Home Office

NON-TECHNICAL SUMMARY

Bone Repair

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

Bone repair, Regeneration, Orthopaedics, Medical devices

Animal types	Life stages
Rabbits	Juvenile, Adult
Mice	Adult
Rats	Adult
Sheep	Juvenile, 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 primary purpose of this service licence is to enable orthopaedic medical device companies to assess the safety and effectiveness of novel products, therapeutics and surgical techniques which are aimed at improving fracture repair and replacing bone that is lost due to either disease, trauma or surgery.

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?

Bone defects are serious conditions in which a part of a bone is damaged or missing owing to either disease, trauma or surgery, and needs to be repaired through interventional techniques and products such as bone grafting (using transplanted bone to repair and rebuild diseased or damaged bones), synthetic bone void fillers (synthetic materials designed to mimic bone which remove the need to transplant real bone) and/or bone adhesives/cements. In 2021 an estimated 2.2 million orthopaedic procedures involving bone grafting took place worldwide, with the incidence rate projected to increase by 13% each year.

Orthopaedic medical device companies continue to develop new and refined bone repair products intended to facilitate a superior bone repair, last longer than current products and/or lead to faster recovery times. All of these aspects will further improve patient's lives, reduce the need for early revision surgeries or further surgical interventions and thus reduce healthcare costs.

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

The repair therapies being evaluated within this service licence will be being developed with the intention of improving fracture repair and the replacement of bone that has been lost due to either disease, trauma or surgery.

It is expected that the data from successful studies (those showing no adverse effects as a result of the novel therapies and/or those showing improved bone repair) will be submitted to the relevant regulatory authorities for approval and launch of these new products.

The data from unsuccessful studies can be used to either stop the progression of work on technologies that do not appear provide the anticipated patient benefits or can be used to refine these technologies during their development.

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 that have lost bone due to either disease, trauma or surgery will benefit. New repair therapies are likely to promote faster patient rehabilitation and better healing than current therapies and the resultant repair is expected to last longer. Longer lasting therapies will reduce the need for revision surgeries.

The surgical implantation of new repair therapies could be simpler as well as being more robust which will benefit surgeons.

Both of 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 repair models as a service to others 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

- Mice: 100
- Rats: 100
- Rabbits: 210
- Sheep: 510

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 animal models contained within this service licence have long histories of use and are well documented in scientific literature and international testing standards for their intended purposes. The use of adult animals ensures that normal healing rates are sufficiently similar to the clinical situation.

The rodent model will be used to screen different materials prior to their assessment in larger animals. This model has been shown to be highly reproducible permitting the precise comparison of a variety of bone graft substitute materials within a non-load bearing site which enables accurate analysis of bone repair.

Clinical implants i.e. those designed for use in humans, can be evaluated in the larger animals without the need to scale up or down making the results much more likely to be accepted by a Regulatory Authority. In addition, the bones are of a size suitable for mechanical testing and histological analysis which are the endpoint measures that will be used to determine success.

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

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

Where sheep are being used they may have previously been pre-screened for use on another project and found to be unsuitable for that project. The pre-screening may have required imaging such as x-rays under anaesthetic and the animals will only be used once they have fully recovered from the anaesthetic.

Blood may be taken according to general principles on blood sampling.

On the day of surgery animals 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 bone grafts, bone void fillers and/or bone adhesives into bones to repair or fix surgically created defects. These defects could be in the hind limb, fore limb or skull. The harvesting of bone marrow from the rabbit or sheep pelvis or long bone could also be conducted so that the bone marrow can be incorporated into the repair therapy to improve its effectiveness. Surgical sites will be closed and the animals will be recovered from the anaesthetic. Post surgery painkillers will be used.

Following recovery, images such as x-rays may be taken to assess healing. An additional anaesthetic will be required each time images are taken, so because of this they will be taken no less than 1 week apart.

At the end of the procedure the animals will be humanely killed 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 which will be controlled by painkillers. This isn't expected to last longer than 24-72 hrs following surgery.

Rodents and rabbits are expected to be group housed both pre and post-operatively but 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 sight 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
- Kept alive at a licensed establishment for non-regulated purposes or possible reuse

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. In-vitro (lab based) cell culture studies cannot replicate the in-vivo (in a living body) loading, physiological and anatomical conditions required to demonstrate the safety and efficacy of novel bone repair therapies, therefore animal studies are necessary in their development.

In addition, the endpoint measures required to study the strength of repair and the tissue/cell types making up that repair are biomechanical and histological, both requiring the use of living tissue of a size and structure appropriate to the intended clinical environment.

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 healing/repair is studied.

However, in-vitro cell culture studies cannot replicate the in-vivo loading, physiological and anatomical conditions required to demonstrate the safety and efficacy of novel repair therapies, therefore animal studies are necessary in their development.

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 the 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 as appropriate so that the results from novel test items can be compared against known controls. Test and control groups will be randomised within timepoints on each study and blinding methods will be used for both surgical implantation and for analysis where possible as this reduces potential bias towards test groups.

Animal variability will be reduced as much as possible by the sourcing of a consistent and reproducible supply and by incorporating acceptance criteria and weight ranges into study designs.

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.

The animal models contained within this service licence have long histories of use and are well documented in scientific literature and international testing standards for their intended purposes. For those reasons they are expected to cause the least pain, suffering, distress, or lasting harm to the animals.

The proposed models are as follows;

1. Rabbit segmental defect model - large segmental bone defects (where segments of long bones are missing, diseased or damaged) are a very serious problem in clinical practice. The primary purpose of this model is to determine the effectiveness of novel devices on bone regeneration. The model utilises a critical sized defect (one that would not spontaneously heal), which allows the effects of the test articles to be determined. The rabbit segmental defect model is described in American Society for Testing and Materials (ASTM) International standard F2721, Standard Guide for Pre-clinical in vivo Evaluation in Critical Size Segmental Bone Defects.

2. Rodent calvarial defect model – This is a well-established model for studying bone regeneration in a controlled environment and is one of the most commonly used experimental models for assessment of bone healing. It permits the assessment of bone formation in a critical sized defect in a non-load-bearing site (the flat and compact bones of the skullcap) in a reliable manner with minimal injury to the animals and provides preliminary screening data prior to further large animal and clinical trial assessment.

3. Sheep shallow defect model - The purpose of this model is to evaluate the efficacy of bone adhesives/cements under minimal to low weight bearing conditions. The bone piece is removed intact from a long bone in the hind limb and then replaced back into the defect held in place by either an adhesive or cement or a control item such as conventional orthopaedic hardware, e.g. screws.

4. Sheep contained defect model - This model is required for studying the biological response of host bone to a material in a large animal model. The sheep is a recognised orthopaedic model and the long bones are suitable anatomical sites for orthopaedic studies allowing implantation of similar sized implants to those used in humans. The model is described in International Standards Organisation (ISO) standard for Biological evaluation of medical devices 10993-6, Tests for local effects after implantation.

There is also a protocol to enable blood sampling from rabbits or sheep. The purpose of this protocol is to obtain blood for processing and compatibility experiments with prototype materials prior to any implantation studies being performed.

The animal models proposed have been developed, validated and refined under four previous successive Project Licences over a period of 20 years. Clinical implants i.e. those designed for use in humans, can be evaluated in these models without the need to scale up or down making the results much more likely to be accepted by a Regulatory Authority.

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

The use of rodents ensures that a proportion of this work is conducted in a lower sentient species.

Use of adult rabbits and sheep ensures the models are clinically relevant for pivotal studies and, as both models are described in international standards, the data generated are more likely to be accepted by a Regulatory Authority.

Juveniles would have smaller limbs which may not have a sufficiently similar structure in which to study the required repair therapies. These would also heal much quicker potentially masking any improvements provided by the novel therapies. For these models less sentient species are unsuitable due to their size.

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

The animal models contained within this service licence have long histories of use and are well documented in scientific literature and international standards for their intended purposes. 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 cage/pen mate will be provided by not having solid cage/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 for large animals when housed indoors and when possible, these will be moved out to pasture.

Environmental enrichment methods will be utilised. In rodents and rabbits these can include the use nesting materials, materials to gnaw, shelters or tunnels, social interaction, scattering of treats for foraging, use of treat balls or puzzles, having something to climb and having the use of a mezzanine or loft space. 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.