Home Office

NON-TECHNICAL SUMMARY

Spine surgery: a new treatment

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

Key words

Orthopaedic, Surgery, Minimally invasive, Ultrasound, Implant

Animal types	Life stages
Cattle	adult
Sheep	adult
Goats	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 assess the safety and feasibility of novel medical devices, injectable implants, test articles or test substances used either as part of or in association with surgical procedures, or as part of or in association with non-invasive or minimally invasive procedures for tissue disruption or treatment, or for the treatment of conditions which may be simulated by surgical procedures. The context of this work is spinal disorders and in the first instance we are focusing on lower back pain.

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?

Around 500 million people suffer from lower back pain, the 1st cause of disability and the 3rd largest cause of healthcare spending ($87.6 billion) globally. Patients with persistent, recurrent lower back pain currently only have two diametrically opposed treatment options: conservative therapy, involving either physiotherapy or minimally invasive injections; and major surgery, most commonly spinal fusion, a complex high-cost procedure associated with significant complications ultimately leading to reduced range of motion and quality-of-life. In 2017/2018, the NHS undertook 211,000 pain injections and 52,523 spinal procedures, whilst in the US there were 9m treatments and 520,000 surgeries. Across Europe and the US, some 120,000 patients present with discogenic pain and an intact annulus, the initial target population for the technology at the heart of this application. The aim is to provide these patients with an intermediate treatment option, enabling percutaneous, minimally invasive nucleus pulposus replacement as a day case procedure, at a fraction of the cost ($15K vs $113K) of current surgical options, and leading to restoration of spinal function.

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

At the end of this project, in the first instance the expectation is a validation of the new spinal treatment and prototype, plus the collection of data for regulatory submission.

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

The outcomes from this study will feed into a clinical trials application that has the potential to impact sufferers of lower back pain. Around 500 million people suffer from low back pain, the 1st cause of disability and the 3rd largest cause of healthcare spending ($87.6 billion) globally. Patients with persistent, recurrent lower back pain currently only have two diametrically opposed treatment options: conservative therapy, involving either physiotherapy or minimally invasive injections; and major

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

The outputs from this work will be disseminated to the wider scientific community through publication in peer reviewed journals and by presentation at international meetings. Negative data will also be published and shared within the scientific community. Where appropriate, patients and the public will be informed of the outcomes through appropriate avenues.

Where appropriate, this work will lead to patent applications.

Species and numbers of animals expected to be used

- Cattle: 80
- Sheep: 80
- Goats: 80

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 non-recovery studies approximately 20 animals in total will be used; this may be composed of goats, and / or sheep and / or cattle.

For recovery studies up to 60 animals in total will be used (determined to be the best species from the non-recovery studies); this may be composed of goats, and / or sheep, or cattle.

Adult animals are ideal for this study for fulfilling scientific objectives, based on anatomy, size and expertise of scientists and animal care staff.

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

Animals will be acclimatised and trained for handling purposes.

Each animal will be anaesthetised on up to 2 occasions and up to 5 intervertebral discs will be treated. Analgesia and antibiotic treatments will be provided post recovery and animals will be monitored by clinical observations.

The animals for the long-term study will go through a recovery period of up to 12 months following the final procedure and up to 30 blood tests could be performed for the assessment of the long-term effects.

Animals will be killed and post mortem assessments performed.

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

Some short-term mild pain may be expected following the procedure, which will be controlled with appropriate treatment. Any adverse effects resulting from treatment failure will result in humane killing.

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)?

For recovery studies, moderate in all animal types.

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?

Animals are needed to test this procedure and implant because there is no other alternative that models the acoustic and mechanical properties of a live spine while providing inflammatory, nerve, mechanical, anatomical and behaviour responses.

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

We considered the use of human cadavers and computer modelisation.

Why were they not suitable?

1- Computer models were use to refine the design of our prototype but failed to provide any inflammatory, nerve, mechanical, anatomical and behaviour responses.

2- Human cadavers were not suitable as gas is entrapped in the tissue and blood vessels after death and prevents any attempt to use ultrasound for both therapy and imaging. Embalmed human cadavers were not suitable as the mechanical properties of the tissues were changed having both an impact on non-external technology such as ultrasound and invasive techniques such as needle introduction.

Human cadavers failed to provide any inflammatory response, and any biological live feedback of the procedure.

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?

The present project is divided into a non-recovery pilot study and a long-term recovery study.

One species from goats, sheep or cattle will be selected based on cadaver studies for the majority of the work. It is not expected that the cummulative total of 80 sheep + 80 goats + 80 cattle will be required.

The pilot study is designed as well to spot at an early stage any obvious correction of the protocol that would be required, and the rough quantification of the observed effect can also be assessed.

The animal number for preclinical safety and efficacy studies will be based on the requirements of the relevant testing protocol for the regulatory authority to obtain the preclinical evidence on safety, biocompatibility and biomechanical.

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

Initially, cadavers have been used to evaluate the suitability of the treatment in a large animal model.

Finally, using within the same animal up to 5 spinal segments for the treatment groups will reduce the number of animals needed by up to 5 times.

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

A previous pilot study on 5 sheep under a different license was used to refined the animal model for this study.

Computer modelling: The acquisition of x-ray imaging during or after the procedure will be used to model and adjust the experimental procedure and re-assess further animal need.

Cadavers will be shared with other groups where possible.

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.

Deer had been investigated and rejected based on intervertebral space, therefore a dual model combining goats/sheep and cattle is required.

Cattle have been selected as their intervertebral discs space and intervertebral disc type of cells are similar to human.

In the first instance, the surgical method involves minimally invasive techniques designed to minimise peri-operative pain and replace the disc structure with an implant capable of withstanding the appropriate mechanical strain. In initial cadaver and imaging studies already performed by the PPL holder, cattle have a correct anatomical disc space and furthermore, in recovery studies will provide an optimal model.

Optimisation will be performed under terminal anaesthesia. Once the protocol is defined and refined, recovery studies with general anaesthesia will be started.

Local anaesthetic may be used wherever possible, for example, to reduce stress prior to taking blood samples.

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

The human spine is unique as human are bipedal and have a vertical load bearing. Only mammals can provide the relevant spine mechanical properties, inflammatory response. The prototype that we are creating is unique and is very dependent on the size and the geometry of the subject which requires large animal models. At a later stage, among the large mammals only a subset is losing notochordal cells at an adult age like human.

Terminal anaesthesia studies will be used for the pilot study to refine protocols.

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

To minimise discomfort of repeated procedures such as anaesthesia, we are combining treatments where possible under a single anaesthetic event. The anaesthesia will preferably entail the use of inhalation agents whenever possible. Least invasive route of substance administration and needle gauge will be used where possible. Negative controls are within the same animal.

All animals will receive appropriate operative care in terms of anaesthesia and pain management both during and after the procedure.

Expertise at the facility further enhances animal welfare, by providing close collaboration with dedicated animal care staff and veterinary support with ready access to further highly skilled advice.

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

We will follow the NC3Rs guidelines on the "Responsibility in the use of animals in bioscience research" and consult all the relevant references listed therein. (Reference: NC3Rs/BBSRC/Defra/MRC/NERC/Royal Society/Wellcome Trust (2019) Responsibility in the use of animals in bioscience research: expectations of the major research councils and charitable funding bodies. London: NC3Rs.)

Animals will continually be monitored for signs of pain and distress, especially post-challenge, by experienced veterinarians and animal care technicians with significant experience in these species.

Anaesthetists work to best practice guidelines for large animal anaesthesia and maintain CPD to keep up to date with new practices.

Standard Operating Procedures are employed for animal preparation, surgery and recovery.

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

We will continuously monitor publications and the NC3Rs website for new and alternative models that could be implemented as part of this project. In addition, articles on advances in the 3Rs are regularly published on internal News Forum and other relevant information is circulated by AWERB. Whenever possible we will implement these refinements into our studies.