<table>
<tr><td>Project Title (max. 50 characters)</td><td>The role of copper in diabetes and ageing</td></tr>
<tr><td>Key Words (max. 5 words)</td><td>arteries, kidney, heart, eyes, biomarkers, treatment</td></tr>
<tr><td>Expected duration of the project (years)</td><td>Five</td></tr>
<tr><td>Purpose of the project (as in section 5C(3)[1]</td><td>
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<tr><td>Basic research</td><td>Yes</td><td></td></tr>
<tr><td>Translational and applied research</td><td>Yes</td><td></td></tr>
<tr><td>Regulatory use and routine production</td><td></td><td>No</td></tr>
<tr><td>Protection of the natural environment in the interests of the health or welfare of humans or animals</td><td></td><td>No</td></tr>
<tr><td>Preservation of species</td><td></td><td>No</td></tr>
<tr><td>Higher education or training</td><td></td><td>No</td></tr>
<tr><td>Forensic enquiries</td><td></td><td>No</td></tr>
<tr><td>Maintenance of colonies of genetically altered animals[2]</td><td></td><td>No</td></tr>
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<tr><td>Describe the objectives of the project (e.g. the scientific unknowns or scientific/clinical needs being addressed)</td><td>The overall aim of this programme of work is to understand the mechanisms underlying the key functional changes that take place in various organs in diabetes and to develop therapeutic strategies to reverse or prevent these changes. A comparative study using arteries will also be undertaken to investigate any similarities between diabetes and the normal ageing process.</td></tr>
<tr><td>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)?</td><td>Diabetes currently affects more than 200 million people worldwide and by 2025 the World Health Organisation estimates 350 million people will have the disease. Approximately one in five diabetic patients will present with some degree of organ complication that will be debilitating and will impact on the patient’s quality of life. These complications can affect the kidney and heart for example, and ultimately lead to organ failure. There is currently no effective treatment for diabetic complications once established.

These studies will result in a greater understanding of the mechanisms underlying diabetic organ damage with the realistic prospect of developing novel therapies involving patients in clinical trials. These results will also be of relevance to veterinary practice for those mammals that suffer from diabetes (e.g. the domestic cat).

Cardiovascular diseases (affecting the heart and blood vessels) are the leading cause of mortality and illness in the developed world, being responsible for >40% of all deaths. Hypertension (high blood pressure), which is due largely to abnormalities in blood vessels, is evident</td></tr>
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[1] Delete Yes or No as appropriate.
[2] At least one additional purpose must be selected with this option.

	in around 30% of adults and is a major risk factor for cardiovascular disorders. There is a need to improve understanding of the underlying pathological changes associated with the development and progression of hypertension. This project will increase the understanding of these processes and will thus aid in the identification of new therapeutic targets for the treatment of cardiovascular diseases. This research will be of benefit to academics, policy makers and regulatory bodies with special interests in diabetes and cardiovascular disease, public health and disease prevention and the epidemiology of chronic non-communicable diseases..
What species and approximate numbers of animals do you expect to use over what period of time?	750 rats over a 5-year period.
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?	Rodent models of Type 1 diabetes will be used. The severity is moderate. Animals are monitored regularly. Animals have free access to drinking water and food. Both of these will be provided in extra amounts. Three or more signs of persistent diabetes will be addressed by humane killing of the animal consistent with the law. Animals have raised blood glucose at levels that might be seen in poorly controlled clinical diabetes. Progression of organ disease over the time course of the study will be assessed by collection of body fluids that should not cause any tissue damage or undue stress to the animal. Animals will also undergo MRI and PET imaging to look for changes in the size of their organs. Animals are euthanized at the end of the protocol and tissues/ body fluids collected for molecular and biochemical analysis.
Application of the 3Rs	
1. Replacement State why you need to use animals and why you cannot use non-animal alternatives	Since diabetes is a whole body disease, affecting the hormonal, cardiovascular and nervous systems which all play a role in progression of the disease, it is impossible to wholly mimic diabetes in a culture dish. The complications of diabetes are progressive and take time to develop and are the product of several consequences of poorly controlled diabetes. Hence there is a need for animal models of diabetes. The similarities between the development of diabetes in humans, mice and rats justifies the use of animal models of diabetes to elucidate the mechanisms of the disease process, in characterizing changes in organ systems and assessing the efficacy of therapeutic agents. If any relevant non-animal alternatives become available during the course of the project, we will incorporate these in our studies.
2. Reduction Explain how you will assure	Experiments are designed on the basis of previous work and published data. Full evaluation of previous/pilot data

the use of minimum numbers of animals	and statistical calculations will be performed, such that the minimum number of animals required to provide valid data are used (typically 10 per group for therapeutic studies).
3. 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.	The animal of choice for this work is a mammal, the rat. The streptozotocin-induced Type I model of diabetes will be used. The model's advantages and limitations are well known as well as its specific requirements for animal welfare. The results will be integrated into the continuously expanding body of research conducted on this species and model, and contribute to the emergence of a comprehensive understanding of the development of diabetic organ damage. Numerous strategies are in place to minimize animal suffering. Appropriate anaesthetics and analgesia for any imaging will be used and animals will be handled and acclimatized to minimize any undue stress.