Home Office

NON-TECHNICAL SUMMARY

Development of nerve neuroprosthetic treatments

Project duration

5 years 0 months

Project purpose

- (b) Translational or applied research with one of the following aims:
  - (i) Avoidance, prevention, diagnosis or treatment of disease, ill-health or abnormality, or their effects, in man, animals or plants

Key words

Neuroprosthetic treatments, Nerves, Neural implants

Animal types	Life stages
Mice	adult
Rats	adult

Retrospective assessment

The Secretary of State has determined that a retrospective assessment of this licence is not required.

Objectives and benefits

Description of the projects objectives, for example the scientific unknowns or clinical or scientific needs it's addressing.

What's the aim of this project?

To test, develop, and validate new treatments using neuroprosthetic devices designed to be implanted into nerves to control body function in disease or dysfunction.

Potential benefits likely to derive from the project, for example how science might be advanced or how humans, animals or the environment might benefit - these could be short-term benefits within the duration of the project or long-term benefits that accrue after the project has finished.

Why is it important to undertake this work?

Neuroprosthetic implants consist of implantable devices which connect with the nervous system. By reading / writing electrical information into the nervous system, neuroprosthetic implants can affect the function of the rest of the body. Currently, this technology only has a limited use in human patients, in the form of therapies such as deep brain stimulation or vagus nerve stimulation, which stimulate relatively large areas of the nervous system to treat conditions such as Parkinson's disease and depression. However, recent technological advances now allow us to make much smaller devices, capable of communication with small parts of the nervous system and treat many diseases.

Nerve neuroprosthetic implants are neuroprosthetic implants specifically targeted to the nerves of the body. As nerves connect the brain with most parts of the body (including organs and limbs), devices that are implanted in them have the potential to treat a wide range of diseases. This includes diseases arising from problems in the nerves themselves (e.g. nerve injury, amputations, neuropathic pain) or from the organs which they control (e.g. diabetes, bladder dysfunction). Nerve neuroprosthetic implants can not only offer solutions to specific diseases, but represent a whole new class of treatments - one designed to restore health through the use of electrical communication with the body (electroceuticals), rather than making use of chemical treatments (pharmaceuticals).

What outputs do you think you will see at the end of this project?

By the end of this project we expect to have produced nerve neuroprosthetic implants capable of delivering the following treatments in rodents:

- Achieve control of bladder function - controlling emptying, prevent unwanted emptying, monitor bladder fullness. (**Aim 3**)
- Monitor activity in the pancreas and liver, and modulate insulin release and glucose blood levels. (**Aim 3**).
- Ameliorate neuropathic pain (chronic pain, arising from damage to the nervous system). (**Aim 4**).
- Partially restore sensation and movement to fully paralysed limbs due to nerve injury. (**Aim 2**).

These three devices will be shared with the scientific community via publications. The first three will also result in devices ready to be introduced into the next stage of work to develop them for use in humans (larger animal studies, human trials). The last one, given its more ambitious scope, will move onto a new licence for further development, with the aim of producing a device suitable for use in human patients in the future.

We also expect to produce (as part of **aim 1**) a general nerve neuroprosthetic platform (a "general" type of nerve neuroprosthetic implant) - on which we will base all of our other devices. We will share this platform with other labs aiming to develop nerve neuroprosthetic treatments for other diseases. This will also be shared with the wider community through publications.

Who or what will benefit from these outputs, and how?

The development of a"general" nerve neuroprosthetic platform, that can be applied to any type of nerve (**aim 1**) will be of immediate benefit to the wider scientific community. This will become available before the end of this project, as it will be developed before we begin work on our other project aims. We aim to make a platform that is simple for others to make while providing high resolution connectivity combined with high biocompatibility, increasing its generability and the ability for its translation. There are many other diseases that nerve neuroprosthetic implants could potentially treat aside from those we work on in this licence. Therefore, providing a simple-to-use platform that allows integration of recording and stimulation on a smaller device, designed to integrate and spatially map to nerves at different locations with different sizes will allow other labs to apply these techniques to study a wider range of diseases, beyond those that we will work on under in this licence.

In the medium term, our organ (bladder, liver, pancreas) modulating nerve neuroprosthetics (**aim 3**) which we expect to have developed by the end of this project will be of use to patients suffering from improper organ function. This includes dysfunction of the bladder (as seen in spinal cord injury patients, 1.5 million patients worldwide), as well as diabetes patients (422 million patients worldwide). Type 2 diabetes would be the most directly treatable condition (by driving insulin release from the pancreas). However, type 1 (as well as 2) could also be treated with these implants (for example, supressing glucose release from the liver). Our neuropathic pain-treating devices (**aim 4**) are also expected to be of use to patients suffering from chronic pain (an estimated 7% of the population worldwide). In many of these conditions, patients already have access to some treatment options involving implantable electrical devices. This makes it likely that our devices developed in this licence will be ready to follow the path leading to use in the clinic.

In the long term, our sensorimotor-controlling (restoring sensation and movement) nerve implants (**aim 2**) will in the future be of use to patients suffering from paralysis and/or sensory loss due to nerve injury. Nerve injuries are frequent, with over 200,000 cases of nerve injury reported annually in both the United States and Europe. Given their ability to control sensation and movement, they could also be adapted for use in a wide range of conditions in which these are impaired. This includes other types of injuries to the nervous system (spinal cord injury - affecting over 1.5 million patients worldwide; traumatic brain injury - with an estimated 69 million new cases worldwide every year), amputations (an estimated 320,000 patients in the UK alone, potentially treated with this technology combined with robotic limb prostheses), severe skin damage, etc. Given their more ambitious aim, and the complexities associated with fully reproducing natural nerve activity (instead of simply modulating it),

we anticipate a timescale of 5-10 years following the end of this project before this technology is ready for use in humans.

Through an amendment requested in February 2024 we sought to add some adverse effects (breathing disruptions) and extend certain endpoints (weight loss post surgery) in certain protocols. We expect these changes to bring significant benefit to this work, by allowing us to reach our scientific goals and therefore project aims with minimal impact to animal welfare, as experiments relating in particular to aim 3 are currently limited by these adverse effects/endpoints.

How will you look to maximise the outputs of this work?

Our group has an expertise in the design and fabrication of neuroprosthetics, as well as in nerve physiology. However, our expertise in the conditions we aim to treat with these devices is more limited. To address this, we have established a network of collaborations with other groups with expertise in these fields. This includes collaborations with other groups working on fields such as bladder dysfunction in spinal cord injury, or diabetes. We will continue to expand our network of collaborations as we search for new conditions which could be addressed with the treatments we are developing. Once the projects are running, we will disseminate our results through scientific publications, as well as presentations at conferences and seminars.

Species and numbers of animals expected to be used

- Mice: 525
- Rats: 1450

Predicted harms

Typical procedures done to animals, for example injections or surgical procedures, including duration of the experiment and number of procedures.

Explain why you are using these types of animals and your choice of life stages.

Implantable medical devices such as the nerve neuroprosthetic being developed in this licence need to be validated in animal models. In order to show that a device is effective, the model needs to realistically simulate the same condition that the device is meant to treat in patients. This is due to the fact that implants face a wide range of challenges - they need to resist temperatures, movement, and chemical and immune system attacks associated with being inside an organism. They also need to avoid causing damage to the tissue around them. Finally, they need to continue delivering therapy despite these challenges for years after being implanted. This combination of characteristics can only be replicated inside of a body.

Rodents have a peripheral nervous system which is anatomically and structurally very similar to that of humans. They can also be trained to perform skilled behavioural tasks. This allows experimenters to develop therapies that attempt to restore advanced skills such as grasping, which also exist (and can be impaired) in human patients. Rodents are also frequently used in the field of neuroprosthetics,

meaning that certain experimental results will be available in published literature, and will not have to be repeated.

Typically, what will be done to an animal used in your project?

Approximately 35% of all animals in this work will be used for non-recovery work (terminal anaesthesia). They will not experience any notable pain or discomfort.

For the remaining 65%: animals will typically be trained in a specific behavioural task for 2 weeks. Such a task may be, for example, reaching and grabbing a sugar pellets. After learning the task, they will then undergo a single surgical procedure during which a neuroprosthetic device will be implanted on one of their nerves. The wires from the implant will be run under the skin to a small port fixed to the animal's head. In a fraction of these animals as part of the surgical procedure the nerve may will also be lesioned or ligated.

The animal will be allowed to recover and become accustomed to the implant for 1 week after the procedure. It will then be reintroduced to the behavioural task in which it was trained. Typically, this will involve 3 sessions per week for 4 weeks. During the behavioural task, a wireless port will be plugged onto their head connector, and electrical signals will be recorded from their implanted nerve device. As part of certain behavioural tasks (approximately 50% of animals in behavioural tasks) animals may have to be food restricted. This is a commonly carried out procedure in behavioural tasks, done to motivate them to seek food rewards given during the task. We are commited to minimise the welfare impact of food restriction, applying it only when absolutely necessary, and limiting as much as possible when applied. For example, we will typically restrict access to food only the day when the behavioural task is performed.

In a fraction of the animals that have undergone behavioural training and surgery (approximately 30% of all animals), some additional procedures will be carried out. In the weeks when these animals are performing a behavioural task while having their device implanted, some procedures will be carried out to gather more information about the performance of the implant (e.g. imaging, or blood sampling), or to make the implant more stable in the body (e.g. delivery of substances). These additional procedures will provide little additional discomfort to the animal and may be carried out with only a brief period of anaesthesia or (more commonly) no anaesthesia at all.

Some animals (<10%) will also receive one or more injections as part of certain protocols/steps. Approximately half of these will receive only one injection, with the other half receiving multiple - usually a maximum of one injection per week.

What are the expected impacts and/or adverse effects for the animals during your project?

A significant portion of animals under this licence (approximately 65%) will undergo surgery. Animals will generally be drowsy and show limited movement for approximately the first 24 hours as part of the normal recovery from the anesthetic. Animals will also experience some degree of pain around the operated region over the first few days, which will be treated with pain relieving medication (normally over two days post-surgery). In rare occasions (<5%) animals may experience postoperative complications, such as wound dehiscence or loss of body weight, the latter generally expected to recover within the first 6 days.

A subset of these animals (approximately 5% of all animals) will undergo surgery to access the vagus nerve. In very rare occasions (<1%) animals will experience temporary changes in the breathing rate as a result of irritation during surgery of the phrenic nerve, which plays a crucial role in controlling the diaphragm and respiratory functions. In previous experience, these temporary changes in breathing do not result in any effect on normal behaviour, such as locomotion around cage, eating or drinking etc, and naturally recover within 4 days.

A portion of animals undergoing surgery (approximately 15% of all animals) will receive a nerve lesion. This lesion will occur on a nerve connecting to one of the limbs (forelimb or hindlimb) and will lead to impaired movement and feeling on the affected limb. The nerve lesions will not cause full limb paralysis, as not all limb nerves are injured in the procedure. Depending on the type of lesion and implant used, animals may recover full movement and feeling over the course of ~4 weeks following injury, whereas in the rest no recovery will be seen (approximately 50% of nerve injuries). In hindlimb nerve lesions animals will typically drag the affected limb and show overall limited mobility over the first few days. In forelimb lesions animals will typically retract (lift) the forelimb while moving, but can continue to bear weight on it as only the paw is affected by the forelimb nerve lesion. Lesions will not cause animals to show any difficulty in feeding and drinking. Animals will quickly adapt within days to move around the cage unaffected by their affected limb. Despite dragging the operated limb during the first few days animals rarely develop sores on it, and the ocurrence of this can be further minimised by providing soft bedding for the animals. Nerve lesions do not lead to additional pain aside from that expected from the surgical procedure, and will be treated with the same analgesia regime.

A separate small subset of animals (approximately 5% of all animals) will undergo a nerve ligation procedure during surgery. This leads to the development over several days of hyperalgesia (enhanced pain sensation) and allodynia (pain sensation in response to non-painful stimuli) on their operated paw. This models neuropathic pain in humans. Depending on the severity of the ligation, in the most severe cases animals may keep their paw retracted and bear their bodyweight on the opposite leg. Animals will nonetheless be able to move around the cage and perform daily activities with no major difficulty. A fraction of these animals may also exhibit nibbling of their nails in the operated limb (which may eventually reach their nail bed), but in our experience this is a rare occurence (<5% of operated animals).

Expected severity categories and the proportion of animals in each category, per species.

What are the expected severities and the proportion of animals in each category (per animal type)?

We expect the majority of animals in this work to fall under either the non-recovery or the moderate severity category. Non-recovery should contain all animals used for terminal anaesthesia work (approximately 35%), for both rats and mice. In these animals, all work will be done under anaesthesia, from which animals will not recover. These animals will therefore not experience any pain or discomfort. Moderate severity should contain all animals used in the remaining protocols, for which surgery is performed (approximately 65%). This surgical procedure will mainly be for the implantation of a nerve neuroprosthetic device. These animals will experience short-term moderate pain as a result of the surgical procedure but are generally expected to recover within a few days of the operation.

What will happen to animals at the end of this project?

- Killed

Replacement

State what non-animal alternatives are available in this field, which alternatives you have considered and why they cannot be used for this purpose.

Why do you need to use animals to achieve the aim of your project?

Nerves make up the circuitry connecting higher structures of the nervous system (brain, spinal cord) with the rest of the body. As such, they are an ideal structure to target to develop therapeutics for a wide range of structures (bladder, pancreas, muscles, etc.).

An effective nerve neuroprosthetic device must be able to interact with nerves for prolonged periods of time. This must occur despite the numerous challenges that a body poses (immune system, movement of muscles, degradation of implant materials). An effective device must also be able to deliver therapy with no side effects - for example, activating nerves to contract the bladder, but without unintentionally activating other fibers carried by the nerve leading to a sensation of pain.

The wide range of interconnected body systems that play a role in the effective delivery of electroceutical therapy using nerve neuroprosthetics makes the use of animal models essential in their development.

Which non-animal alternatives did you consider for use in this project?

The following systems were considered for use in this project instead of animal work:

- *Ex vivo* (tissue in-a-dish) nerve systems - culture systems in which nerves, harvested from animals, are kept in dishes for periods of days to weeks. We considered testing, developing and validating our nerve neuroprosthetics on these nerve in-a-dish systems.
- Computer simulations - simulations incorporating properties of nerve tissue and of materials from which the implants are made. We considered designing and developing our devices based on the information gathered from these simulations.

Why were they not suitable?

While all of the above mentioned alternatives will be used for this project (optimising nerve neuroprosthetic technology before moving it into the animal testing stage), these techniques cannot fully replicate the complexity of living organisms.

Ex vivo nerve culture systems can be used to test the interactions between implants and nerve tissue itself, but present many limitations. Firstly, nerves can only be cultured for a maximum period of weeks. This is too short of a period to model long-term (months) interactions between tissue and implant. Secondly, this culture has to be done outside of the body, with no blood circulation and therefore little presence of the immune system (a key player in implant rejection). This further limits the relevance of

ex vivo systems in studying long-term interactions. Finally, while good for studying the effect of neuroprosthetics on the nerves themselves, delivery of treatment with neuroprosthetic implants is not limited to a simple interaction with nerves. Nerves need to be activated in specific patterns to produce a desired effect in its target organs/muscles. Alternatively, nerve activity needs to be carefully read and disentangled to understand what particular patterns of nerve activity mean. *Ex vivo* nerve systems lack both target structures and naturally-occurring nerve activity, and are therefore insufficient to simulate the complexity of a full organism needed for use patients. Further, the immune system is lacking in *ex vivo* models, resulting in an insufficient mimicry of the actual implantation and subsequent healing process. To adequately observe and design for immune response (foreign body response, immune reaction, etc.) with regard to placement of implants, *in vivo* studies are necessary.

Computer simulations help in understanding the nerve-tissue interactions. However, they present similar limitations as *ex vivo* systems in providing an understanding of the effect the implants will have on the entire body. Simulations can be used to predict how implants will activate nerves, or whether nerve activity will be able to be read by an implant under given conditions. However, there is currently not a deep enough understanding of the how natural patterns of activity are distributed throughout nerves, or how activating different portions of a nerve or in different temporal patterns can result in different effects in their target organ. These factors are key in order to ensure that the nerve activity introduced with the implant results in the desired changes in the target organ to treat a condition.

Reduction

Explain how the numbers of animals for this project were determined. Describe steps that have been taken to reduce animal numbers, and principles used to design studies. Describe practices that are used throughout the project to minimise numbers consistent with scientific objectives, if any. These may include e.g. pilot studies, computer modelling, sharing of tissue and reuse.

How have you estimated the numbers of animals you will use?

Estimates of animal numbers are derived from a combination of 2 factors. The first is our experience in developing nerve neuroprosthetic devices - particularly that derived from our previous licence. The second is our engineering knowledge on the typical number of iterations (versions of devices) necessary to develop a successful neuroprosthesis. Over the course of this licence, we expect to develop a progressively improved neuroprosthesis device. From our previous experience, we expect to have to go through approximately 15 iterations of devices before arriving to its final version. This final device will then be applied to different areas: sensorimotor (nerves controlling movement and sensation), organ modulation (nerves controlling organ function), and neuropathic pain (dysfunctional nerves causing chronic pain) models to develop electroceutical treatments. Each of these will likely require a further 10 iterations to optimise the device for each specific application.

From our experience, each individual iteration of devices/electroceutical treatments requires approximately 25 animals to test and obtain decisive feedback on. While difficult to predict the exact numbers at this stage, this calculated estimation provides a good approximation to the number of animals we expect to use.

What steps did you take during the experimental design phase to reduce the number of animals being used in this project?

During experimental design, we accounted for the large volume of work we will include in each iteration of devices prior to testing them in living animals. This includes engineering tests (testing devices on the bench), computer models, and cell culture tests. This will reduce the number of iterations necessary to reach the "final" device or treatment.

We also made use of PREPARE guidelines and the NC3R experimental design tool, ARRIVE guidelines, power calculations, and knowledge of literature in our field (neuroprosthetic devices) to provide an accurate estimation of the number of animals that will be necessary to test each iteration/ We will continue to use these tools to design our future experiments. The estimation of 25 animals per iteration accounts for pilot studies, non-recovery work, and surgical implantation with behavioural testing to provide conclusive results with the least number of animals.

What measures, apart from good experimental design, will you use to optimise the number of animals you plan to use in your project?

A typical experiment will involve pilot studies with a few animals to explore the efficacy of an implant being tested. If these look promising, a larger number of animals will be implanted with devices. Numbers for experiments will be estimated based on the initial pilot studies, together with statistical power calculations. This will increase the likelihood that if our device is effective we will be able to observe and measure it in an experiment.

We will also include numerous non-animal tests for our devices prior to moving them on to animal work. This will include in vitro tests, engineering characterisation, and computer simulations of their short- and long-term behaviour when implanted. This will allow us to increase the success rate of our implantation experiments and minimise the number of *in vivo* experiments required.

In our experiments, data will typically be acquired and processed using automated equipment and software wherever possible, in order to minimise bias.

In almost all cases, animals in our licence will be obtained from commercial suppliers (including immunodeficient lines). This should eliminate any animal waste due to inefficient breeding.

Refinement

Give examples of the specific measures (e.g., increased monitoring, post-operative care, pain management, training of animals) to be taken, in relation to the procedures, to minimise welfare costs (harms) to the animals. Describe the mechanisms in place to take up emerging refinement techniques during the lifetime of the project.

Which animal models and methods will you use during this project? Explain why these models and methods cause the least pain, suffering, distress, or lasting harm to the animals.

The work in this project will be carried out in mice and rats, with the majority of the work carried out in rats. Mice will be used in cases where further work (not covered by this licence) leading to clinical translation is likely to require certain models found only in mice. For example, mouse models of neurodegenerative diseases which develop motor deficits - these deficits may be addressed using our neuroprosthetic devices and translated to the clinic for treatment of patients suffering from these conditions but will require preclinical validation in mice.

Most experiments will require the implantation of a nerve neuroprosthetic device into the body. In some cases, a nerve injury will also be carried out. This will be done to simulate a human condition we aim to treat with the implants.

Implantation of a nerve device is well tolerated in rodents, when surgery is performed under adequate aseptic conditions and pain relieving medication is provided. The implants are developed and optimised *in* vitro (i.e. using cells cultured in-a-dish) prior to use in animals. Our devices are also typically made to be small, flexible, and overall compatible with tissue. This makes them unlikely to cause any discomfort to the animal while remaining implanted.

Nerve injuries in this licence will only be carried out on one nerve per animal. This nerve will always be a sensorimotor nerve - a nerve that provides feeling and movement to a limb. This results in a partial loss of movement and lack of sensation in one of the animal's paw. This class of injury is well tolerated by rodents. Within a few hours of recovery from anaesthesia, animals can typically be seen moving around the cage making use of their three limbs and some function preserved in their affected fourth limb. Despite causing little trouble during normal behaviour (movement around the cage, grooming), this injury does impair finer tasks such as pellet grasping. The experimenter can make use of this to test devices aimed to restore similar deficits in patients. The effects on welfare combined with its use as an injury model make limb nerve injuries an ideal model for the development of this technology.

Why can’t you use animals that are less sentient?

Certain parts of this project can be carried out in terminally anaesthetised animals - including short-term tests of nerve neuroprosthetic devices and testing of electrical parameters. For this reason, protocol 1 of this licence is centred around non-recovery work and makes up a significant portion of the animals used in this licence. However, an effective implantable neuroprosthetic treatment not only has to activate/monitor a structure, but it must also do so throughout prolonged periods of time. This presents challenges due to factors such as animal movement, inflammation, and degradation of materials. All of these factors are expected to occur in human patients, and can only be reproduced in animals where the implant remains in the body for long periods of time.

While less sentient animal species do have nerves in their bodies, the system of nerves found in humans is unique to vertebrates. Rodents, specifically, have an anatomical distribution of nerves very similar to humans. Further, some of these nerves are of similar order of magnitude in size to those of humans, increasing the translatability of the devices. Rodents, and rats in particular, are also frequently used as surgical models, and their anatomy is very well characterised in published literature. Rodents are also able to learn a wide range of behavioural tasks and can be used to test the effectiveness of treatments in situations similar to those potential patients benefitting from these treatments may encounter. These factors make rats an ideal model in which to develop nerve neuroprosthetic devices to develop electroceutical treatments aimed at human use.

How will you refine the procedures you're using to minimise the welfare costs (harms) for the animals?

Animals will be group housed whenever possible. Group housing can be problematic when animals have been implanted with devices for electrical recordings. This is because rats often nibble on the ports which house the wirings of the implants - referred to as the headcaps. We will use strains such as Lewis rats which more rarely exhibit this behaviour. We have also optimised the shape and material of our headcaps as part of our previous work to the point where animals are able to be group housed while wearing them.

These headcaps are also often the main source of discomfort for animals with an implanted neuroprosthesis. Headcaps are designed to protect the wires while providing a point of connection to the device for the experimenter to use. However, they can be bulky, difficulting animal movement around the cage and normal grooming. In order to minimise the impact of our headcaps, we are designing and fabricating our own headcaps using 3D printing. This allows us to make the headcaps as small as possible to fit our devices, and with materials and structures which minimise their weight. Our current headcap designs weigh approximately 12 grams, which is <5% of the bodyweight of rats typically used in these studies. We will continue to optimise our headcap designs as we carry out our project.

To minimise weight loss and improve animal welfare, animals are kept in enriched environemnts following surgical procedures. These enriched environments features different highly palatable foods to encourage nutritional intake and recovery, such as seeds, dried fruit, and chocolate spread.

Surgical procedures will be carried out by licence holders competent in the procedure and following LASA guidelines for aseptic surgery. Preoperative and postoperative care will be provided to animals by trained animal technician staff. Following surgical procedures, all animals will be provided with wet mash food or gel to support them during postoperative recovery. Analgesia will be used post-surgery on all cases (typically over two days post-surgery).

Behavioural tasks often requires animals to be food restricted to provide an incentive for animals to learn a particular task. We will work to minimise the amount of time during which animals have to be food restricted. We will only limit access to food only to the day of training (fasting). Fasting will typically be done three days (maximum five days) per week, allowing for one day of free access to food between each session.

Supervisors teaching new PILs will do so following LASA guiding principles to ensure new users are properly trained to perform any procedures necessary.

What published best practice guidance will you follow to ensure experiments are conducted in the most refined way?

All users of this licence will be required to read the published ARRIVE and PREPARE guidelines prior to start of any work and integrate these into their plan of work.

Supervisors teaching new licence holders will do so following LASA guiding principles to ensure new users are properly trained to perform any procedures necessary. This includes developing and making

use of training protocols for each procedure. All work will generally be carried out in the same facility, allowing new users to have routine contact with supervisors to ensure good transfer of knowledge.

All surgical work will be carried out following LASA guiding principles on preparing and undertaking aseptic surgery. LASA guiding principles for behavioural laboratory animal science will be followed when undertaking behavioural work.

How will you stay informed about advances in the 3Rs, and implement these advances effectively, during the project?

Individuals involved in this project will remain updated on advances in the 3Rs through a variety of sources, such as: participation in animal facility user meetings, subscription and participation in relevant mailing lists and workshops in our institution, routine browsing of the NC3R website and of relevant published literature. We will also hold periodic meetings to review the current state of all work under this licence and coordinate the implementation of any improvements to our work based on the 3Rs.