**G: PROJECT ABSTRACT**

NOTE: This abstract will not form any part of the licensed programme of work. However, the Secretary of State considers the project abstract an essential step towards greater openness and expects them to be provided in every case. Use lay terms and avoid confidential material or anything that would identify you or your place of work. This abstract will be placed on the Home Office website at [http://scienceandresearch.homeoffice.gov.uk/animal-research/](http://scienceandresearch.homeoffice.gov.uk/animal-research/). Examples of other abstracts can be viewed on this site.

**NAME OF APPLICANT**

**DESIGNATED ESTABLISHMENT**

University of Cambridge

**PROJECT TITLE (Section 1) (<50 characters including spaces)**

Developmental regulation of physiological systems

**KEYWORDS** (Insert up to 5 keywords)

Fetus, Pregnancy, Developmental physiology, Early life programming

In no more than 500 words:

- Summarise your project (1-2 sentences)
- Explain why you are doing this project. Describe the scientific unknown(s) or clinical or service need you are addressing. Give a brief scientific background or other explanation of why the work is needed.
- Outline the general project plan.
- State why you have to use animals and cannot use non-animal alternatives. Where appropriate, say how you will use non-animal studies in parallel with the project.
- Explain how you will ensure that you use the minimum number of animals. Indicate approximately how many animals of each species you propose to use.
- Explain why the protocols and the way they are carried out should involve the least suffering.
- Explain why you chose the particular species of animal.
- Give a brief description of the procedures to be applied to the animals used in this project and describe the expected adverse effects.
- Outline in a few sentences how science will advance, or people or animals will benefit from this project.
The aim of the project is to identify the factors regulating physiological development during normal and suboptimal environmental conditions with the ultimate goal of improving pregnancy outcome and offspring health. Previous human epidemiological and experimental animal studies have shown that the pattern of intrauterine growth is an important determinant of adult physiological phenotype with impacts on health, disease risk and lifespan. In particular, low birthweight is associated with adult dysfunction and overt disease of the cardiovascular, metabolic and endocrine systems. However, the mechanisms programming physiological development during early life remain largely unknown.

Mothers and their offspring will be exposed to common environmental challenges (such as unbalanced nutrition, hypoxaemia, exposure to stress hormones) before and after birth, with and without therapeutic intervention (e.g. nutritional supplements, drugs, antioxidants), and the consequences for key physiological systems determined in the offspring subsequently by comparison to normal patterns of development. Physiological systems to be monitored include the cardiovascular, metabolic, endocrine, pulmonary and nervous systems plus the placenta. Where possible, in vivo measurements of physiological variables (e.g. blood pressure and flow, metabolite concentrations and uptakes, hormone secretion and bioavailability, electrical activity of muscles and nerves) will be made in normal and challenged offspring via indwelling catheters and measuring devices and related to in vitro analyses of organ and tissue function and of tissue gene and protein expression. Adverse affects are rare, even in surgically instrumented animals, and any discomfort is alleviated by use of analgesics and antibiotics. All animals are inspected regularly and most deliver uneventfully but, when problems arise, veterinary assistance is sought. All protocols start with the least invasive procedures on small numbers of animals and, then, progress to additional numbers or more extensive investigations on the basis of positive results. Power calculations are used to determine minimum numbers required for statistical significance.

As interactions between mother and offspring are dynamic and multifactorial, control of development can only be determined by using conscious animals, which coupled with in vitro analyses allows a comprehensive, integrated assessment from gene to systems level. The project uses five species (sheep, pigs, horses, rats and mice), each of which provides a unique element while collectively allowing identification of unifying mechanisms relevant to human and animal health. Farm animals, unlike rodents, are large enough to be studied before and after birth across multiple physiological systems whereas rodents with their short lifespan are good for identifying critical developmental windows and intergenerational consequences of environmental change. Mice can also be manipulated genetically. These species also differ in litter size, placental morphology, nutrition, metabolic constraints and mechanisms of pregnancy maintenance. In farm species, 4-7 animals are generally used per treatment group, whereas, in rodents, the number is 8-10 to allow for litter variations.

The results will advance understanding of the basic biological processes governing mammalian development with benefits to researchers, clinicians, other health professionals and the population at large. Overall, the output from the project is likely to improve quality of life, reduce health care costs, increase livestock productivity and generally raise awareness of the early life origins of adult health and disease.