Home Office

NON-TECHNICAL SUMMARY

Enhanced Bone Ingrowth into Orthopaedic Reconstruction devices

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
- (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

Orthopaedics, Bone Ingrowth, Osseointegration, Medical Devices, Spinal fusion

Animal types	Life stages
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?

This project will enable orthopaedic medical device companies to study bone ingrowth into novel porous bone contacting surfaces intended for use in orthopaedic reconstruction devices such as hip and knee replacements and spinal fusion 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?

Joint replacements have dramatically improved the quality of life for millions of people by removing the pain associated with degenerative joint disease and by restoring motion. Traditionally, artificial joints were anchored in place using a cement to hold the artificial joint to the bone in which it was implanted. However, problems associated with cements have led to the development of cementless implants. Such implants rely on bone to grow into a porous surface on the artificial joint to provide anchorage.

Back pain is one of the most common reasons for work absence and doctor visits and is often accompanied by substantial leg pain. Some of the leading causes of pain are narrowing of the spinal canal and degeneration of spinal discs (the portion of the spine in which motion is achieved). This can result in the impingement of nerves and an overall instability of the spine. In these cases, studies have indicated that surgical treatment is, in general, more successful than conservative management. The goal of a spinal fusion is to restore the space between adjacent vertebrae (the bones in the spine) and to fuse them together, thereby removing any motion of the joint.

To achieve the strongest fusion and the best clinical outcomes, several surgical procedures and fusion devices have been developed. Interbody cages, placed between two vertebrae, allow for a bone graft (transplanted natural or synthetic bone) to be placed within the spine and can achieve bone integration with adjacent vertebrae. Many different cage materials have been used, but limitations have been identified for each material.

Novel structures and materials are being developed to enable more bone to grow into these porous surfaces and interbody cages which will improve implant fixation, reduce implant loosening and will ultimately lead to longer lasting orthopaedic implants and fewer early revision surgeries.

It is therefore essential to have robust in vivo models, predictive of the environment in which new implants will be used, in which the degree of bone ingrowth and implant fixation can be assessed.

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

The products being developed and evaluated are intended to promote greater bone ingrowth compared with existing orthopaedic reconstruction devices. This will improve implant fixation and therefore improve patient's lives. It is expected that the data from successful studies will support regulatory approval and launch of new products.

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

This is a service licence which will enable orthopaedic medical device companies to access expertise and models that have been developed and validated over the last two decades in order to evaluate new products.

It is anticipated that members of the human population requiring knee or hip replacements or spinal fusion surgeries will benefit from the work conducted under the authority of this licence. These patients' everyday activities will have likely been impacted by degenerative joint disease leading to the requirement of a replacement joint or spinal fusion. If the long term fixation of available joint replacements and spinal fusion devices is improved they will last longer than current products which will improve patient's lives.

It is also anticipated that the surgical implantation of novel structures and materials is simplified so orthopaedic surgeons will also benefit.

These benefits will in turn reduce the cost burden on healthcare providers.

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

The offering of validated bone ingrowth models as a service means that numerous medical device companies will be able to evaluate their products in these models. Where confidentiality is not breached data will be shared across organisations and where possible, publications of the work conducted under this licence will be considered.

Species and numbers of animals expected to be used

- Sheep: 450

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.

The adult sheep is our large animal model of choice for implantation studies designed to assess implants of a size representative of the clinical situation. The hind limbs and lumbar spine of adult sheep contain sufficient cancellous (spongy) bone to allow the assessment of bone ingrowth into an implant of a size that is suitable for subsequent mechanical testing and histological analysis.

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

Sheep will be acclimatised to the facility and handling procedures prior to use.

On the day of surgery they will receive a pre-medication containing an analgesic (painkiller) and will then be anaesthetised for the surgical procedure. The surgical procedure will be performed aseptically (in a sterile manner that is free from harmful bacteria and microorganisms) and will involve the implantation of small coupons of material into the cancellous bone in the hind limbs or lumbar spine. Surgical sites will be closed and the sheep will be recovered from the anaesthetic.

Post surgery analgesics will be used as required.

Following recovery images such as x-rays may be taken to assess bone ingrowth into the implants no less than 2 weeks apart.

At the end of the procedure sheep will be humanely euthanised and the implant/host tissue construct will be removed for testing and analysis.

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

It is expected that there will be a degree of post-operative discomfort and lameness which will be controlled by analgesics. This isn't expected to last longer than 24-72 hrs following surgery.

Sheep will be single housed during the immediate post-operative period. This is to prevent injury before the sheep have fully recovered but as they are a herding animal this could cause some distress. To minimise this distress a line of site will be provided to adjacent pen mates and group housing will normally be re-introduced 24-72 hrs following surgery. Re-introduction to group housing is expected to be without incident.

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)?

All animals are expected to experience a moderate severity procedure.

What will happen to animals used in 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?

Bone repair is a complex process involving cellular repair mechanisms and inflammation which cannot be studied using in vitro cell culture studies.

The endpoint measures required to study the amount of bone that has grown into the implants and the strength of repair provided by the implants are both histological and mechanical requiring the use of living tissue.

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

In vitro cell culture studies involving the use of synthetic bone scaffolds either unloaded or under some load to try to emulate the clinical environment in which the final products will be used.

Why were they not suitable?

In vitro cell culture studies are useful as a screening method to assess the effects of novel materials on the viability of cells. These types of studies will be used to screen out any potentially harmful structures or materials before bone ingrowth is studied. However, for the bone ingrowth studies themselves, animals need to be used to study inflammatory responses and repair mechanisms.

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 total number of animals has been estimated based on typical study sizes and expected numbers of studies required for the duration of the project.

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

As this is a service licence the experimental design phase for each required study has not yet happened.

When it does FRAME and NC3Rs guidance will be followed regarding reduction opportunities and the NC3Rs Experimental Design Tool (EDT) will be used where appropriate to inform the design of studies. Statisticians will be consulted in the planning stages of in-vivo studies to determine the appropriate study design, number of groups and number of animals required. Studies will typically be designed to 80% power, although this could differ, and could be designed, for example, as either superiority or non-inferiority studies with appropriate limits depending on specific study objectives.

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

Historical data will be used to power studies where it exists. Otherwise pilot studies will be utilised to inform the design of subsequent pivotal studies. Control items will be used in all studies ideally to provide intra-animal comparisons, where test groups and control groups are implanted in the same animal. Animal variability will be reduced as much as possible by the sourcing of a consistent and reproducible supply of sheep.

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 sheep will be used in this project as they contain bones which are of a sufficient size to study clinically relevant sized implants. They also have a sufficient volume of cancellous bone to ensure that the implants are fully surrounded by bone and normal healing occurs at a rate that is clinically relevant. The models proposed have been developed, validated and refined under four concurrent Project Licences over a period of 20 years.

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

Adult sheep contain bones which are of a sufficient size to study clinically relevant sized implants. Juvenile sheep would have smaller bones which may not have sufficient cancellous bone to study the required implants. These would also heal much quicker potentially masking any improvements provided by novel implants. Less sentient species have been ruled out due to their size.

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

The models within this licence have been developed, validated and refined over the last two decades however, opportunities for further refinement will always be considered. Guidance from institutes such as NC3Rs will be followed where appropriate.

Acclimatisation periods will be utilised and refinements in post-operative care and pain management will be utilised where these are proven to reduce harms to the animals.

Animals will be group housed where possible and where single housing is required following a surgical procedure, a line of sight to a pen mate will be provided by not having solid pen sides. Group housing will be reintroduced as soon as possible after a surgical procedure which is expected to be without

incident. Good ventilation is essential when animals are housed indoors and when possible, animals will be moved out to pasture.

Environmental enrichment methods will be utilised. In sheep these are mainly limited to providing a variety of feed and feeding methods. In addition to feeding good quality hay/haylage ad-lib a scoop of pelleted diet can be added for variety, mineral licks and additional feeds may also be provided and supplements e.g. beet or other appropriate fruit/veg may be fed as a form of environmental enrichment. The method of feeding can also be regularly changed to add variety.

Surgical implantations will be practiced and refined in cadaver tissues as required.

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

LASA Guiding Principles for Preparing for and Undertaking Aseptic Surgery (2017), NC3Rs, ARRIVE and PREPARE guidelines will be followed where appropriate.

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

Through general literature review, review of NC3Rs website, dialogue with the Named Information Officer and Named Training and Competency Officer as well as other establishments.