Home Office

NON-TECHNICAL SUMMARY

Exploring Bioelectronic Approaches to Nervous System Restoration in Large Animals

Project duration

5 years 0 months

Project purpose

- (a) Basic research
- (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
  - (ii) Assessment, detection, regulation or modification of physiological conditions in man, animals or plants

Key words

Bioelectronics, Neurological restoration, Brain injury, Spinal Cord Injury, Peripheral nerve injury

Animal types	Life stages
Sheep	adult
Pigs	adult
Minipigs	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?

The aim is to create about three small electronic devices that can be placed inside the body (bioelectronic devices) to help fix lost nerve functions due to injuries in three parts of the nervous system: the brain, the spinal cord, and the nerves outside the brain and spinal cord (peripheral nerves).

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?

This work is essential because it tries to create new ways to treat nerve-related diseases and problems that have been hard to solve before, like paralysis, Parkinson's Disease, epilepsy, and injuries to the brain or spinal cord. Also, these devices will help us learn more about these diseases and might help find even more new treatments.

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

A. Devices: This project will lead to the creation and improvement of three devices designed to work with nerves in humans, which will:

1.
    - Give detailed, long-lasting recordings of nerve structures, helping us understand different nerve-related conditions and diseases better and create focused treatments.
    - Fix nerve functions by reconnecting and reshaping damaged nerve pathways.
    - Help us learn more about how electronic devices can work with our nerve system.

B. Data: The devices will gather lots of information from both the main part (central) and the outer parts (peripheral) of the nerve system. This data can be used, for example, to help create computer programs and teach special math formulas (algorithms) for more advanced research and medical uses.

C. Sharing what we learn: We will tell other scientists about our discoveries by writing articles for important science magazines that other experts check (peer-reviewed journals) and talking at science meetings (conferences). We will also share with the public to help people understand science better and make them more aware of nerve-related diseases.

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

Nerve-related disorders affect up to 1 billion people all over the world, with about 6.8 million people dying from them each year. Brain injuries, spinal cord injuries, and injuries to nerves in other parts of the body are big reasons for disability and not being able to do everyday tasks.

In the short term, our technology will help us learn more about the complicated connection between electronic devices and the nerve system. In the medium and long term, the devices we create to work with nerves will have many benefits for patients suffering from different nerve-related conditions:

- Allow us to record nerve activity and control how nerves work.
- Fix broken nerve connections in people with injuries or damage.
- Give new ways to treat patients with hard-to-control epilepsy, long-lasting pain, Parkinson's, and Alzheimer's disease.

By working on these problems, our project could help make life better for millions of people who have trouble with their nerves because of diseases or injuries.

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

To get the best results from our work, we will:

- Use strong research methods and work together with experienced researchers.
- Share our findings (including unsuccessful approaches) in important medical journals that other experts read and talk about early results at big conferences around the world.
- Keep good relationships with top groups in the field of electronic devices that work with nerves, so we can share new knowledge effectively.
- Involve people who can make decisions early in the process and work to quickly turn our technology into something that can be used in real life.
- Watch and measure how well our research is doing and change our approach if needed to get the best results.

Species and numbers of animals expected to be used

- Sheep: 100
- Pigs: 250
- Minipigs: 100

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.

We have chosen to use bigger animals, like adult sheep and pigs, for these reasons:

1. Early testing: We've already tested the three devices we made at our place in the lab, on the computer, and in smaller animals like mice and rats. These tests showed that the devices work well in recording nerve activity and helping to control how nerves work.

2. Limits of using mice and rats: While mice and rats are helpful for testing in the early stages, they are quite different from humans, so the results might not work the same way in people.

3. More similar to humans: By testing our devices in bigger animals like adult sheep and pigs, we can get more useful information about how safe and effective our technology is. This will also help us make the devices, surgical methods, and how we put the devices in the body better for people.

By using bigger animals with bodies more like humans, we can learn important information for making and fine-tuning these devices, making sure they are safe and work well for people.

The animals we've chosen for our experiments are adult sheep, pigs, and minipigs. Here's why:

Sheep: Sheep's brains are very similar to humans in some ways. This makes them useful for our experiments, where we are testing devices that interact with the brain. Sheep are also generally easy to work with and are very docile, which helps make sure they stay comfortable and stress-free during our work.

Pigs: Pigs are often used in medical research because their bodies respond to treatments in ways that are similar to humans. For our experiments, we're particularly interested in their nerves. Pigs' nerves are a lot like human nerves, which is important for our research into devices that can help control nerves.

Minipigs: Minipigs are a smaller kind of pig that we'll be using in later, long-term experiments. Like regular pigs, they're similar to humans in important ways. Because they're smaller, they're easier to handle, but they still give us the benefits of working with a larger animal that's a lot like a human.

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

In this project, animals will be given medicine to make them fall asleep and not wake up again (non-recovery). Small devices will be put into their brain, spinal cord, or nerves in other parts of their body, including muscles. After the experiment is over, the animals will be killed in a kind and humane way, following a method that causes the least suffering.

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

In this project, animals will be given medicine to make them fall asleep and not wake up again, making sure they don't feel any pain or discomfort (non-recovery). Since the experiments are non-recovery, there won't be any long-lasting effects on the animals. After the experiment is over, the animals will be killed in a kind and humane way, following a method that causes the least suffering.

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)?

Animal Type	Category (Expected severity)	Proportion
Sheep	non-recovery	100%
Pigs	non-recovery	100%
Mini-Pigs	non-recovery	100%

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?

We're working on a project that studies diseases that affect the entire nervous system, just like they would in people. To do this, we need to work with a full, working nervous system. This allows us to record, control, and stimulate nerve activity in a way that is close to what happens in humans. It's important for us to be able to work directly with nerves that are still inside the body and working normally because of the kind of devices we're testing.

There are other ways to study nerves, like working with them in the lab outside of the body (in vitro), or using computer simulations (in silico). However, these methods don't completely recreate the complex interactions and processes that happen inside a living, working nervous system. They also can't give us all the information we need about how safe our devices are, how well they work, or how they interact with living tissue.

Because of these reasons, we need to use animals for our research. This will help us get reliable data that can be used to develop and improve treatments for nerve diseases in people.

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

We thought about using the following non-animal options for this project: Lab-grown models, like human stem cells; Computer simulations; Organoids (small groups of cells that act like an organ); Studies of dead humans and large-scale studies of people.

Why were they not suitable?

The non-animal alternatives we considered were not suitable for our project for the following reasons:

- Lab-grown models, like human stem cells: These models don't have the same complexity and organization as a whole nervous system, so they can't copy the interactions and processes we need to study.
- Computer simulations: Although they're helpful for designing and improving devices at first, computer simulations can't fully tell us how safe, effective, and compatible our devices will be in a living being.
- Organoids (small groups of cells that act like an organ): Even though organoids can act like some parts of the nervous system, they don't have the full complexity and interactions with other systems that we find in a living animal. This makes them less suitable for our project.
- Studies of dead humans and large-scale studies of people: These methods can give us important information about the structure and function of the nervous system, but they don't let us see how our devices work, how safe they are, and how effective they are in a living being.

Due to these limitations, we determined that the use of animals is necessary to achieve the aim of our project.

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?

Our estimation of the number of animals needed for this project is based on several factors. Pigs will be the main animals we use because they're often used in research for small devices that go inside the body, and they're similar to humans in many ways. We anticipate using 250 pigs in our experiments.

Sheep will be used sometimes because they're a good choice for studying how computers can connect to the brain. Based on our experience and the specific requirements of the experiments, we estimate that 100 sheep will be needed.

Minipigs, which are smaller pigs, are used when we want to study something for a long time and gather early information. We have allocated 100 minipigs for these purposes.

The total number of animals is based on at how much work we're doing now with rodents, how much our lab can do, and our experience with similar research. We've thought carefully about these things to make sure we use the smallest number of animals possible while still reaching our project's goals.

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

What did you do during the planning stage to use fewer animals in this project? - While planning our experiments, we took several steps to use as few animals as possible:

- Collect more data from each animal: We carefully set up our experiments to get the most information we can from each animal, making sure we only use the smallest number of animals needed to get important and reliable results.
- Improve our tests: We always try to make our experiments better, which helps us need fewer animals to get the information we want. For example, we do a lot of computer simulations, which helps us test fewer things in living animals.
- Test more than one device on one animal: Whenever we can, we will test more than one device on a single animal. This means we need fewer animals for each experiment.
- Use a special online tool: We use the NC3Rs Experimental Design Assistant, a website that helps us plan strong and repeatable experiments. This tool helps us use fewer animals in our research.

By doing these things, we work to use as few animals as possible while still reaching our project's goals.

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

Besides planning our experiments well, we will do several other things to make sure we use as few animals as possible:

- Test things on a small scale first: We will try out new methods and steps in small experiments before doing them on a larger scale. This way, we can make sure we don't use more animals than we need to.
- Use computers and data analysis: We will use advanced computer programs to help us look at our results and make computer models. If we can, we will use special techniques to get more information from our data, which means we need fewer animals.

- Share samples and work together with other researchers: We will work closely with other scientists and share the samples we get from the animals after the experiments are done. This can help save animals in other studies and make better use of our resources.

By doing these things, we try to use as few animals as possible and make sure our research is ethical while still reaching our project's goals.

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.

During this project, we will use pigs, minipigs, and sheep as our animal models. To minimize pain, suffering, distress, or lasting harm, we will implement the following measures:

- Anaesthesia: Animals will be placed under anaesthesia (medicine that causes loss of sensation and consciousness) during the device implantation process (putting devices into the brain, spinal cord, and peripheral nerves), ensuring they do not experience any pain or discomfort. The anaesthesia will be provided by a trained Veterinary Anaesthetist or a competent PIL holder.

- Non-recovery procedures: Animals will not be allowed to regain consciousness following the implantation procedures, eliminating the possibility of experiencing postoperative distress or suffering.

- Humane euthanasia: After each session, animals will be euthanized (put to death humanely) using an overdose of anesthesia, ensuring a swift and humane end.

By implementing these methods, we aim to minimize any negative impacts on the animals involved in our research while still effectively achieving our project's goals.

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

We cannot use less aware animals or animals at a younger life stage because our devices are intended for people. Although earlier testing allowed us to avoid using large animals, our project has now reached a stage that requires testing on fully grown, working, and healthy nervous systems similar to those of people.

Using larger animals like pigs, minipigs, and sheep, which are more like people in terms of their body structure and how their body works, allows us to better apply the results to tests involving people. Furthermore, to minimize any potential suffering, all animals involved in the project will be given

anesthesia so they don't wake up, ensuring they do not experience pain or distress during the procedures.

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

Before surgery:

- We will give animals time to get used to their new surroundings after they arrive and spend time with them (e.g., 15 mins twice daily) to help them feel less stressed before giving any medicine.
- We will make the pigs' living area more fun by adding things that let them do natural behaviors like digging and looking for food, and prevent them from getting bored.
- If we need to hold animals still during any procedures, we will teach them to be comfortable with it so they feel less stress.
- We will take steps to make sure the animals don't feel too stressed while they're being moved.

During surgery:

- We will pick the right animals: Healthy animals that are the best fit for the tests we need to do.
- We will use the right kind of sleep medicine: Making sure the sleep medicine we use is the best choice for the type of animal and the procedure we're doing.
- We will keep an eye on the animals while they're having surgery: Watching their heartbeat, how fast they're breathing, blood pressure, and other important signs, as well as how they react to things during surgery. This will let us change the sleep medicine if we need to, making sure the animal is asleep but not too much, which can help avoid problems and animals dying when they shouldn't.
- If we need to keep an animal by itself for some time, we will explain why, how long, and what extra care and fun things we'll give them during that time.

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

We will follow these published guides to make sure our experiments are done in the most refined way:

- The Animals (Scientific Procedures) Act 1986
- The Code of Practice for the Housing and Care of Animals Used in Scientific Procedures
- The Guidance on the Operation of the Animals (Scientific Procedures) Act 1986
- The ARRIVE Guidelines

- The NC3Rs Guidelines: The National Centre for the Replacement, Refinement, and Reduction of Animals in Research (NC3Rs)
- The PREPARE guidelines
- Species-specific resources from the Norecopa website for animals in research (https://norecopa.no/species/farm-animals/) and minipigs (https://norecopa.no/species/farm-animals/minipigs)
- Pig Housing & Handling resources from the NA3RsC

We will also monitor and have ongoing discussions with the NVS (Named Veterinary Surgeon) and NACWO (Named Animal Care and Welfare Officer) about using non-UK resources to make sure we follow the best practices for animal care and handling.

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

We are committed to providing the best care for the animals we work with and will actively stay up to date on improvements in the 3Rs by:

- Subscribing to the NC3Rs newsletter (https://www.nc3rs.org.uk/news) to receive regular updates on new ideas and research related to the 3Rs.
- Making sure that all team members know and understand the idea and values of the 3Rs. We will use online training resources such as the Procedures With Care website (https://researchanimaltraining.com/article-categories/procedures-with-care/) and the Experimental Design Assistant website (https://www.nc3rs.org.uk/3rs-resources/search?topic%5B0%5D=497) to teach new team members and remind everyone of the importance of the 3Rs in our research.
- Reviewing our research plans every three months to see if we need to make any changes or updates. Improving the way we work with animals is an ongoing process, and we know that we might need to take more steps as we learn more.