Home Office

NON-TECHNICAL SUMMARY

Tendon and Ligament 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

Tendon repair, Ligament repair, Scaffolds, Fixation devices, Medical devices

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 medical device companies to study the safety and efficacy of novel therapies such as soft tissue grafts, scaffolds or fixation devices aimed at repairing tendons and ligaments in 2 main clinical areas, the rotator cuff in the shoulder and the anterior cruciate ligament (ACL) in the knee.

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 rotator cuff is a group of muscles and tendons that surround the shoulder joint, keeping the head of the humerus (upper arm bone) firmly within the shallow socket of the shoulder. Rotator cuff injuries are common and increase with age. These injuries may occur earlier in people who repeatedly perform overhead motions and they are also common in athletes. Physical therapy exercises can improve flexibility and strength of the muscles surrounding the shoulder joint and for many people with rotator cuff problems, these exercises are all that's needed to manage their symptoms. Sometimes, however, rotator cuff tears may occur from a single injury or from degenerative diseases and in these circumstances surgery is often required involving the use of scaffolds or fixation devices. An estimated 450,000 rotator cuff repairs are performed in the United States per year costing up to $19,000 USD per procedure and over 9,000 are performed in the UK costing up to £8,000 GBP per procedure.

Knee ligaments connect the femur (thigh bone) to the tibia and fibula (the lower leg bones). They are classified into two main groups; collateral ligaments which connect the sides of the bones together and cruciate ligaments which provide fixation and stability within the joint itself. Sprained and torn ligaments are common especially among athletes. They may be mild requiring merely rest and simple treatment or they may be more severe, requiring surgery. More than 175,000 Anterior Cruciate Ligament (ACL) reconstruction procedures are performed each year in the US alone costing up to $50,000 USD per procedure and an estimated 30,000 procedures in the UK, costing up to £8,500 GBP per procedure. ACL reconstruction aims to reinstate the functional stability of the knee; in turn, preventing further damage to the knee cartilage and reducing the risk of degenerative osteoarthritis.

Current products do not always facilitate the anticipated return to normal patient activities and some can fail sooner than expected resulting in the requirement of a second repair procedure. Therefore, the fixation devices and repair therapies anticipated to be evaluated within this licence will be being developed with the intention of improving tendon healing and soft tissue graft fixation to accelerate healing responses, patient rehabilitation and to facilitate the return to normal patient activities.

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

The fixation devices and repair therapies will be developed with the intention of improving tendon and ligament healing and soft tissue graft fixation to accelerate healing, patient rehabilitation and the return

to normal patient activities. The benefits to patients should be a stronger repair, improved range of joint motion when compared with current therapies and longer lasting repairs reducing the need for revision surgeries.

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

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

It is anticipated that members of the human population requiring rotator cuff tendon or knee ligament surgery will benefit. These patients' everyday activities will have likely been impacted by a traumatic event or through degeneration of the tendon or ligament. 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 through the implementation of improved surgical instrumentation and techniques 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 tendon and ligament repair 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: 900

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 tendon and ligament repair studies as the anatomy and the size of the structures to be repaired are both similar to humans. In this way clinical implants i.e. those designed for use in humans can be evaluated without the need to scale up or down making the results much more likely to be accepted by a Regulatory Authority. In addition there is an adequate supply of suitably sized sheep in the UK (ideally aged between 2-5 years with a weight range

between 60-100kg) and the joints are of a size that is 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?

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

Blood may be taken according to general principles on blood sampling on more than one occasion.

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 scaffolds, grafts or fixation devices to repair or fix surgically created injuries in knee ligaments or shoulder tendons. Surgical sites will be closed and the sheep will be recovered from the anaesthetic.

A typical procedure will take approximately 1 to 2 hours from anaesthetic induction to wound closure.

A cast or splint may be used for up to three weeks following the surgical procedure to immobilise and/or unload the joint to protect the surgical site and prevent initial dislodgement of the repair therapy (scaffold, graft or fixation device).

Post surgery analgesics (painkillers) will be used as required.

Following recovery, images such as x-rays may be taken to assess implant fixation and/or healing. An additional anesthetic will be required each time images are taken, so because of this they will be taken 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.

A cast or splint may be used for up to three weeks following the surgical procedure to immobilise and/or unload the joint to protect the surgical site. It sometimes takes a few hours (<24hrs) for the sheep to get used to these immobilisation devices but they are typically well tolerated and the sheep will be closely monitored during their use.

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?

Tendon and Ligament 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 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. Power calculations will be used to determine the number of animals required for each study and this will be dependent on the specific study objectives.

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 conducted 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. 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 (ideally aged between 2-5 years with a weight range between 60-100kg) will be used in this project as they have limbs which are of a sufficient size to study clinically relevant sized implants.

Several models are being proposed to evaluate the safety and efficacy of novel therapies such as soft tissue grafts, scaffolds or fixation devices aimed at repairing tendons and ligaments in 2 main clinical areas, the rotator cuff in the shoulder and the anterior cruciate ligament (ACL) in the knee.

The models proposed have been developed, validated and refined under three previous concurrent Project Licences over a period of 15 years.

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

Adult sheep have limbs which are of a sufficient size to study clinically relevant sized implants. Juvenile sheep 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. Less sentient species are less suitable to meet the objectives of this work due to their size but the safety/biocompatibility of any novel materials may have been previously assessed in less sentient species as required by the relevant International Standards.

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 15 years 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.