February 2017

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>
<tr><td>Project Title (max. 50 characters)</td><td>Evaluation of cognitive function in animal models</td></tr>
<tr><td>Key Words (max. 5 words)</td><td>Rat, behaviour, cognition, schizophrenia, new drug treatments</td></tr>
<tr><td>Expected duration of the project (yrs)</td><td>Five</td></tr>
<tr><td>Purpose of the project (as in section 5C(3)[1]</td><td>
<table>
<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</td><td></td><td>No</td></tr>
</table>
</td></tr>
<tr><td>Describe the objectives of the project (e.g. the scientific unknowns or scientific/clinical needs being addressed)</td><td>Overall aim
This work will continue to develop animal models for cognition, mood, motivation and social behaviour deficits in psychiatric illness.
Schizophrenia presents considerable personal burden to the sufferer and an economic burden to society as a whole, estimated at £11.8 billion per year in the UK. Existing drugs</td></tr>
</table>

[1] Delete Yes or No as appropriate.

	are not effective enough and have unpleasant side effects reducing compliance. Better treatments are therefore required, particularly for memory and social communication in schizophrenia. Critical for the development of improved treatments is improved understanding of the cause and biological basis of such disorders which can only be achieved through carefully validated animal models.
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)?	Humans will benefit from the project in a variety of ways. Schizophrenia reduces the quality of life for patients and carers dramatically and has a large economic cost. Improved treatments have not been successfully developed due to a lack of understanding of the biological basis of these diseases due to limited animal models. For any disorder, prevention is better than cure and early treatment is more successful than late treatment. Our work aims to identify new treatments for debilitating aspects of the illness, memory, mood and motivational disturbances with reduced side effects and improved effectiveness over existing medication. This will limit the detrimental effects to the patient's social, academic and home life. The benefits will be both in quality of life for patients and carers and economic in terms of restoring function in patients who can then work and make a contribution to society. We also aim to improve understanding of the mechanism(s) by which new treatments (drug and non-drug e.g. exercise) produce their beneficial effects on cognition and aspects of negative symptoms, mood, motivation and anticipation of reward. Animals (in our lab and others) will benefit from development of improved, food-rewarded tests based on naturalistic behaviour.
What species and approximate numbers of animals do you expect to use over what period of time?	3000 rats over 5 years
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 level of severity is expected to be moderate. Only minor, short term, brief behavioural effects of drug treatments are anticipated as these interact with brain systems. These may include increased or decreased activity and/or increased repetitive movements. Behavioural techniques are generally not stressful and can, in certain cases, be considered enrichment for the animals. Environmental enrichment and wheel running are examples of the methods we use. At the end of the study, or as part of the experimental procedure (e.g. to perform detailed assessment of brain

	changes induced by the interventions) rats will be killed humanely and quickly by a Schedule 1 procedure.
Application of the 3Rs	
1. Replacement State why you need to use animals and why you cannot use non-animal alternatives	It is difficult to mimic brain and behaviour interactions in cell systems, and whole animal experimentation is therefore vital to obtain a greater understanding of mechanisms and to test effectiveness of new molecules. This work must use whole animals as behaviour is a central feature of the project. Thus effects of new drugs on complex behaviour patterns may only be studied in whole animals and not using in vitro preparations, although CNS studies can also be conducted *ex vivo* and *in vitro*. To date there is no suitable alternative to the use of whole animals for behavioural research that doesn't involve human subjects. However, wherever possible the whole animal studies will be accompanied by isolated culture systems and using samples from patients. If any relevant non-animal alternatives become available during the course of the project, we will implement these in our studies. The behavioural studies are complemented by detailed post-mortem brain analyses which may identify a biomarker that could be used to develop subsequent isolated culture systems to study the pathology of these disorders. We collaborate with colleagues with brain recording and imaging technology and others who have replaced some animal testing with human studies. One research group in particular, use animals but also human samples (collecting samples from CNS epilepsy operations) while another group uses human subjects to explore effects of new drugs on brain function and behaviour through e.g. brain imaging studies. Their approach is to replace animal studies once drugs have successfully completed Phase I safety trials. We test molecules prior to Phase I trials following toxicological testing, it is unlikely this approach would be considered by our colleagues, but it is a replacement approach that is used successfully and is important for us, if the opportunity arises, in addition to performing our animal studies.
2. Reduction Explain how you will assure the use of minimum numbers of animals	We will minimise the number of animals by re-using the same animal in different behavioural tests, and testing more than one drug in the same animals. Numbers will be further reduced by repeated measures designs where possible. So far this has reduced our animal usage by approx. 40% All these repeat studies will only be conducted following an extensive examination of the animal by the Nominated Veterinary Surgeon. We have consulted a statistical expert and conducted power calculations to ensure we have minimum number of

	animals for maximum statistical power.
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.	Rats are a popular choice because of the detailed existing knowledge of their brain structure and function and its similarity to that of humans. The rat has been chosen as a subject for the present work for several reasons. Primarily much is already known about memory and brain mechanisms controlling complex behaviours in rats. We have extensive experience of studying behaviour in rats, all our current tests are validated for rats and our tissue analysis systems are validated using rats. Rats are larger than mice and more suitable for brain imaging and recording studies. We have refined our techniques in the continued review of our current work. For example we recently made a refinement to our social discrimination experimental protocol. We observed that Lister Hooded rats were aggressive toward juvenile con-specifics in a pilot study. We changed to the strain of rat to Wistar rats and completed a series of successful experiments without any further aggression. Welfare is critical for successful experiments and we have extensive experience in behavioural analysis of rats which we will continue to use in order to ensure that all our rats are subjected to the minimum adverse events and that undue stress is minimised at all times, particularly when rats are handled and drugs are given. Specific on-going refinements include: reduced use of food restriction, increasing use of naturalistic tasks involving enrichment eg wheel running and environmental enrichment. The use of smell and digging media to guide rats' behaviour, different grades of sandpaper to run along, improved handling and dosing techniques, including reduced restraint for blood sampling.
For Office Use Only	
Will the project be subject to Retrospective Assessment?[1]	Yes / No / Date due[2]:

[2] 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).