Home Office

NON-TECHNICAL SUMMARY

Targeted treatment of blood-borne disease

Project duration

5 years 0 months

Project purpose

- (a) Basic research
- (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

Blood filtration, Sepsis, COVID-19, Extracorporeal, Anti-inflammatory

Animal types	Life stages
Pigs	adult
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?

The aim is to assess the safety and feasibility of a novel medical device, a Magnetic Blood Filtration System, which is used in an extracorporeal system (outside the body) to remove harmful pathogens from the patient's blood stream.

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?

Magnetic Blood Filtration has the potential to provide targeted and fast treatments for blood-borne diseases. The magnetic blood filtration technology enables the selective removal of harmful components, such as cells, bacteria, toxins and inflammatory cytokines directly from a patient's bloodstream. The ability to precisely extract unwanted disease causing substances in this way has the potential to revolutionise the treatment of deadly blood-borne diseases, such as sepsis and COVID-19, leukaemia and malaria. Regulatory animal studies are required prior to human clinical trials.

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

The expectation is to validate this novel treatment, (the Magnetic Blood Filtration system), for blood-borne diseases, including COVID-19 and sepsis. This will include data for regulatory submission prior to entering human clinical trials. In addition to safety studies for regulatory submission, efficacy studies will also be performed which will lead to advancement of knowledge in treating these diseases and publication of this.

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

The ability to safely and effectively remove blood-borne pathogens via a targeted approach has huge potential to treat a number of serious medical conditions and diseases. These range from inflammatory diseases such sepsis and COVID-19, to blood-borne cancers, to malaria. Work using this filtration system for Malaria is already in human clinical trials.

In the short term this work will focus on COVID-19 and sepsis. COVID causes an intense 'hyperimmune' response and studies have shown that over 50% of hospitalised COVID patients

develop sepsis. Sepsis is caused by pathogens from an infection which circulate in a patient's bloodstream. COVID and sepsis can both elicit a abnormal immune response that can escalate to multiple organ failure and death. The challenge in sepsis is that both the pathogens and the body's own response contribute to the disease. The ability to immediately and effectively treat and control the inflammatory response could significantly improve mortality and morbidity in these patients.

In particular, there is an urgent need for new therapeutic tools to help clinicians reduce the severity and mortality of COVID-19 and the number of patients that end up on ventilators. Clinical studies have shown that much of the harm done in severe cases of COVID-19 results from the body's overactive or hyper-immune response. Using the magnetic blood filtration system (MBF) to reduce this hyper-inflammatory state without systemic delivery of biologics, provides an early opportunity to control the immune response without causing long-term immunosuppression. MBF could treat both the hyperinflammation seen in the lungs that drives hospitalisation and the secondary sepsis in COVID-19 patients that results in significant mortality.

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

The outputs from this work will be disseminated to the wider scientific community through publication in peer reviewed journals and by presentation at international meetings. Negative data will also be published and shared within the scientific community. Where appropriate, patients and the public will be informed of the outcomes through appropriate avenues.

Species and numbers of animals expected to be used

- Pigs: 40
- Sheep: 20

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.

Adult animals are ideal for this study for fulfilling scientific objectives, based on anatomy, size and expertise of scientists and animal care staff. Sheep and / or pigs may be used for these studies as suitable models for both the safety and efficacy work, based on our already gained scientific knowledge working with both these species in this specific scientific field.

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

Animals will be acclimatised and trained for handling purposes.

In the first study, animals will be anaesthetised and connected to the Magnetic Blood Filtration System, before being terminated (first group) or recovered (second group). Animals in the recovery group will be recovered for up to 1 month following the procedure and serial blood tests could be performed for the assessment of the longer term effects. Analgesia and antibiotic treatments will be provided post recovery and animals will be monitored by clinical observations. Animals will be killed and post mortem assessments performed.

In a second terminal study, animals will be anaesthetised and efficacy testing performed by administering compounds designed to elicit an inflammatory response (e.g. LPS) whilst connected to the Magnetic Blood Filtration System designed to remove or reduced inflammatory factors released.

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

The impact of any adverse effects expected for animals receiving compounds to elicit an inflammatory responses are expected to be minimal as this is performed under terminal anaesthesia.

Previous animal studies conducted in sheep have shown use of the magnetic blood filtration system has minimal adverse effects, however, there is always a risk of thrombosis of the jugular vein, which would pose a minimal overall risk to the animal but which could lead to local swelling. There is a small risk of thrombophlebitis (infection of the veins) in the recovery period, which could potentially lead to systemic infection; this risk will be mitigated by antibiotic administration and jugular vein access only being used briefly and in a clean surgery room.

In the recovery studies the procedure itself and the recovery are anticipated to be associated with very little discomfort. If there is any short-term mild pain this will be controlled with appropriate treatment.

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)?

For recovery studies, moderate in all animals.

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?

Pre-clinical safety studies conducted in animals are required as part of the performance validation of a medical device. International standards (ISO10993 part 4) detail the requirements for biological evaluation of medical devices and list the selection of tests required for the pre-clinical testing of devices interacting with blood. These tests require the use of animal models.

For efficacy studies only a whole biology systems approach will give conclusive evidence of treatment of the hyper-inflammatory conditions the device is designed to treat.

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

There are no non-animal alternatives to achieve the aims of this project for the reasons stated above.

Why were they not suitable?

N/A

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 first pilot studies will likely use 1-4 animals to validate the set-up and management of the magnetic filtration system and are designed to test at an early stage any obvious correction of the protocol that would be required. Pilot studies will also inform the status of physiological status of the animals prior to embarking on recovery studies.

Recovery studies will be designed to satisfy regulatory requirements using the minimum number of animals.

Finally terminal studies designed to test efficacy will be conducted . Work involving administration of the inflammatory compounds in large animal models is already established as a known working model at the test facility, as well as bench top testing of blood and a known ability to measure outcomes in the blood; these together will reduce numbers of animals as some optimisation has already been done. The information from these previous studies has been used to inform the number of animals required for this project application.

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

The present studies are designed to provide data on safety and efficacy of the device, as such, there is no formal calculation of number required that is possible.

The number of animal appropriate to satisfy minimum MHRA regulatory requirements for the safety studies will be used.

In the efficacy studies, optimisation of the inflammatory large animal model has already been performed which will reduce animal numbers. Regular review of data after each study will optimise the use of data and

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

Training with the MF system will be conducted at the test facility with blood from a cadaver to familiarise the test facility team with the system prior to use in animals.

We will use data/ experience from previous research performed at the test facility to provide the initial validation data for the efficacy studies and to inform animal numbers. Studies will be staged to allow data to be reviewed between animals as the efficacy work progresses.

Cadavers will be shared with other groups where 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.

Pigs and sheep have been selected to appropriately test the system with regards blood flow, blood volume and a whole systems biological approach. The procedure is anticipated to cause minimal pain and adverse events are predicted to be seen quickly, while animals are still under anaesthesia hence optimisation will be performed under terminal anaesthesia. Once the protocol is defined and refined, recovery studies with general anaesthesia will be started.

Local anaesthetic may be used wherever possible, for example, to reduce stress prior to taking blood samples.

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

Adult large animal models are required for the safety testing of the system due to the necessary blood flow, blood volume and large enough access points via the cannulae in the veins.

Terminal anaesthesia studies are being used for the pilot study to refine protocols prior to starting the safety study and will be used for the efficacy studies involving inflammatory compounds. Terminal aneasthesia is not appropriate for the longer safety studies.

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

Prior to surgery, recovery animals will be trained as appropriate to the species, to co-operate and tolerate procedures, thus minimising stress during handling for observation / conscious procedures. Training may include clicker training and/or food rewards.

Post-operative care will include regular monitoring, including overnight care where necessary to ensure animal recovery is optimal and welfare of the animal is maintained. All animals will receive appropriate peri-operative pain management during and after the procedure. Surgical expertise at the test facility further enhances animal welfare, by providing close collaboration with dedicated large animal surgeons and veterinary anaesthetists, and ready access to advice in the case of unforeseen complications or intercurrent illness. For clarity on care in such circumstances, we will refer as appropriate to the NVS, in the first instance.

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

We will follow the NC3Rs guidelines on the "Responsibility in the use of animals in bioscience research" and consult all the relevant references listed therein. (Reference: NC3Rs/BBSRC/Defra/MRC/NERC/Royal Society/Wellcome Trust (2019) Responsibility in the use of animals in bioscience research: expectations of the major research councils and charitable funding bodies. London: NC3Rs.)

Animals will continually be monitored for signs of pain and distress, especially post-challenge, by experienced veterinarians and animal care technicians with significant experience in these species.

Anaesthetists work to best practice guidelines for large animal anaesthesia and maintain CPD to keep up to date with new practices.

Standard Operating Procedures are employed for animal preparation, surgery and recovery.

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

We will continuously monitor publications and the NC3Rs website for new and alternative models that could be implemented as part of this project. In addition, articles on advances in the 3Rs are regularly published on internal News Forum and other relevant information is circulated by AWERB. Whenever possible we will implement these refinements into our studies.