Home Office

NON-TECHNICAL SUMMARY

Supporting the development of medical / surgical devices

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
- (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

medical devices, ISO10993, safety, efficacy, surgical devices

Animal types	Life stages
Pigs	adult
Sheep	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 provide a service to biotechnology companies or research groups for the pre-clinical development of medical / surgical devices.

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?

There are many unmet medical needs within human medicine that may be solved or patients outcomes improved by the development of new medical devices.

For example: Improvements in visualization systems for conducting minimally invasive procedures will lead to reduced procedure time and improved patient outcomes. Development of an off-the-shelf nerve regeneration device that will allow functional repair of nerves without the morbidity associated with nerve grafting.

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

The primary data outputs will be clinical, clinicopathological, histopathological, diagnostic imaging data to support or refute development and use of new medical or surgical devices for use in humans and / or animals. Data will relate primarily to clinical efficacy, safety and underlying biological mechanisms and will:

- enable an objective decision to be made regarding whether or not to progress a novel device or technique through further stages of product development
- provide an understanding of any potential adverse effects and allow for appropriate contraindications and precautions in any subsequent clinical trials
- increase the number of novel safe and effective medical devices available for a range of conditions affecting humans and/ or animals.

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

The benefit of this Project Licence is to support the development of novel medical devices in the management of disease in humans. There are a wide range of unmet medical needs, requiring new devices to be developed as approved medical devices for therapeutic use or supporting surgical or diagnostic techniques. This licence seeks to improve the treatment of spontaneous disease in humans.

Short term benefits:

- The acquisition of data to support development and improved design of medical devices.
- The acquisition of data to inform the regulator on the safety and or efficacy of novel medical devices.

Long term benefits :

- Patients : Improved patient outcomes: advancing surgical devices should offer new treatment options to improve patient outcomes either by offering a solution to an unmet clinical need or by improving on current medical devices to reduce surgery time or patient trauma, thus enabling lower morbidity and/or quicker recovery.
- Economy:
    - advancing surgical procedures will reduce the cost burden on health care institutions by reducing surgery time and reducing hospital stay;
    - UK plc through successful commercialisation of product for unmet health needs
- Environmental: advancing surgical procedures will reduce patient recovery times, thus reducing hospital stay and consumption of medical consumables and resources;
- Political: more effective surgical procedures align with government goals of reducing waiting lists while advancing the standard of care.
- Social: patient benefits by having a more effective, timely treatment reducing the time to return to society or to work;

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

This work will provide data on safety and potential efficacy with respect to a novel or improved medical devices. If successful, it will support progression to further, substantive studies of a later prototype. Data will be used by the Client to progress the medical device to clinical trials and market authorisation.

Studies conducted as a service or collaboration with academic research groups will likely be published by the relevant research group.

The Establishment has a cadaver sharing policy; methods of euthanasia include those that may allow unused tissues from this project to supplement other research projects.

Species and numbers of animals expected to be used

- Sheep: 70
- Pigs: 340

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.

Young or adult pigs and sheep will be typically be used for all experiments because they are the most appropriate species to determine efficacy and safety with respect to the devices tested. Their size, anatomy and physiology have similarities to the human that make them the most appropriate models for testing of medical devices, especially those devices of a larger size.

Non-rodent species are typically required by the regulatory authorities as part of the safety testing package to be submitted with the application for medical device marketing authorisation.

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

Typically animals will undergo a surgical procedure under general anaesthesia for implantation of the medical device (eg orthopaedic implant) or to use the device (eg surgical laparoscopy system) under sham surgery conditions. This may be a terminal procedure with no recovery or a recovery procedure for short or long term testing of the medical device. Some testing of the device or imaging of the device may be applied under general anaesthesia. For recovery animals, appropriate animal monitoring and analgesia plans are established with NVS prior to surgery.

Animals may undergo repeated general anaesthesia to allow non invasive (eg CT/ MRI / Xray) or invasive assessment of devices (eg contrast angiography) at scheduled timepoints during a long term study.

Blood samples may be collected throughout the study to monitor for known substances that can be released from the surface of components being tested (leachables), to provide pharmacokinetic data for any substance incorporated into the device or to provide clinical pathology data for the implantation period.

All animals will be humanely euthanased at the end of the study and appropriate tissue harvested for post mortem assessment - eg histology or biomechanical testing.

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

The impacts of any conscious regulated procedures on the animal are typically expected to be mild and transient eg when performing blood / fluid sampling procedures only or conscious imaging

procedures or data collection from implanted devices.

Those protocols involving recovery surgical procedures or imaging under anaesthesia are classified as moderate. Surgical procedures for implantation of medical devices will typically incur some pain. An expected recovery plan with appropriate monitoring and analgesia will be clearly defined in each protocol. Pain would be expected to improve during throughout the expected recovery period and scheduled post operative monitoring and endpoints will be clearly defined.

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)?

100% of sheep and pigs undergoing recovery general anaesthesia in this PPL would be expected to be of Moderate severity.

Where appropriate, non recovery models will be used.

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?

ISO10993 guidance stipulates the testing requirements for regulatory testing of medical devices - these outline the in-vivo and in-vitro pre-clinical requirements prior to application for clinical trials. The Medical Device Regulations 2020 outline the approval process to achieve a Marketing Approval.

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

Clients using this service would be expected to have completed any relevant in-vitro bench testing prior to moving into animal models to ensure the device has been optimised before proceeding to live animal use. The regulatory authorities approving medical devices stipulate the requirement for in-vivo testing to satisfy the Medical Device Regulations

Why were they not suitable?

Non-animal alternatives are not acceptable to the regulators that approve medical devices for use in humans.

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?

Each study is individually assessed and the predicted animal numbers indicated on the relevant project protocol. For Pilot studies this will include a plan for the number of animals required to set -up or validate the model. For efficacy studies and regulatory studies, animal numbers will be designed to satisfy the study design and/or regulatory requirements.

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

Within each study animal numbers typically reflect the engineering development pathway and regulatory requirements for the device.

All clients are requested to provide information on previous in-vivo testing they have conducted to provide assurance that no unnecessary duplication of work is being commissioned across different sites.

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

Typically any new surgical model is first tested in a cadaver and/or terminal animals to optimise surgery techniques. For new models, a small-scale study of 1-2 animals is then planned to optimise recovery protocols before progressing to larger groups.

The Establishment has a cadaver sharing policy; methods of euthanasia include those that may allow unused tissues from this project to supplement other research projects.

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.

Pigs and sheep will be typically be used for all experiments because they are the most appropriate species to determine efficacy and safety with respect to the devices tested. Their neuroanatomy and physiology are very similar to that in humans.

We will work with manufacturers and academic experts to ensure a continued refinement approach is adopted for all medical devices.

Recovery studies will only be performed once the surgical technique has been defined as much as possible using cadavers and/or terminally anaesthetised animals.

All methods used for recovery animals will be refined to minimise any pain; these include appropriate provision of analgesia, use of local anaesthetics where possible for conscious biofluid sampling and close monitoring of animals by large animal veterinarians and advanced trained animal technicians to recognise any adverse effects. All animals will be trained and habituated to the environment, staff and handling techniques prior to study to minimise stress.

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

This PPL is aimed at large animal models to allow appropriate testing of devices at their intended scale for use in humans. Less sentient animals will not be appropriate for the models proposed under this PPL. Typically sheep or pigs will be used for all experiments as their size, anatomy and physiology, is similar to that in humans and allows appropriate testing of the device at its intended scale. For example, testing of laparoscopic equipment requires a pig around 70kg to reflect the size of an adult human abdomen.

Devices that are designed for implantation in humans are required to have safety and efficacy data for a time period designed to reflect use in humans or indicate longer time effects. These require implantation, recovery and long term observations. Where appropriate, acute studies in terminally anaesthetised animal may be used in pilot studies or for those medical devices that do not require long term contact.

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

Wherever possible devices will be optimised using cadaver models prior to live surgery.

To minimise discomfort/harm to the animals where possible studies are non-recovery in terminally anaesthetised animals with defined humane endpoints.

All animals will receive appropriate peri-operative care in terms of anaesthesia and pain management both during and after a surgical intervention.

Our in-house large animal vets’ expertise further enhances animal welfare by providing close collaboration with dedicated animal care staff and ready access to highly skilled advice. Specific recovery plans have been designed to ensure the best recovery of any animal post-procedure and involve high levels of monitoring.

All animals are habituated to the environment and all recovery animals are trained prior to use for all handling procedures, such as use of a restraining crate.

Least invasive route of substance administration, appropriate needle gauge and local anaesthesia will be used where possible. Negative control groups (baseline groups) will be minimised whenever statistically feasible.

All individual study plans are reviewed by the Client, Study Manager, PPL Holder and key study staff including consideration of justification and implementation of refinement and reduction as part of the local protocol review process.

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, e.g. NC3Rs Blood sampling resource.

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

Monitoring publications and the NC3Rs website for new and alternative models that could be implemented as part of this project, or for review purposes prior to starting new models. In addition, articles on advances in the 3Rs are regularly published on the Internal Users News Forum and other relevant information is circulated by AWERB. Whenever possible we will implement these refinements into our studies.