G: NON-TECHNICAL SUMMARY (NTS)

Please attach the Non-technical Summary as generated by your application in ASPeL.

Describe the aims and objectives of the project (e.g. the scientific unknowns or scientific/clinical needs being addressed):

Diseases of the heart and blood vessels remain the commonest cause of death in Western society. Two very common conditions are atrial fibrillation, also commonly known as AF, and heart failure. Atrial fibrillation is where the normal rhythmic electrical activity of the heart becomes irregular and heart failure is where the heart is unable to pump enough blood to meet the demands of the body.

Atrial fibrillation occurs in up to 20% of elderly people and it is associated with a dramatic increase in the risk of having a stroke. It is commonly treated using a technique called ablation where electrical energy is used to isolate the affected part of the heart. However, this procedure frequently fails because doctors are unsure whether they have applied enough energy to the heart.

In this programme of work we intend to test a new device that will allow doctors to immediately know if the high energy pulses from the ablation device have been successful in preventing the abnormal electrical activity travelling around the heart.

Heart failure, like atrial fibrillation, is also very common and occurs frequently after people have had a heart attack which is caused by a blockage occuring in the blood vessels in the heart . Following a heart attack, doctors try to restore blood flow to the area of the heart affected by the blocked blood vessel by inserting a device known as a stent into the blood vessel. However, in some people these stents eventually fail and become blocked again as the body reacts to their presence in the blood vessel.

In this second part of this programme of work we aim to test a new stent design where the coils that make the stent springy are arranged in a different way and they are also designed to be slowly absorbed by the body. By being absorbed once the hearts blood vessel has recovered, the stent no longer acts as a source of irritation to the body and we anticipate the blood vessels will be less likely to become blocked again.

What are the potential benefits likely to derive from this project (how science could be advanced or humans or animals could benefit from the project)?

This study has two major parts:

In the first part we will be investigating a new device that will help doctors determine if a procedure that they perform to treat patients with atrial fibrillation and other rhythm disturbances in the heart is performing optimally. Specifically we will be testing if a light based detection system incorporated into these devices which are known as ablation catheters, can be used to tell when the ablation catheter has applied enough high frequency energy to the part of the heart being treated. This is important because in order to ensure the best patient outcomes the doctors aim to stop the abnormal activity in the part of the heart being treated from influencing the rest of the heart without excessively damaging the heart and causing serious complications associated with this type of treatment. However, at the present moment in time, doctors either treat the part of the heart they are interested in for a fixed amount of time or until a certain temperature is reached in that part of the heart without actually knowing if this has successfully treated that part of the heart. With the proposed device doctors will know exactly when to stop treating the heart and are therefore more likely to successfully treat the underlying condition (e.g. atrial fibrillation). Additionally, by knowing when to stop applying high frequency energy to the heart, doctors will be much less likely to damage the heart walls and thereby protect patients from the one of the main risks associated with this type of surgery.

2. In the second part of the study we will also be testing a new device for the treatment of patients who have had a heart attack or, in whom, the blood vessels supplying the muscular parts of the heart have become narrowed or partially blocked. In these patients a spring like device known as a stent is normally placed in the blocked or narrowed vessel in order to keep the vessel open and to re-establish blood flow to the affected part of the heart. However, there are some common problems associated with conventional stents which, over time, lead to the vessel becoming blocked again. Here, we will be testing if a new stent design made using a material that is absorbed by the body over time, is better at preventing the blood vessels from blocking again. If we find that this new stent design is less prone to causing vessel blockage than conventional stents then these can be rapidly adapted for use in patients. This will lead to fewer long-term complications associated with stent placement in the blood vessels of the heart. Additionally, because the stents are designed to be absorbed over time and therefore disappear from the body, patients may not need to be treated with drugs for as long after they have had the stent implanted compared to the current situation with conventional stents.

What types and approximate numbers of animals do you expect to use and over what period of time?

The programme of work will use sheep and the initial studies establishing proof of concept effectiveness in both strands of the project will require approximately 32 animals and we anticipate this work will be completed in about two years. Farm animals have much more similar heart properties to man than rodents and are therefore more relevant. If the initial studies are successful then follow-on studies may be undertaken subject to amendments to the programme of work and we would expect these to last for a further 3 years. Such follow on studies will be designed in light of the outcome of the present studies and animal usage determined in light of the acquired knowledge.

In the context of what you propose to do to the animals, what are the expected adverse effects and the likely/expected levels of severity? What will happen to the animals at the end?

The overall severity level for the two arms of the study will be different; in the first part all the invasive procedures are all performed in terminally anaesthetised animals. In the second arm, animals will recover from anaesthesia following surgery and will be monitored for a period of up to 5 months before undergoing a final surgical procedure performed under non-recovery anaesthesia. The severity limit for this second arm will not exceed moderate.
In both work packages of the study, animals will also undergo a limited number of investigations to assess the function of their heart; this will entail blood sampling, echocardiography and ECG measurements. These procedures are non invasive and do not require sedation; animals are gently restrained by the assistant whilst the operator takes the measurements. These investigations are the same as occur in patients and are not expected to cause any form of lasting harm or discomfort and would either be categorised as sub-threshold or potentially mild.

For both arms of the study the adverse effects that we may encounter are similar and include stroke, heart attack and abnormal rhythms in the heart. Whilst each of these adverse effects is potentially of a severe nature, if they were to occur they would arise whilst animals are anaesthetised and undergoing procedures. Through careful surgical, physiological and anaesthetic monitoring evidence that these adverse events had occurred would result in the humane killing of the animals such that no animal would experience these symptoms whilst conscious.

However, given that animals will be being treated with drugs that prevent these adverse events and procedures will be performed by experienced operators we do not anticipate an incidence rate of more than 1% each.

All animals are maintained in group housing within the facility and provided with enrichment including food toys, protected areas and rubbing posts.

Application of the 3Rs

Replacement

State why you need to use animals and why you cannot use non-protected animal alternatives

Replacement

- In order to assess the applicability of these novel devices it is necessary to undertake in vivo experiments that closely mimic the real-life settings in which they would be employed clinically. This requires that we use the same surgical approaches and assess the suitability of the devices in situations where the heart is working and experiencing all the neurohumoral inputs and controls the heart experiences in the body.
- computer models are not clever enough to accurately predict the complex signalling outcomes involved in the inflammatory response, the only way we can investigate this is in a situation where all the elements of the inflammatory system are present and working.
- even with blood perfusion it is not possible to maintain functioning organs (human or animal) ex vivo for the amount of time required to complete these experiments and recapitulate the bodies responses which occur naturally over the time frame of months rather than minutes.
- before these devices could be translated to the human setting we have to demonstrate that the novel devices are at least as effective as conventional devices in animal models

Reduction

Explain how you will ensure the use of minimum numbers of animals

Reduction

- consideration of experimental design and good practice before undertaking in vivo experiments; we will work with an independent statistical consultant to ensure appropriate design strategies are implemented
- the use of a large animal model allows multiple 'tests' to be undertaken simultaneously in the same heart thus reducing the overall animal numbers required to achieve target outcomes

  To elaborate how experimental design is pivotal to reducing animal numbers we will exemplify the stent arm of the programme of work:

  - animals are randomly assigned to the two treatment groups based on pre-surgical assessments (e.g. age, weight, cardiac indices assessed by echocardiography, blood biochemistry)
  - each group will receive one stent type and be monitored post operatively.
  - Depending on within and between animal variability it is estimated that 9 animals per stent will allow a difference in neointimal thickness of between 19 and 28 µm to be detected.
  - Differences between groups with these sample sizes are detectable at the 5 % level and with at least 80 % power.

Refinement

Explain the choice of animals and why the animal model(s) you will use are the most refined, having regard to the objectives. Explain the general measures you will take to minimise welfare costs (harms) to the animals.

Refinement

- procedures are refined to be as minimally invasive as possible
- we follow the same approaches that are employed clinically
- the choice of animal model means that devices and approaches require no modification to be suitable for use experimentally
- animals are housed in social groups and are provided with enrichment objects in the housing environment
- where animals are individually housed post-operatively, this is for the minimum amount of time to ensure full recovery from surgery and wound integrity. Additionally, the singly housed animals are in sight of and can still interact with their group peers.
- animal welfare is assessed at least once daily by experienced care staff and the investigators involved in the programme of work
- there is an open and bilateral relationship between the investigators and all named personnel thus ensuring animal welfare and well-being is at the forefront of studies