Home Office

NON-TECHNICAL SUMMARY

Reconditioning of marginal donor hearts for transplantation with machine perfusion

Project duration

2 years 0 months

Project purpose

- (b) Translational or applied research with one of the following aims:
  - (ii) Assessment, detection, regulation or modification of physiological conditions in man, animals or plants.

Key words

transplantation, machine-perfusion, marginal-donors

Retrospective assessment

The Secretary of State has determined that a retrospective assessment of this licence is not required.

Objectives and benefits

Description of the project's objectives, for example the scientific unknowns or clinical or scientific needs it's addressing.

What's the aim of this project?

Although it has almost been 50 years since the first successful human heart transplant, it remains the gold standard treatment for end-stage heart failure. Unfortunately, the ever growing demand for heart transplantation vastly out-strips the limited number of available donor hearts. Consequently, more than half of the patients accepted onto waiting lists will never receive a heart transplant. Currently, of the donor hearts made available from "*donation after brain death*" (DBD), less than 30% are eventually retrieved and transplanted. This alarmingly low rate of donor heart utilization is due largely to the harmful effect of brain death on donor heart function, rendering many organs too damaged to be transplanted.

Our intention is to minimize and ameliorate these injuries on donor hearts thereby increasing the proportion of donated hearts that could safely be transplanted. In doing so, it would allow the wishes of more donor and donor families to be fulfilled. At the same time, it would afford more patients on the heart transplant waiting list the chance to undergo this life saving operation.

The process of brain death in the donor has many deleterious effects on the heart. In order to maintain an adequate blood flow to all the vital organs in the donor, intensive care units often have to use powerful drugs to drive these injured hearts to work harder, thereby compounding the injury. Once a donor heart has been surgically removed from the donor, it is placed in a "picnic" box packed with ice and transported to the recipient hospital to be transplanted. The heart receives no oxygen during this time and deteriorates further inside the cold box. This makes it hard for the transplanting surgeon to be confident that the donor heart will have sufficient power to keep the recipient alive once transplanted. In fact, as many as 1/3 of the carefully selected donor heart that are currently transplanted go on to develop so-called "primary graft failure" and put the life of the recipient at risk.

After years of systematic research, we have established a world leading "*donation after circulatory determined death*" (DCD) heart transplant programme during 2015. These DCD hearts are very different from the DBD donor hearts described above in that they have suffered even more damage and had already arrested in the donor. Over the decades, cardiac surgeons have universally dismissed the possibility of transplanting hearts from DCD donors. By using a mechanical circulatory support system (extracorporeal membrane oxygenation system or ECMO), we have been able to restore good function in a high proportion of DCD hearts to the extent that they satisfy our standard acceptance criteria to be retrieved for transplantation. In order to avoid inflicting further injury to these carefully reconditioned DCD hearts during transportation, they are placed in a specially designed machine instead of a "picnic" box with ice. This machine manufactured by TransMedics Inc. (Andover, USA) maintains the retrieved donor heart in the ideal condition by providing it with warm blood enriched with oxygen and essential nutrients. By using a combination of machine perfusion before and after donor heart retrieval, we have successfully reconditioned and transplanted 32 DCD hearts to date.

We aim to use the same approach that has proven to be so successful in our DCD heart transplant programme to recondition and retrieve injured DBD hearts that are rejected by transplant teams. By using ECMO to provide the necessary blood flow to vital organs in these DBD donors, powerful drugs that are used to drive the donor heart could be stopped and the injured donor hearts are allowed to rest and recover. Once retrieved from the donor body, machine perfusion is used to maintain these recovering DBD hearts during transportation to avoid further injury.

We shall validate this approach in a large animal model, similar to the model that we have successfully developed for our DCD heart transplant programme. We have found this large animal model to be an invaluable platform in the process of translating our research hypothesis from bench to the bedside with

an immediate positive clinical impact. Furthermore, with our experience of this experimental model and our expertise in the field of heart transplantation, we are very well placed to conduct this research.

We hope to move swiftly to deploy this innovative use of technology into a clinical programme. This will enable more effective use of the valuable donor hearts thus realising the wishes of the donors and their families who have kindly offered their organs for transplantation and the hopes of those patients who are dying from end-stage heart failure in having the chance of a life-saving heart transplant

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.

What are the potential benefits that will derive from this project?

The number of patients on the heart transplant waiting list has more than doubled in the last 5 years with a number of patients waiting more than 3 years for a heart transplant or unfortunately dying on the waiting list. We hope that we can double the number of hearts used with these strategies as well as improve the outcomes for patients following their heart transplant.

Species and numbers of animals expected to be used

What types and approximate numbers of animals will you use over the course of this project?

Based on our previous experience and other published literature using large animal models we believe that the study groups should have at least 10 animals each. As we have 4 groups including the control group this will mean a minimum of 40 animals being operated on. However, we have accounted for 80 animals to allow for an attrition rate based on our previous experience and the advice of AWERB to ensure that at the end of completion of the study we have sufficient data to allow for meaningful interpretation.
Additionally, we have requested for upto 300 animals to have blood sampling to enable the identification of suitable blood donors to obtain cross-matched blood. However, a number of these animals will be destined for re-use as following the blood sampling there will be no lasting distress or physical impairment. We hope to complete all our experiments over a one year period but will be analysing the data and results after each case to ensure that the minimum number of animals are used.

Predicted harms

Typical procedures done to animals, for example injections or surgical procedures, including duration of the experiment and number of procedures.

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

The donor animals that will undergo some mild stress of anaesthetic induction but following this no further intervention will be performed until general anaesthesia is established. The animal will continue

to be under general anaesthesia which will eventually be terminal with measures taken to monitor the depth of anaesthesia. These animals will not be allowed to recover and all procedures will be done with the animal under general anaesthesia including the removal of the heart. This will ensure that no further distress is experienced by the animal. The animals who are tested for suitable cross-matching will experience some mild distress during the blood sampling but will have no lasting distress or physical impairment. Suitably cross-matched blood donors will under an approved Schedule 1 killing method to collect the donor blood - thereby the animals will not be recovered and any stress to the animal will be at the absolute minimum.

Replacement

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

The porcine heart and anatomy is very similar to the human and has been used reliably as a model to investigate heart transplantation. We hope that the positive findings from this study will allow for further validation in the human setting and the use of a porcine model has previously allowed for the rapid translation into clinical practice with reproducible findings.

This is vital to ensure that no harm is done to potential human heart recipients and that potential transplantable donor organs are not wasted without sound scientific evidence to support our proposed interventions.

Reduction

Explain how you will assure the use of minimum numbers of animals.

Previous work done by our group using large animal models have aimed to use groups of 10. Similarly, other published work which has also translated into clinical practice and further human research has shown us that using groups of 10 will give us sufficient evidence to justify validating any positive findings in a clinical human setting.

We have designed the study such that our control group mimics the current standard of practice, therefore we hope that any positive results will be directly translatable into clinical practice.

All surgical procedures will be performed by cardiothoracic surgeons who have experience with the surgical technique and equipment used to ensure that the minimum number of animals are lost due to technical difficulties.

Refinement

Explain the choice of species 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.

We have chosen the pig model as they are very similar in size, anatomy and physiology to the human. Similar methods of resuscitating the heart have been validated in rodent models and therefore a translatable large animal model needs to be validated in order for any positive findings to be then investigated in a human clinical trial. Previous work carried out by our group using similar equipment was also carried out in a pig model, therefore we believe the use of the pig model is the most appropriate to further this work to allow for rapid translation of any positive findings into clinical practice. Our experience with this model will also ensure that the minimum number of animals are lost due to technical errors. We have designed the study to test two interventions such that it minimises the number of pigs required and employed a non-recovery model to minimise suffering and potential complications to the animals. Additionally, the procedures have been designed such that the interventions being studied are all performed following the establishment of general anaesthesia in order to minimise distress to the animal.

Also, final outcome are measured on a device after the animal has expired rather than using a transplant recovery model. This will ensure that the minimum number of animals are used and avoid any potential complications and distress to animals should a recovery model have been opted for.