Private & confidential: *Please be aware that the contents of this form may be made public resulting from the "Freedom of information Act". Personal details will not be released.*

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>Modelling therapies for renal malformations</td></tr>
<tr><td>Key Words (max. 5 words)</td><td>Kidney, ureter, bladder, malformation, therapy</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[2]</td><td>Yes</td><td></td></tr>
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<tr><td>Describe the objectives of the project (e.g. the scientific</td><td>We will assess the feasibility and efficacy of new therapies to treat kidney and urinary tract</td></tr>
</table>

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

unknowns or scientific/clinical needs being addressed)	malformations. Our studies show that: a. we have animal models with kidney and urinary tract malformations and genetic defects similar to those found in patients. b. we understand the biological mechanisms why development is going wrong in these animals. c. we have potential new medicinal therapies, such as 'growth factors', to make the kidneys and urinary tracts grow normally. In this project, we will bring these lines of work together to treat animals with these therapies. These studies will pave the way for the human trails evaluating human kidney precursor cell therapy.
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)?	In the UK, 1000 children have such severe kidney disease that they require long term dialysis or kidney transplantation. Half of them were born with abnormal kidneys and urinary tracts. Moreover, around 3,000 UK adults with severe renal failure were born with similar malformations. These numbers exclude individuals found on fetal screening to have kidney and urinary tract malformations who subsequently die after elective termination of pregnancy. Being on long term dialysis confers a high risk of death, exceeding that found in certain cancers, and there are insufficient numbers of donors available to rescue all dialysis patients by kidney transplantation. Moreover, treatments for these kidney patients costs £30-70,000/year and they comprise a great social burden on affected families. Currently, no treatments exist to prevent the malformations themselves. So, there is an urgent need to define new treatments for these conditions. The current project, using animals with experimental disease, is a step towards this end.

What species and approximate numbers of animals do you expect to use over what period of time?	(N.B. these numbers exclude embryonic forms) Mice 3000 over five years (of which 1000 will be fetuses in the last third of gestation) Frogs (Xenopus) 2000 over five years (of which 1000 will be free-feeding larvae)
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 project has a 'Moderate' severity level. We will use breeding programmes so that, typically, clinically healthy parents (each carrying a mutant gene) are mated to produce litters containing animals with two mutant genes. The latter animals will have kidney and urinary tract malformations. Treatments (e.g. growth factors transferred by non harmful virus vectors) will be delivered to embryos *via* the mother, or directly into embryos, or into baby animals. In some experiments, we will study mouse embryos and fetuses, and frog embryos and larvae. In other experiments, when the malformations are anatomically mild or moderate, we will cautiously follow the progress of mice in the year after birth. Should signs of ill health become apparent, the animal will be killed by a humane method.
Application of the 3Rs	
1. Replacement State why you need to use animals and why you cannot use non-animal alternatives	We aim to determine whether therapies, for example using 'growth factors', can prevent or treat kidney and urinary tract maloformations. We, and others, have shown that human stem cells can form 'mini kidneys' in culture. These experiments provide fascinating biological insights and we are using them as test beds for therapies. However, neither normal kidney function nor the complex tissue changes of kidney disease, can currently be reproduced in cell culture. So, given the need for realistic preclinical models, there is currently no alternative to using live

	animals. Moreover, the administration of treatments to whole animals we ensure that we can detect any (albeit unanticipated side effects) on other organs.
2. Reduction Explain how you will assure the use of minimum numbers of animals	The use of (e.g. ultrasound and magnetic resonance imaging) scans to monitor both the structure of kidneys and the urinary tract is a feature of this project. While these techniques require general anaesthesia, they are 'minimally invasive' and so can be used recurrently on a single mouse to monitor disease, obtaining a large amount and variety of data. This will reduce the total number of mice used in the study. The scanning results will be compared with kidney and urinary tract at autopsy.
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.	At present, the mouse represents the best species with which to test the efficacy of new kidney therapies. The mouse has a kidney of similar structure and anatomical complexity (e.g. with glomeruli and branching collecting ducts) to humans. In many experiments, we will study embryonic and fetal animals that have malformations. Note that, in mice, the kidneys are not needed for life before birth because the placenta gets rid of fetal waste products. In other experiments, will be closely monitored after birth. Particular attention will be paid to their weights and behaviour. Should these parameters deviate markedly from normal, mice will be humanely killed. We will also study the frog called Xenopus, a lower organism. It has a very simple embryonic kidney, with a glomerulus and tubule similar to those found in mammals. Its embryonic kidney, however, lacks branching tubules that are often at fault in human kidney malformations. Moreover, the embryonic

<table>
<tr><td></td><td>frog does not have a ureter or physiologically functional bladder.

Despite the above limitations, the inclusion of frogs in the current study is highly desirable because large numbers of embryos can be quickly generated and it is simple to manipulate gene expression in these embryos. Thus, the information obtained from frog studies can complement and inform the mouse studies.</td></tr>
<tr><td>For Office Use Only</td><td></td></tr>
<tr><td>Will the project be subject to Retrospective Assessment?[1]</td><td><table><tr><td>Yes</td><td>No</td><td>Date due[3]:</td></tr></table></td></tr>
</table>

[3] 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).