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>Genetic Determinants of Cardiac Arrhythmias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key Words (max. 5 words)</td>
<td>Arrhythmias, heart disease, Sudden death, Genetics</td>
</tr>
<tr>
<td>Expected duration of the project (yrs)</td>
<td>X Basic research</td>
</tr>
<tr>
<td>Purpose of the project as in ASPA section 5C(3) (Mark all boxes that apply)</td>
<td>X Translational and applied research</td>
</tr>
<tr>
<td></td>
<td>Regulatory use and routine production</td>
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<td>Protection of the natural environment in the interests of the health or welfare of humans or animals</td>
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<td>Preservation of species</td>
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<td></td>
<td>Higher education or training</td>
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<td></td>
<td>Forensic enquiries</td>
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<td></td>
<td>Maintenance of colonies of genetically altered animals¹</td>
</tr>
</tbody>
</table>

¹ At least one additional purpose must be selected with this option.

The Home Office, in line with the rest of HMG, has implemented the Government Security Classification (GSC). Details of the GSC can be found at https://www.gov.uk/government/publications/government-security-classifications. Please note that documents and emails you receive may contain specific handling instructions.

Handling Instructions: Contains personal sensitive information, subject to confidentiality requirements under the Data Protection Act. This should only be circulated in accordance with ASPA Guidance and stored in a locked secure location.

All government information may be subject to an FOI request and subsequent assessment.
Describe the objectives of the project (e.g. the scientific unknowns or scientific/clinical needs being addressed)

Our objectives are to improve the assessment and treatment of cardiac arrhythmia that cause much suffering, disease and death in people.

Our work has initially focussed on single large effect genetic causes of risk that are usually manifest in young people and may result in the sudden death of an individual due to arrhythmia. This aspect continues but we would now like to extend the range of our experimental programme in order to know more about the burgeoning impact of metabolic disease on cardiac arrhythmias.

We already know from much clinical observation that those with obesity and who are metabolically ‘unhealthy’ get more cardiac arrhythmias than would be otherwise anticipated. The principal objective of the next 5-year project is to understand how the genetic controls of metabolism cause arrhythmias in mice.

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)?

The potential benefits are probably best considered under two headings: first, we will be better able to understand risk factors for arrhythmias and who is at risk so that we can take appropriate pre-emptive actions; second, our findings are likely to provide leads for the identification of new drug approaches for the treatment of patients.

What species and approximate numbers of animals do you expect to use over what period of time?

We will use approximately 2500 mice.
<table>
<thead>
<tr>
<th>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?</th>
</tr>
</thead>
</table>
| We expect few adverse effects based on the lack of adverse events seen over the last several years in the work of our group. Most of the work is completed on tissues from animals that have already been humanely killed. A new development in the current project is that some mice will have an implant of a monitoring device under the skin or in the peritoneal cavity to monitor heart rate and rhythm, and the placement of such a device has a small likelihood of surgical risk e.g. infection. 

The surgical procedures are procedurally well established and will be conducted by experienced medically trained doctors but if any adverse events are observed then unless readily resolved mice will be humanely killed. 

In addition some mice may receive drugs for short periods (of around one week maximum) in order to look for new approaches to the correction of arrhythmias. The drugs used are likely to have been used before clinically in patients and also be reported as being used in mice in the scientific literature without any significant reported adverse effects. |
| **Application of the 3Rs** | **1. Replacement**  
State why you need to use animals and why you cannot use non-animal alternatives |
|--------------------------|--------------------------------------------------|
|                          | Mice have an established position in heart research as they allow us to identify the way genetic alterations lead to clinically relevant outcomes and improve how we treat patients. We can also study human patients taking heart samples at the time of surgery to address some of our questions. The problem is that our patients usually have complex disease and will be treated by many drugs that will tend to confound obtaining robust scientific answers. In addition the development of new drugs for the treatment of patients need to use mice to most efficiently advance drugs to the clinic through identifying drug targets and then assessing drug responses.  
Genetically engineered fish have been used by other workers and provide complementary data but whilst they are vertebrates they are much removed from human physiology. In addition stem cell models offer promise but have unresolved technical issues. The work of this project cannot be addressed scientifically therefore without the use of mice. |
|                          | **2. Reduction**  
Explain how you will assure the use of minimum numbers of animals |
|                          | We design our experiments very carefully with statistical guidance so that we use the least number of animals to give us a robust and scientifically useful set of answers.  
In addition we are very experienced in the use of animals allowing us to obtain the maximum amount of scientific data possible from animal tissues to aid in answering our scientific research questions. |
### 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.

Our work is designed to address how genetic make-up determines the risk of arrhythmia. We can obtain much information from patients in the clinic but using mice we can work out in a very robust way how genes affect arrhythmia risk in mammals and this has significant clinical importance. The mouse has been established as the mammal most readily open to genetic manipulation and is ideal in this role.

We are always looking at ways to refine further our procedures to minimise any possible suffering and as much work as possible is done ex vivo rather than in the live animal. Further refinement will be achieved through limiting drug administration to animals in cases where likely promising outcomes in live animals are anticipated. Accordingly only after thorough trials have been completed in isolated hearts and cells will drugs be administered to animals.

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Will the project be subject to Retrospective Assessment?  

| No | Date due: |

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