutaneous implantation of an iontophoresis drug delivery device on the flank of the mouse. Three incisions were made for the implant: one on the flank and two ports on the back. This procedure is classified as moderate under the applicable PPL. The other mouse that underwent the same surgery on the same date did not exhibit any significant bleeding, listlessness, or notable signs of pain. The mice were checked twice daily for any symptoms of pain. The affected mouse was found by an animal technician in the next morning. Post-operative care was provided to monitor her recovery. The animal was kept in a heated chamber with a vet bed in for an hour after surgery to support better recovery and was returned to her cage once she became alert and active. The heat pad was attached on their cage. Both animals that got the same surgery on the day got fully recovered after the surgery before the cage was returned to the rack. The animal was observed eating nutrient gel. Metacam was administered in the evening at 18:00.

2.4 What percentage and number of animals had to be killed or died unexpectedly before the end of the experiment? Please provide a brief summary of each incident by protocol(s) where this occurred.

Protocol No.	% and number of animals killed or unexpectedly found dead
No.2	50% of the animals (6 out of 12, Athymic Nude Mice). 5animals were humanely sch1 for the reasons described above. 1 additional animal was lost unexpectedly due to failure of the heat pad (stop working) during surgery, causing hypothermia

2.5 Were your estimated animal numbers accurately reflected in your actual animal usage as provided in Table 2.1 above? **YES** **NO**

If no, please explain the why there was a difference. Please do this on a protocol-by-protocol basis.

Protocol No.	If your numbers were less that estimated please explain why.

1	Fewer animals were used than originally specified in the protocol, as efforts were made to minimise animal use in accordance with the principles of reduction. The study is currently paused while further refinement of the device is underway.
2	Fewer animals were used than originally specified in the protocol, as efforts were made to minimise animal use in accordance with the principles of reduction. The study is currently paused while further refinement of the device is underway.
3	Fewer animals were used than originally specified in the protocol, as efforts were made to minimise animal use in accordance with the principles of reduction. The study is currently paused while further refinement of the device is underway.

2.6 Have you re-used animals? **YES** **NO**

If so, why have you re-used animals and what has been the impact of re-use on the welfare of your animals? Please also provide the species and number of animals re-used by protocol where re-use occurred.

Species	Protocol No. on which animals where/will be returned as re-used, why and what impact, if any, this re-use had on the welfare of your animals

2.7 Has there been any animal wastage? **YES** **NO**

For example, this may occur when breeding and maintaining genetically altered animals or when animals have been ordered and cannot be used for some technical reason.

Where wastage has occurred, please explain the circumstances and nature of the wastage plus an indication of the numbers of animals. Please also provide either the number or percentage of animals that were wasted.

Circumstances and nature:
Estimated number or percentage of animals wasted and if appropriate provide this information by protocol:

2.8 For licences that authorise the breeding and maintenance of genetically altered animals:

a) explain how you optimise breeding efficiency, and
b) explain what use is made of any excess stock animals, and
c) explain if, and how, you have used any transgene repository – national, international, or internal.

N/A

2.9 If you breed genetically altered animals are your strains recorded on a database (e.g., MCMS) that can be

a) accessed by other researchers at the University? **YES** **NO**
b) accessed by researchers outside the University? **YES** **NO**
c) would you allow other researchers at the University to use your strains? **YES** **NO**
d) would you allow external researchers to use your strains with an MTA applied? **YES** **NO**

If you have answered YES to any of these questions, please elaborate below:

N/A

If you have answered NO to any of these questions, please explain why.

N/A

2.10 Have you been able to refine and/or reduce the impact of contingent harms arising from your use of animals (contingent harms are harms for example that arise from the transportation of animals, single housing animals or housing animals in non-Code of Practice accommodation, etc.). **YES** **NO**

Please explain/provide examples.

Animals were single-housed a few times when necessary to prevent interference with, or damage to, the implanted devices and each other's skin.

2.11 By species and percentage please indicate the source of your animals.

Species	Source	Approx. percentage
athymic nude mice	Charles River Laboratories	80%
C57BL/6	Charles River Laboratories	20%

2.12 During the tenure of the licence have you requested an amendment to increase/decrease animal numbers? **YES** **NO**

If so, which protocols were amended and were numbers increased or decreased, and by how much?

Protocol No.	Original estimated Number	Amended estimated number
N/A		
N/A		

If you have increased or decreased animal numbers, please explain why this was necessary?

N/A

2.13 During the tenure of this licence have you requested an amendment to increase/decrease the severity of any protocols? **YES** **NO**

If so, which protocols were amended and were the severity categories increased or decreased?

Protocol No.	Original severity category	Amended severity category
N/A		
N/A		

If you have increased or decreased the severity category of any of your protocols why was this necessary?

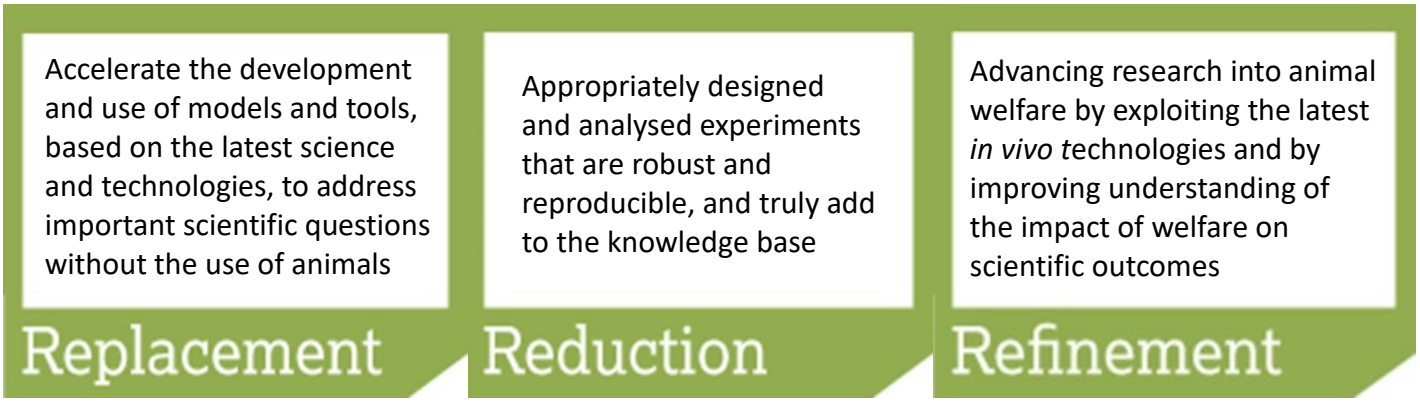
N/A

3. **3Rs:**

In this section, please explain what steps you have taken during the tenure of your licence that resulted in 3Rs gains. This might include working with collaborators to refine your model, changing the anaesthetic regime or equipment, etc. Consider every change you have made and its impact on the 3Rs – even small changes and initiatives can result in 3Rs gains.

The following definitions come from the NC3Rs website and are included to help you provide information under the most appropriate R below:

Definitions



3.1 Have you attempted or been able to replace any of your techniques or models with non-animal alternatives? **YES** **NO**

Please explain.

A parallel alternative experiment using cancer cells was also undertaken; however, it was concluded that this approach was not suitable for reliable assessment of physical tumour size.

3.2 Have you been able to reduce your animal usage? **YES** **NO**

If so, how have you achieved this (e.g., through experimental design, changes to the regulated procedures used)? Please give an indication of the actual numbers reduced.

No animal experiments were performed under this PPL last year. Although it would have been possible to conduct some studies using the devices with the previous design to obtain general tumour growth curves, this was not pursued in order to avoid the use of animals that might not yield optimal or necessary data. Animal work has therefore been deferred until refinement of the new device design is completed, which is planned for January 2026.

3.3 Are you involved with any tissue sharing either within the University or more widely?

Please explain:

N/A

3.4 Please LIST the techniques and/or animal models you have used on your licence (include GA models). Later on, you will be asked about the 3Rs achievements – please do not detail your 3Rs achievements in this box.

Administration of substances by intraperitoneal route (IP) for IVIS imaging, Administration of substances by subcutaneous route under anaesthesia (AB) for cancer cell injection, Subcutaneous, intramuscular or intraperitoneal implantation of any device, substance or delivery system, Aseptic surgical technique for implantation of a device. Athymic nude mice and C57BL/6 mice have used (NO GA models used)

3.5 How successful have these techniques and/or models been?

Tumour models were successfully established in both mouse models, and device implantation was completed without technical issues. IVIS imaging was successfully performed throughout the study period. The device design is currently undergoing refinement to improve implantation procedures and minimise discomfort to the mice.

3.6 What limitations, if any, have you encountered? Were you able to overcome these limitations and, if so, how?

Although the device is less than 1.5cm in size, it still remains relatively large for a mouse. Efforts are currently underway to further reduce its size to improve animal welfare and ease of implantation.

3.7 Have you attempted or been able to refine any of your techniques or models?

YES **NO**

Please provide a list of techniques or models you have been able to refine and the refinements you have made. Please indicate if you have published or disseminated this information during the tenure of this licence and attach a copy of the publication.

https://doi.org/10.1002/admt.202301641. Published paper on the previous device we had used for the study. The size of the device is currently undergoing refinement by another researcher.

3.8 Do you use systems to monitor the welfare of your experimental animals (e.g., scoring sheet)?

YES **NO**

If not, why?

If you do use a welfare monitoring system, what do you use? Did you refine or modify your system during the tenure of your licence and what impact did this have?

Animal weight monitoring. General score sheet including responsiveness, posture, behaviour, facial grimace.

3.9 Were the end points detailed in your project licence appropriate? **YES** **NO**
Have you needed to modify them during the tenure of your licence? **YES** **NO**

Please explain.

End points: 1. Any animal that loses 15% of their pre-treatment body weight will be culled. 2. Any animal that has a tumour bigger than a mean diameter of 1.5 cm will be culled. 3. Any animal that develops an ulcer with a surface area greater than 5% of the area of the tumour will be culled. Modification: The end point of the tumour size was 1.2cm at the beginning of the study but it the amendment was made to 1.5 cm later after a discussion and a meeting with UBS license managers.

3.10 Please review the non-schedule 1 methods of killing authorised on the protocols on your licence. In the box below, list each method and beside each clearly indicate which you have used? Examples of non-schedule 1 methods include: exsanguination, decapitation and perfusion fixation.

Exsanguination, Cervical dislocation

Were these killing methods the most refined? **YES** **NO**
Were they the most appropriate for your experimental data? **YES** **NO**

If you have answered NO to either of the above questions, please explain. If you were able to refine the way your animals were killed, please explain how this was achieved.

N/A

3.11 Have you received awards or funding specifically targeted at the 3Rs? **YES** **NO**

If so what was the source of your funding, when did you receive it and what did the funding allow you to achieve?

N/A

The AWERB 3Rs committee is particularly interested in this section of your review because information you provided here could be of interest and use to other researchers at the University.

Information that you have included in this section will be included in the UBS 3Rs Search Tool unless you complete the box below. UBS will only add information to the UBS 3Rs Search Tool section on the UBS website that University staff can log into using their Raven Access. You should however disseminate all 3Rs finding more widely.

I do not agree to information provided in this section to be added to the UBS 3Rs Search Tool for the following reason(s).

4. Scientific Progress and Benefit Achievements:

4.1 Taking into consideration that your licence may not be due to expire, has your research progressed as you expected? **YES** **NO**

4.2 When your licence is due to expire will you have completed the programme of work described in this licence? **YES** **NO**

4.3 Regardless of whether you managed to complete your programme of work, what have you achieved/discovered during the time since this licence was granted? (Please copy your key scientific questions/objectives which appear at the beginning of Part D, or in the Action Plan, of your project licence into the box below and against each explain what you have achieved/discovered).

We have confirmed that the materials of the device were biocompatible, ensuring no adverse effects on animals. Our findings demonstrate that the device is capable of drug delivery, successfully targeting tumours in vivo. We also could check the significant reduction in tumour size among the treated group through IVIS image in our experiments that was conducted late last year.

4.4 For key scientific questions/objectives you could not complete either fully or partly, please include an explanation as to why you were not able to achieve what you set out to achieve when the licence was granted (reasons could for example include lack of funding, the model took longer than expected to develop, another group published data which meant continuing the work would equate to repeating the work, etc.).

The initial researcher who was responsible for the device design graduated and left the team. Following their departure, we reviewed on the previous design of the device and then determined that the original device was too large to be suitable for mice. A new researcher has since taken over and is currently focused on refining the size of the device. We expect the redesigned version to be ready by mid-January 2026.

4.5 In the expected benefits section of your licence, you described the benefits you believed would be likely to arise from your programme of work. Please explain what benefits have actually been achieved and, if appropriate, explain how these differ from what you anticipated you could achieve when you wrote the licence.

The aim for the programme was described that the work would develop and test an implantable device capable of delivering chemotherapeutic drugs directly to brain tumours. The anticipated benefits included improved localisation of drug delivery, reduction in the need for multiple systemic injections, and minimisation of off-target effects. To date, preliminary results have demonstrated that the device can successfully deliver drugs to the targeted tumours in mice, as confirmed by IVIS imaging. This confirms one of the key expected benefits—effective localised drug delivery in a preclinical model. While these results are promising, the full benefits for clinical application remain to be established. In particular, precise therapeutic schedules and dose levels suitable for patient use still need to be determined through further in vivo testing. Overall, the benefits observed so far align with the anticipated outcomes in terms of device functionality and targeted drug delivery, though the full clinical translation of these benefits will require additional optimisation and testing.

4.6 Specifically, if you were unable to address any or even all your key scientific questions/objectives what impact did this have on the benefits arising from your work?

While the project has demonstrated that the implantable device can deliver chemotherapeutic drugs to targeted tumours in mice, some key scientific questions remain partially addressed. Specifically, the optimal dosing regimen, therapeutic schedule, and surgical protocol suitable for clinical translation have not yet been fully determined. This limitation impacts the benefits arising from the work in that, although we have confirmed effective localised drug delivery, we have not yet been able to define the precise parameters required for safe and effective use in a clinical setting. Consequently, the full potential benefits for patient treatment, such as optimised efficacy, minimised systemic toxicity, and streamlined clinical application, remain to be realised. Further in vivo studies are planned to address these remaining questions, which will allow the programme to deliver the anticipated benefits more completely.

4.7 Were you able to identify/develop/implement any new scientific or technical developments during the tenure of this licence? **YES NO**

If so, what were these and what were/was the benefit(s)?

In a departure from conventional use of the iontophoresis technique, including epidermal patches or wearable devices, this project successfully utilised iontophoresis implanted inside the body internally to target tumours with high precision, marking a significant advancement in localised drug delivery (https://doi.org/10.1002/admt.202301641). This work demonstrated the potential of using iontophoresis as a targeted drug delivery system for tumours. This approach could be highly beneficial in the future, particularly for delivering therapeutics across the blood–brain barrier (BBB) into glioblastomas, a major challenge in current clinical practice, by controlling ion movement and charge.

4.8 Using the headings below please provide a list of publications and meetings attended where research arising from work undertaken under this licence has been disseminated.

Please highlight in bold the publications which contain and meetings at which 3Rs achievements were disseminated.
Please only include publications arising from research undertaken under the authority of this licence. If you have papers in press, please include these.

Publications in scientific journals: -
Publications pending, or under review: -
Presentations at scientific meetings: -

Have you remembered to highlight in bold the publications which contain and meetings at which 3Rs achievements were disseminated?

4.9 Have you engaged with the general public by giving interviews about your work on radio, television, at a public meeting or debate or in a newspaper article? **YES NO**

If you answered NO: why?

I didn't have any opportunity to participate in such events.

If you answered YES: how, where (i.e., what medium did you use) and when did you engage with the public, what sort of information did you disseminate and what was the outcome?

5. **Project Licence management information.**

5.1 Amendments (if applicable):
Provide dates and a summary of all amendments made to this licence (i.e., what each amendment requested and why it was required) since the licence was granted (or if appropriate since the licence was last reviewed).
Please read questions 2.11 and 2.12 – for amendments that apply to this question including those that apply to either 2.11 or 2.12, please provide the date of the amendment here and, if relevant, a note that further information can be found in Section 2.11 or 2.12.

A few amendments were made on 25th September 2024. I believe this was before the licence was last reviewed, but I am including it here for completeness. The amendment added a new optional step for animal identification in all protocols. Identification methods might include ear biopsy, microchipping, or micro tattooing. Additionally, terminal cardiac exsanguination under anaesthesia followed by Schedule 1 killing was also included to maximise blood collection for analysis. Another amendment was made to the tumour size endpoint, increasing it from 1.2 cm to 1.5 cm. This change was made because, as the study focuses on tumour size reduction, 1.2 cm was too small to detect significant differences between control and treated groups. Additionally, published studies with similar tumour models have used a 1.5 cm threshold, suggesting this is a more appropriate endpoint.

5.2 Project licence Standard Condition 18 Reports (if applicable):
Provide dates and copies of all Condition 18 reports sent to the Home Office since the licence was granted (or if appropriate since the licence was last reviewed). Copies of any reports should be attached/supplied as separate documents please.

Submission: 2nd of December, 2024
Please find the attached.

5.3 Non-Compliance (if applicable):
Provide the date, a summary of the nature of any non-compliance and the outcome (or if appropriate since the licence was last reviewed). Include the RCA reference number.

5.4 Have there been any other issues that have affected the management of this licence that you feel should be taken into consideration, (e.g., equipment failure, absence of key staff, change in the health status of the animal unit etc.)?

During the procedure, the disfunction of the heating pad led to unintended hypothermia in the mouse. The analgesic dosage initially recommended by the NACWO was suboptimal, resulting in adverse effects in several mice leading to unexpected culling, which was unfortunate.

5 Retrospective Review:

Project Licence Holder check list:

AWERB requires the following documents	Documents sent to AWERB
Completed copy of this form	2nd January 2026
Copies of Condition 18 reports (if applicable)	2nd January 2026