Home Office

NON-TECHNICAL SUMMARY

Cartilage repair and replacement

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

Key words

Orthopaedic, Knee, Cartilage, Biomaterials, Therapy

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?

To determine the effectiveness and durability of novel orthopaedic replacement therapies. As well as to assess the best attachment methods for this novel technology.

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?

Osteoarthritis is a crippling disease caused by damage to cartilage and the underlying bone in the body's joints. Arthritis Research UK have estimated that osteoarthritis will cost the NHS £118.2bn between 2017 and 2027. The only widely accepted surgical treatment for osteoarthritis is replacement of the joint with a large, permanent implant. This requires major surgery which takes several months to fully recover from and while often successful there are variable outcomes and it is not recommended for younger patients. As osteoarthritis can develop early in a person's life this means many patients cannot currently be treated effectively.

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

The initial outputs will be information regarding the attachment suitability and device longevity, integration and function. Which will form the basis of longer term studies, in the future, for regulatory approval of the device. With the aim of creating clinically available implants, potentially benefitting thousands of patients, in the UK alone, improving their mobility and, as a result, improving their overall quality of life.

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

According to the UK National Joint Registry over 117,000 surgical knee procedures were carried out in 2019 in the UK alone with over 4 million knee cartilage lesions discovered by routine arthroscopy in the EU and US each year. Whilst this technology would not necessarily be useful to all of these patients, over 1.1m of the knee cartilage lesions discovered were full thickness with associated osteoarthritis in many cases, and these form the primary target clinical population for this technology.

However, as the technology could potentially also be applied to alleviate similar problems in joints other than the knee, the products developed under this licence could be useful in many times this initial number of patients. As a result, while it is not possible at this stage to provide a meaningful estimate of the total number of people this technology would benefit it is clear that the number is very large and a conservative estimate of 50,000 patients annually in the UK may benefit.

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

As much of the work is for the development of commercial products and is therefore, covered by non-disclosure agreements, it may not be possible to publish data from this study until after the product is

in clinical use, due to patent and confidentiality issues. However, it may be possible to share the animal model information independently of the product information and it may also be possible to share/publish the information arising from subsequent human clinical trials/usage.

Species and numbers of animals expected to be used

- Sheep: 200

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 hind leg of a sheep is a proven model for human knee research because the anatomy of the sheep knee is very similar to that of humans. We need to use adult sheep as the animals need to be skeletally mature and also adult sheep body weight is comparable to that of an adult human.

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

Animals will be brought in and allowed to acclimatise for a few weeks - this helps them to relax in their new surroundings, gets them used to the staff and human contact and enables them to be monitored for general health or other issues. Prior to surgery they will undergo general observations as to their overall health and specifically how they walk. Food will be withheld immediately prior to surgery, as is done with human patients, to prevent possible problems with regurgitation (vomiting). Animals will also be individually housed (but within close proximity and line of sight to the rest of the 'flock') in the 24-48 hours prior to surgery. In our experience, individual housing for a couple of days prior to surgery means it is often less stressful for them when they are individually housed post-operatively.

On the day of surgery the animal will be anaesthetised (including pain relief), blood taken and non-invasive imaging (e.g. x-ray) may be performed on the hind legs. The relevant area will then be exposed and a defect created in the bone, and/or meniscus (a pad of cartilage, between bones, which acts as a shock absorber), to which the new implant/therapy will be applied, to simulate humans undergoing damage repair surgery. The operative site will then be sutured closed and the animal given pain relief, allowed to recover from the anaesthesia and returned to its pen. The animals will be observed closely for the first week, given more pain relief as required, and monitored for general health and mobility for the duration of the study. At several time points throughout the study the animals will be specifically assessed for how well they are able to walk, as well as x-rays taken, and/or other non-invasive images or assessment methods used. Blood samples will also be taken over the course of the study.

Initial studies are planned to be of 3-6 month duration with follow up studies being up to 2 years long to assess long term recovery and implant integration.

Where necessary, animals will be housed singly during the early phases of their post-operative recovery but group housed again as soon as possible. The reason for individual housing is to allow healing to begin and reduces the risk of problems as the sheep has time to recover before re-joining the group.

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

Based on previous experience using this model, we would expect to see:

- A slight weight drop (usually less than 10%) after surgery followed by a return to normal weight, within a few weeks. Some of which may be due to clipping of the fleece as part of the surgical access/preparation.

- Some evidence of pain/discomfort related to the original surgical incision and manipulation of the joint, usually controlled with medication and resolving within a few weeks.

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)?

Sheep – moderate – 100%.

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?

Cartilage is a complex tissue which interacts with the surrounding bone and joint tissue and whose growth and maintenance is affected by the mechanical stimulation of joint motion and weight bearing. These conditions are almost impossible to replicate in synthetic models or dead tissue, especially when looking at healing over longer time frames (i.e. months). Also, it is not possible to use smaller species as the size of implant used, the weight applied to it and associated surgery becomes far less comparable to humans.

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

We could not find any suitable, non-animal alternatives, however, the devices will have undergone in vitro and ex vivo testing, where appropriate, prior to the in vivo phase of the work.

Why were they not suitable?

It is not yet possible to fully simulate an intact biological system such as the knee especially under the conditions that occur during walking and other movement. A living system is necessary to assess fixation strength, integration, healing and remodelling under these conditions.

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?

Based on several years' experience using this model (over 100 sheep), we found that:

  A pilot study, usually of shorter duration (e.g. 1 month) and using fewer animals (e.g. 4 or less)

  Followed by longer (e.g. 3, 6, 12 or 24 months), larger studies (less than 10 animals per test group at each time point)

Gives the best results, with the least number of animals used.

It is sometimes necessary to carry out more than one pilot study, depending upon initial results.

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

The knee joint at the end of the femur is made up of two separate, but similar, boney structures called condyles. As we only operate on one of these condyles, it is possible to use the other as a control (within the joint) and the matching condyle on the opposite hind leg can be used as an unoperated knee control.

Non-invasive imaging will also be used, where possible, to allow data collection at various time points, without surgical site disruption or the need to kill animals at each timepoint. Previous studies using identical or near identical surgical techniques have been carried out by the same team (surgeon and pathologist), including just-defect-creation controls, as such, unless we make a major modification to the operative technique, these data can be used as controls, removing the need to have separate controls for each individual study.

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

The use of dead tissue to refine any changes to surgical technique.

The increased use, where possible, of non-invasive imaging to avoid having to kill animals at multiple time points.

Tissue sharing wherever 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.

The sheep model is considered the closest mechanical representation of the human knee joint (although there are several acknowledged differences) and the animal weight is similar and should not alter significantly over the course of the study. There should be little discomfort for the animal from the surgical site and any discomfort would more likely arise from the surgical access. As this is a surgical operation on the knee as opposed to an uncontrolled traumatic injury to the knee (which often involves significant damage to multiple parts of the knee joint) this should be more than adequately controlled by standard post-operative pain killers.

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

Due to the size restriction of this technology it is not possible to work on smaller animals nor is it possible to work on animals that are not skeletally mature due to growth/expansion issues.

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

The use of best surgical practice and adherence to the principles set out in the LASA (Laboratory Animal Science Association) guiding principles document combined with good pre-, intra- and post-operative care and monitoring will minimise unnecessary suffering. The use of non-invasive assessment (e.g. MRI or X-ray), whilst potentially increasing the number of anaesthetics an individual animal has over the course of a study, can significantly increase the amount of information gained per animal and therefore reduce to overall number of animals used. Also, with a degree of animal training and familiarisation and the correct pre-medication (often delivered in food rather than by injection), the stress/suffering to the animal can be minimised - this applies to medication delivery, acclimatisation to single housing, blood sampling and any other events that require interaction with the animal. By combining as many procedures as possible, it should be possible to reduce the number of anaesthetic events each animal undergoes.

Again input/ support from the local NIO, NACWO, NVS and other local animal care staff will greatly help with this.

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

The Norecopa, NC3Rs and LASA (and similar animal research and welfare) websites

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

Review of the current literature (also encompassing changes in veterinary, research and human surgery) and any revisions to the regulatory guidelines along with input from the local Named Information Officer (NIO), Named Animal Care Welfare Officer (NACWO), Named Veterinary Surgeon (NVS) and other local animal care staff. As well as checking the Norecopa, NC3Rs and LASA (and similar animal research and welfare) websites