Home Office

NON-TECHNICAL SUMMARY

Evaluation of new devices to be used in human surgery

Project duration

3 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
  - (ii) Assessment, detection, regulation or modification of physiological conditions 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

Surgical devices

Animal types	Life stages
Pigs	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 aims to evaluate and further develop novel surgical devices and to identify those which have the potential for use in human surgery. Then to progress these devices, from the bench testing phase, through the necessary pre-clinical regulatory assessments to be registered by, for example, the Medicines and Healthcare products Regulatory Agency (MHRA), the European Medicines Agency (EMA) and/or the US Food and Drug Administration (FDA) for human use.

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?

All devices which are intended for human clinical use need to undergo rigorous safety and efficacy assessment before progressing from pre-clinical to clinical use. Some of these assessments are to establish which of several potentials is the most appropriate to progress to patient use and some are to definitively establish safe use of the final chosen instrument. All devices under this licence are intended for use in human surgery and are designed to increase positive surgical outcomes, enable new surgical approaches and/or minimise the impact of the surgery itself.

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

The devices successfully evaluated will be made available to clinicians and surgeons worldwide.

These evaluations should allow rationalisation of potential devices, to defined products, to progress through relevant regulatory bodies, to human clinical use and be used to inform the next generation of a device or new ideas for novel energy delivery.

'Energy delivery' includes the use of microwave-, radio- and ultrasound-frequencies, all of which can be used in patient diagnosis and/or treatment by focusing them in different ways. For example, ultrasound is currently commonly used as a safe, standard method of monitoring a baby's health in the womb however, it is also possible to use ultrasound to treat patients - by using a different form of ultra sound, high intensity focused ultrasound (HIFU), it is possible treat conditions such as uterine fibroids or gall stones.

Several minimally invasive devices (including those for endoscopic, laparoscopic and robotic use) could be registered for human clinical use over the course of this licence.

Most of the work carried out under this licence will probably be for device development therefore publication may be limited by the companies' intellectual property concerns and, as such, it may not be

possible to publish it, although there now seems to be an increasing interest in publishing data from such studies.

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

Benefits should be felt immediately upon the release of devices for clinical use, leading to feedback and the next generation of devices thereby providing long-term benefits to patients who currently need repeat or additional treatments which can extend their dependence and treatment regime.

These evaluations may provide safe additional, or replacement, devices (or combinations) for patients with varying conditions. Many of which could be applicable to several conditions from wound care to complex surgical interventions and thus improve the lives of a wide spectrum of patients.

These benefits may improve surgical outcome thereby improving quality of life for patients together with a reduction in surgical procedure duration, and the related anaesthetic requirements, as well as recovery time and therefore length of hospital stay, which would also decrease NHS costs and free up much-needed bed space. In some cases, these new devices may allow surgical intervention where currently it is not possible, thus increasing the options open to patients with several different medical conditions. For example, previous advances in endoscopic tool and technique development have changed patient treatment from open bowel surgery (requiring significant theatre time and several days hospital stay) to endoscopic surgery (which can be done as a day case, requiring no overnight stay).

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

Where possible, publication in peer-reviewed journals, dissemination at national and international meetings, workshops and seminars. Also, getting new, effective devices/compounds into clinical use as quickly and safely as possible will maximise patient benefits and healthcare savings.

Species and numbers of animals expected to be used

- Pigs: 150

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.

For device testing, we need an animal of a similar size to humans as the devices to be tested will be the same size as those intended for human clinical use. Adult pigs are therefore the animals of choice for these evaluations due to their size and anatomical similarities.

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

Devices will be evaluated for safety and efficacy.

Initially these studies will be non-recovery and only devices showing good results will be carried through to recovery studies. Some of these results may be obtained with the aid of endoscopic or minimally invasive surgery and/or the use of non-invasive imaging such as X-ray, MRI or ultrasound.

For the recovery studies, this will be done by the anaesthetised animal undergoing surgery in a similar way that of a human patient. The effects monitored in a similar way for example using a combination of the following: observation of general health and behaviour, regular blood tests, non-invasive imaging (e.g. x-ray, ultrasound or MRI) or via further endoscopic assessment to visualise the operated area and potentially to also take biopsies. It may be possible to carry out ultrasound and even, in some cases, x-ray without the use of anaesthesia however, the other imaging/assessment options would require general anaesthesia both to enable precise imaging and positioning but also to reduce stress for the animal.

For example, for an endoscopic access to the bowel for simulated polyp removal, under recovery anaesthesia an endoscope would be introduced via the anus and navigated to the appropriate area of the intestine (it may be necessary to flush the intestine at this point to remove any faeces present). The area would be marked, an endoscopic injection used to raise a 'polyp' and the mucosal tissue excised (approximate area: 3-6cm in diameter), this may be repeated several times (to replicate the human clinical situation). The treatment sites would then be checked and the scope removed and the animal allowed to recover from the anaesthesia. Blood samples may be taken pre- and post-operatively as well as at several later time points to assess any change in general blood chemistry. Possible re-scoping time points for an eight week study would be days 0, 3, 7, 14, 28 and at termination this would allow a visual assessment of the treatment site- any necessary blood samples would also be taken at these times. These blood tests and scoping 're-looks' would also serve as a method of monitoring overall animal health and any significant deviations from normal that could cause unnecessary animal suffering would constitute a humane endpoint. As these animals would have no external wounds or cannula there should be little or no need for individual housing. Where possible, blood sampling, scoping and minimally invasive imaging will be carried out at the same (or at least overlapping) time points to minimise the number of instances of anaesthesia the animal has to undergo thereby stressing the animal as little as possible. This should mean that, for a 4 week study, there would be no more than 6 instances of anaesthesia including the initial surgery and at termination.

At the end of the experiment the animal will be humanely killed and the operated site examined and removed for further examination by a pathologist.

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

For endoscopic procedures:

From previous experience, we do not expect to see any adverse events. Following complete recovery from anaesthesia the animal should appear normal and show no signs of pain, weight loss, or abnormal behaviour.

For laparoscopic procedures:

Potential adverse effects

From previous experience, and because all devices we need to test will have undergone rigorous bench testing and, where possible testing on dead tissue, we do not expect to see any adverse events. However, post-surgical infection is always a possibility following surgery. This will be specifically monitored and, if it does occur, relevant intervention or treatment under veterinary advice, will be applied. If intervention or treatment is inappropriate or ineffective the animal will be killed using a humane technique.

Avoidance of adverse effects

Good sterile technique and good preparation of the subject before surgery will ensure the absolute minimal chance of infection. Good use of pain relief medication will minimize the possibility of anything more than minor discomfort associated with the surgical procedures. Good monitoring for signs of pain will allow timely intervention under veterinary advice.

Humane endpoints

If any animal shows unacceptable changes to behaviour or physiology, full consultation with the vet and other local animal welfare staff will be undertaken to determine the best clinical care for the animal. If improvement is unsatisfactory 24-48 hours after any intervention or treatment, the animal will be killed using a humane procedure.

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)?

Pigs:

Non-recovery - 75%

Moderate severity - 25%

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?

The assessment of safety, effectiveness of surgical devices, requires full biological systems to show that they do not cause any unacceptable reactions in living tissue but that they have the appropriate

effect in as 'human-like' an environment as possible. It is not yet possible to accurately and reliably simulate this complete system.

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

We have considered virtual reality for testing of the devices and we do use these systems and simulations for ergonomic testing and early instrument development. We use tissue from dead animals for all initial tests where possible, but ultimately we need to know that the material or material/instrument combination is safe and effective in a fully functional biological system.

Why were they not suitable?

Virtual reality systems are not safety or efficacy predictive and as such they are not yet accepted by regulatory bodies. And it is not possible to assess healing, or the ability to stop bleeding, in dead tissue.

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?

For all safety and efficacy studies we will reduce numbers as far as possible by utilizing data as predicate where devices/materials are similar and by using as many sites as possible per animal without impacting upon the data obtained or negatively affecting the animal's welfare.

The number of animals is based upon previous device testing studies we have carried out over a number of years where the number of animals used was based on the advice from bio-statisticians. For any significant changes to protocols, further statistical advice may be sought.

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

Where possible tissues are retrieved from animals killed following the completion of other studies to reduce the number of animals used for tissue retrieval and instruments will have been progressed through assessments using dead tissue, prior to progressing to full evaluation in a live model. We will continue and expand this philosophy to reduce the numbers of animals needed in the pre-regulatory studies and follow the Norecopa PREPARE checklist. Norecopa is Norway's National Consensus Platform for the advancement of "the 3 Rs" (Replacement, Reduction, Refinement) in connection with animal experiments

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

As we retrieve more knowledge from these studies and build an "in house" data bank we will be able to refer to these results thus reducing the numbers of animals used.

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.

Surgical devices need to be assessed in an appropriately sized animal whose anatomy mirrors that of humans as closely as possible and the pig is typically used for this, especially with respect to the abdomen and gastro-intestinal tract. Safety and efficacy evaluation of the instruments and material/instrument combinations needs to take place in as close a situation to human use as is possible. Some models have been developed by us over several decades of device testing and others can be taken from the literature but there may be some incidences where a model will have to be developed to adequately and specifically answer the study questions. Any models developed to test instruments or materials will take direct note of the potential for discomfort to the animal. As these evaluations are to facilitate translation from pre-clinical to clinical human cases we feel there is little point subjecting an animal to a procedure which would not be well tolerated by a human subject and, as with human subjects, anaesthesia and pain relief will be used to minimise pain and discomfort.

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

For the device testing we need an appropriately sized animal as the devices to be tested will be those intended for human clinical use. The pig is therefore the animal of choice for these evaluations. Also, the majority of the initial testing will be carried out on animals that never recover once anaesthetised at the start of the experiment.

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- and intra- operative care and monitoring will minimise unnecessary suffering. The use of minimally and non-invasive assessment (e.g. MRI or X-ray) as well as scoping, whilst 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 (by allowing internal assessment at multiple time points) 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 from a cannula 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 PREPARE and NC3R and ARRIVE checklists coupled with reviews of the current literature and any revisions to the regulatory guidelines along with reference to the LASA guidleines on undertaking aseptic surgery (2017 edition). I have also been referred to standard, established, well regarded reference books, for up to date anaesthesia advice/techniques.

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

Review of the current literature 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