



Home Office

NON-TECHNICAL SUMMARY

Biocompatibility of a prototype fully implantable auditory implant microphone

Project duration

2 years 0 months

Project purpose

- (c) Development, manufacture or testing of the quality, effectiveness and safety of drugs, foodstuffs and feedstuffs or any other substances or products, with one of the following aims mentioned in paragraph (b)

Key words

Deafness, Hearing rehabilitation, Microphone, Biocompatibility, Cochlear implantation

Animal types

Guinea pigs

Life stages

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 assess whether or not it is possible to successfully implant a functioning microphone into the ear of guinea pigs without it being rejected. This will eventually be incorporated into a fully implantable cochlear implant that will overcome the issues arising from current cochlear implant technologies.

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?

The World Health Organisation estimates that 430 million people globally have disabling deafness. This amounts to over 5% of the world's population. It is estimated that this will increase to 25% by 2050. Milder forms of deafness can be managed through amplification of sound using hearing aids but profound hearing loss requires cochlear implantation to rehabilitate hearing.

Cochlear implants are electrical devices that consist of two components, an implantable component that consists of an electronic s package and an electrode array that is placed inside the cochlea and a sound processor that picks up sounds, converts them to an electrical signal and transfers the signal by radio to the implanted component. The electrodes in the array are then stimulated and this activates the hearing nerve which sends a signal to the hearing centres of the brain providing the perception of sound.

Whilst cochlear implants are a very effective way of restoring hearing to those with profound deafness, the external sound processor has several disadvantages. It is not well accepted cosmetically as it is quite bulky. It is inconvenient to have to wear the processor all the time. It can be inconvenient during exercise, outdoor sport activities and swimming. It would therefore be desirable to develop a fully implantable cochlear implant.

There have been several attempts to produce auditory implants with a microphone that can be implanted in or around the ear, thus avoiding an external component. Although these look better and are more convenient, those that have been developed to date have significant limitations including loss of signal because of implantation under the scalp, picking up body noises, positioning away from the ear, and bulky size making implantation challenging and prone to complications.

This project aims to develop a fully implantable microphone that addresses the limitations set out above and can be integrated in to existing auditory implant technology as well as preserving existing hearing. This is important because it will make cochlear implants more practical and more effective.

There is a great deal of development work required to produce a microphone that meets these requirements. In particular, it is important to know if the microphone is stable in the implantation site and whether it is able to effectively pick up sounds. It is also important to develop a safe, effective and

quick surgical technique for implantation and to ensure that the microphone is not rejected by the body. It is not practical to carry out this development work in humans without risking significant complications and/or device failure. It is therefore important to use an animal model prior to transitioning to human implantation and as such this study will provide proof of concept.

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

The expected end result of this project is a fully implantable microphone that:

- 1) Can be safely, quickly and easily implanted
- 2) Is able to pick up sounds effectively
- 3) Does not cause any tissue rejection and is stable in its position
- 4) Does not detrimentally impact on the animal's existing hearing

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

Hearing impaired patients who receive auditory implants will benefit from this device.

The device will improve the hearing and quality of life of the recipient through:

- 1) Better sound quality: There will be less sound attenuation because of the thin tissues overlying the implant. This will have positive social and professional implications
- 2) Better cosmesis: The implant will be fully implantable with no visible external components. This will make the implants more widely acceptable without the stigma of wearing a visually prominent sound processor.
- 3) Easier implantation than existing implantable microphone designs: The microphone will be much smaller than the existing devices available and can be implanted easily within the same surgical field as existing cochlear implants
- 4) Reduced body noise: Its location within the ear canal means that the microphone is not prone to body noises such as rustling of the hair
- 5) More natural positioning of the microphone: Its location within the ear canal means that sounds are picked up from the same location that they would be in normally hearing individuals. This will make sound localisation easier and will make the use of a telephone more natural. It may also enable use of headphones.
- 6) Reduced energy requirements and therefore better battery life: Its small size and low energy requirements mean that it does not drain the battery of the device as much as the current generation of implantable microphone
- 7) A wider range of environments in which the implant can be used: The implant can be on all the time no matter what environment the implantee is in. This has significant safety and security

implications. For example, it can function whilst sleeping so that a mother can hear her child; a child can swim whilst the implant is active and therefore hear what their parents are saying; the implant can be used whilst wearing protective head gear eg. Crash helmets, riding hats

8) Activities of daily living will be easier: The device could be conveniently used in the shower or whilst bathing

9) There will be no complications from wearing an external processor, in particular, avoiding irritation of the skin associated with it and avoiding the risk of losing or damaging the processor should it become dislodged.

There are also other potential scientific benefits from the project. It will improve our understanding of the biocompatibility of the materials used in implants and the nature of the host's inflammatory response to the materials used. It is hoped that this will be of benefit to scientists developing and designing implantable materials (not just in the field of auditory implantation) and to the commercial manufacturers of such devices.

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

The results of the project would be distributed nationally and internationally via presentation in conferences and publications.

Once the aims set out above are achieved, the microphones can be incorporated in to existing auditory implants in collaboration with implant manufacturers.

Species and numbers of animals expected to be used

- Guinea pigs: 9

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.

For this project adult guinea pigs will be used. Adult guinea pigs have an ear drum that is a similar size to the human ear drum. They also have an ear canal that is close enough to the human ear canal to make it appropriate for the purposes of this project. Guinea pigs are a common model used for research related to the ear and there is extensive literature demonstrating that they are a good model in projects similar to this one.

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

Approximately 9 animals will be required initially for this study.

- 1) The animals will undergo general anaesthesia(GA)
- 2) The animals will undergo a hearing assessment whilst asleep, prior to implantation to ensure that they have normal hearing. This will involve measuring the brain activity in the hearing centres of the brain in response to sound.
- 3) The animal will be implanted with a microphone. This will involve surgically accessing the ear and placing the microphone in the wall of the external ear canal, covered with ear canal skin.
- 4) A wire from the microphone will be extended through the incision in the skin through which the implantation has been performed. This will enable testing of the effectiveness of the microphone once it is in position
- 5) The animals hearing will be assessed again to ensure that it has not been damaged
- 6) The animal will be humanely killed at defined time points and the microphone and the tissues around it will be assessed for inflammation to determine the stability of the microphone in its implanted location. This will involve analysis of processed tissues under the microscope.

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

After surgery the animals will experience minimal pain for 2-3 days. This will be controlled with simple analgesics. In uncomplicated cases the ear should be fully healed within a week and there should be no adverse effects on the animal. There is, however, a risk of adverse reaction to the general anaesthetic and guinea pigs are known to be more susceptible to this than other animals. Careful anaesthesia will minimise this risk.

There is a risk of adverse reaction to the general anaesthetic, mainly from respiratory depression. From the experience of other research teams, up to 10% of animals may be affected by this. Every effort will be made to minimise this through good quality anaesthesia.

Potential surgical complications include wound infection, infection at the site of implantation, reduced hearing and extrusion of the microphone housing.

The wire extending from the microphone through the wound could be irritating to the animal and if so, this will be cut flush with the skin and the wound allowed to fully heal. This will mean that subsequent testing of the function of the microphone will not be possible but the measurements taken during the initial surgery should be adequate to determine if the ability of the microphone to pick up sounds is adequate.

The implanted animals will be humanely killed at defined time points (either 6 week, 3 months and 6 months after implantation).

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)?

The surgical procedure is regraded as moderate in severity. All animals will be exposed to the same procedures.

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?

The aim of this project is to assess the tissue reaction after a certain period of exposure to the prototype microphone. The animal experiments are required in order to assess the effect on living tissue before being trialled in humans. This will ensure that the microphone is not rejected. Guinea pig ear anatomy resembles human ear anatomy which helps in the development of the surgical technique for implantation and allows assessment of the ideal position of the microphone within the ear. It will also give provisional information on the tissue reaction produced by the presence of the microphone ie. degree of rejection, if any, prior to implantation in humans.

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

Cadaver dissection to develop surgical technique and siting of the microphone prior to commencement of live animal work will be used to minimise the learning curve on the live animals.

Laboratory based tissue culture experiments are also being undertaken to assess if there is a tissue reaction produced by the materials within the microphone. This will ensure that any adverse reactions on a cellular level will be identified prior to implantation in animals and if present these materials will be excluded from the microphone.

The alternative to using a guinea pig model is to use a different animal model or to use human experiments from the outset. There are no other non-animal models that could be used in this project.

Why were they not suitable?

The anatomy of other animal models differs from human anatomy to a greater extent and these models are therefore less suitable. It is inappropriate to go straight to human experiments given the uncertainty around the types of tissue reaction generated by implantation.

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?

Statistical advice has been used to help determine the number of animals required.

It is necessary to assess the tissue reaction to the implant at different time points (6 weeks, 3 months and possibly 6 months). In order to have an understanding of the range of tissue reactions that might occur, and to allow for some anticipated deaths amongst the animals during the study, we would like to implant 6 ears at each time point. This makes a total of 18 ears in 9 animals.

An initial cohort of 3 animals will be implanted bilaterally and then humanely killed and examined at 6 weeks. If there is no evidence of any tissue reaction at that point then a further 3 animals will be implanted bilaterally and humanely killed and examined at 3 months. Again, if there is no tissue reaction then a final 3 animals will be implanted bilaterally and humanely killed and examined at 6 months.

If at any time point there is evidence of a tissue reaction or other issues with the device then the design of the device will be modified to address the issues and a further cohort of 3 animals will be implanted bilaterally and the process repeated. Depending on the severity of the issues that arises, minor modifications will be made or wholesale redesign will be performed.

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

We had detailed discussions with a statistician to reduce the number of animals required as much as possible. The initial 6 week trial will identify any early problems with the device and enable modification as required without using excessive numbers of animals. The stepwise increase in duration of implantation in small groups of animals provides us with the opportunity to determine any issues that might arise with the minimum number of animals.

We will be developing and refining the surgical technique for implantation on cadaveric animals prior to commencement of implantation in live animals so that the risk of complications arising from technical failure is minimised.

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

The initial 6 week cohort will identify any early issues that might arise from implantation and will allow modification of the protocol, as required, for the longer duration of follow up. This will minimise complications and animal deaths in the subsequent, longer follow up, groups. We have reduced the number of animals in each follow up group as much as possible to allow assessment of the tissue reaction to the microphone whilst allowing for unexpected animal deaths.

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.

Adult male guinea pigs will be used during this project. The use of a single sex simplifies the care of the animals operationally.

These animals will be anaesthetised prior to implantation and standard aseptic techniques will be used during surgical procedure. This will prevent any discomfort during the implantation procedure and will minimise the risks of post-operative infection.

The study design has been refined in collaboration with experts in the field. All procedures will be performed by an appropriately trained person. The initial experiments will be undertaken under the supervision of someone experienced in undertaking guinea pig experiments. The NTCO will also be present during the initial experiments to ensure competent conduct.

Postoperatively they will experience minimal pain which will be controlled with adequate analgesia. In recovery, animals will be closely monitored for signs of hypothermia, pain and distress.

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

The ear anatomy of the animal needs to be as similar to the human ear as possible in order to provide as relevant a result as possible. The adult guinea pig ear is closest matched animal model to the human ear.

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

During the surgical procedures adequate anaesthesia, analgesia and monitoring will be used as advised by the NVS to minimise potential harms to the animals. The staff undertaking the anaesthetic will be appropriately trained and experienced. Pain killers will be given following surgery. Following the surgery and during the follow up period, high standards of animal husbandry will be maintained. All efforts will be made to alleviate any distress and any signs of an inflammatory reaction/infection will be treated with antibiotics and anti-inflammatory medication. If this is not successful and the animal continues to show signs of uncontrolled distress then the animal will be humanely killed.

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

Laboratory Animal Science Association (LASA) guidelines will be followed before, during and after the implantation in order to maintain wellbeing of the animals. Peer reviewed publications involving similar experiments will be reviewed to ensure that the experiments are undertaken in the most refined way.

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

ASPA guidelines will be strictly followed and the research team will regularly monitor the N3CR website. In addition, the research team will be in close contact with other researchers involved in animal work and any changes to recommendations around the 3Rs will be discussed. Similarly, the research team will be in regular contact with the NTCO and NACWO to ensure that any potential changes are identified promptly. The implementation of any changes will be in discussion with the NTCO and NACWO.