G: NON-TECHNICAL SUMMARY (NTS)

NOTE: The Secretary of State considers the provision of a non-technical summary (NTS) is an essential step towards greater openness and requires one to be provided as part of the licence application in every case. You should explain your proposed project clearly using non-technical terms which will be understandable to a lay reader: You should avoid confidential material or anything that would identify you, or others, or your place of work. Failure to address all aspects of the non-technical summary may render your application incomplete and lead to it being returned.

This summary will be published (examples of other summaries can be viewed on the Home Office website at http://scienceandresearch.homeoffice.gov.uk/animal-research/).

(WORD LIMIT: 1000 WORDS)

Please complete the following:

<table>
<thead>
<tr>
<th>Project Title (max. 50 characters)</th>
<th>Brain Control of Peripheral Glucose and Energy Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key Words (max. 5 words)</td>
<td>Diabetes Hypoglycaemia Brain</td>
</tr>
<tr>
<td>Expected duration of the project (yrs)</td>
<td>5</td>
</tr>
<tr>
<td>Purpose of the project (as in Article 5)¹</td>
<td>Basic research Yes</td>
</tr>
<tr>
<td></td>
<td>Regulatory use and routine production No</td>
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<tr>
<td></td>
<td>Protection of the natural environment in the interests of the health or welfare of humans or animals No</td>
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<tr>
<td></td>
<td>Preservation of species No</td>
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<td></td>
<td>Higher education or training No</td>
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<td></td>
<td>Forensic enquiries No</td>
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<tr>
<td></td>
<td>Maintenance of colonies of genetically altered animals² Yes</td>
</tr>
<tr>
<td>Describe the objectives of the project (e.g. the scientific unknowns or scientific/clinical needs being addressed)</td>
<td>The overall objective of our work is to characterise how brain helps control blood glucose and other important aspects of peripheral metabolism such as blood lipids and body weight. 1) Some people with diabetes lose defences against a falling blood glucose putting them at risk of suffering from severe episodes. The mechanisms by which this occurs are unknown. We will examine how brain controls defensive responses to a low blood</td>
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</tbody>
</table>

¹ Delete Yes or No as appropriate.
² At least one additional purpose must be selected with this option.

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<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
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<tbody>
<tr>
<td>What are the potential benefits likely to derive from this project (how</td>
<td>All of the above may lead to the identification of potential novel targets for therapies addressing clinical problems to be then tested in human studies.</td>
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<td>science could be advanced or humans or animals could benefit from the</td>
<td>1) To try to reduce the burden of low blood glucose – particularly occurring without warning in people with diabetes.</td>
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<td>project)?</td>
<td>2) To identify novel therapeutic targets for treating diabetes and/or managing obesity.</td>
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<tr>
<td>What species and approximate numbers of animals do you expect to use</td>
<td>Rats and mice.</td>
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<td>over what period of time?</td>
<td>Maximum numbers listed in this licence are 21,500 mice and 4,500 rats.</td>
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<tr>
<td>In the context of what you propose to do to the animals, what are the</td>
<td>Most mice on the licence will be used for breeding/maintenance of colonies. For those mice and rats undergoing more scientific procedures,</td>
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<tr>
<td>expected adverse effects and the likely/expected level of severity? What</td>
<td>these will mostly be of moderate severity.</td>
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<tr>
<td>will happen to the animals at the end?</td>
<td>Typically this may involve injections of insulin to lower blood glucose or glucose to raise blood glucose, measures of feeding behaviour</td>
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<tr>
<td></td>
<td>and activity. Some animals will undergo recovery surgery under general anaesthesia for implantation of tubes to allow subsequent infusion</td>
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<td>of test substances into brain and/or blood sampling. One protocol is graded as severe which involves surgical implantation of tubes into</td>
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<td>blood vessels and subsequent “clamp studies”. During these studies where blood glucose is altered by infusion of insulin with frequent</td>
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<td>sampling of blood. They provide very detailed information about metabolism especially when combined with infusion of radioactive markers</td>
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<td></td>
<td>so that we can trace movement of glucose in the body into muscle and out of liver for example. The protocol has been graded as severe</td>
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</table>
|                                                                         | because the surgery is challenging in small
animals and we typically see that 1 in 3 die before reaching study days. We have refined this over the last 5 years so that most of these deaths are while the animal is under anaesthesia. Animals will be killed at the end of protocols. We will often collect body tissues such as brain which allows us to examine patterns of brain activation in more depth.

### Application of the 3Rs

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

1) Control of energy balance and metabolism occurs at the level of the "whole body" and not simply at a cellular level. We can only partly replace animals with cell culture.

2) There are technical limitations to examining brain metabolism in humans with techniques such as non-invasive brain imaging which are still too crude to visualise changes in small brain cell populations.

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

1. We will use validated and standardised procedures to reduce experimental variability/duplication of efforts.

2. Where possible, we will try to maximise the data obtained from each animal undergoing procedures to reduce overall numbers of animals needed.

#### 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 (harm) to the animals.

Rats and mice are the lowest vertebrate groups on which well-characterised studies have been performed examining brain metabolism for extrapolation into humans. Lower life-forms, eg. fish or insects, regulate metabolism differently from mammals.

We will use both healthy animals initially but also then use validated rodent models of human disease for example rodents with diabetes in order to allow us to extrapolate data back into the clinical setting of human disease.

Most of the procedures are of moderate severity. We routinely use painkillers, anaesthesia and careful monitoring of animal welfare during procedures and we talk regularly with other similar research groups around the world in order to continue refining our methodology to improve animal welfare.
<table>
<thead>
<tr>
<th>Will the project be subject to Retrospective Assessment?</th>
<th>Yes</th>
<th>No</th>
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Date due: **15 November 2017**

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The retrospective assessment should be completed, agreed with the establishment AWERB, and submitted to the Home Office within 3 months of this date (or when the project terminates if earlier).

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