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Version Date	

Applicant to complete version date

PPL No.

Home Office

APPLICATION FOR A PROJECT LICENCE

UNDER THE ANIMALS (SCIENTIFIC PROCEDURES) ACT 1986

PROJECT TITLE Section 1 (<50 characters including spaces)

EDUCATION IN CARDIOVASCULAR PHYSIOLOGY

A. PROJECT LICENCE HOLDER

Under ASPA 5(2), project licences are granted to the person who has overall responsibility for the programme of work specified in the licence

a. Title (e.g. Professor, Dr, Mr)	Dr
b. Surname	Ducator
c. Forename(s)	E.
d. Qualifications	BSc; PhD
e. Position or appointment	Senior Lecturer
If you have previously been known by another name, give that name:	
a. Surname	
b. Forenames	

CONTACT DETAILS

a. Address for correspondence *This will normally be the address of the establishment where you are working and must be within the UK* Post Code	Department of Physiology Any University Anytown Anywhere A1 2TT
b. Telephone number and extension	
c. Mobile phone number (optional)	
d. Fax number	
e. E-mail address	

DATE OF BIRTH *(dd, mm, yyyy)*:	01/10/65

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Your relevant knowledge, skills and experience

Give brief details of your knowledge, skills and experience. Indicate your position within your organisation which makes you a suitable person to take responsibility for this programme of work.
I have given lectures on cardiovascular physiology for the past 10 years. I have previously developed, organised and run courses for undergraduate BSc (Honours) students and postgraduate MRes students covering the cardiovascular and respiratory physiology modules that involve both the use of tissues harvested post mortem and living animals, ensuring that learning objectives are clear and relevant to a future career in physiology and /or pharmacology. I have developed monitoring systems which ensure delivery of a high quality course. I have supervised 2 PhD students in cardiovascular physiology to the successful degree completion.

Unless you hold/have held a project licence within the last 5 years, list the relevant modular training (Modules 1, 2, 5) you have completed successfully within the last five years, with dates and enclose copies of the certificates with your application.
Module 1,2 and 5 completed January 2006.

Funding, expertise and other resources

What resources do you have for this project? What expertise, staffing, facilities, equipment and funding are available to you? Has the proposed work been peer-reviewed? If so, by whom?
All staff used to train on these modules will be of at least lecturer grade. All will have had significant prior teaching experience. Assistance will be provided by experienced personal licence holders. Animal costs and bench fees will be covered from resources centrally within the University. All the necessary equipment to conduct the proposed experiments is available and there are good up-to-date teaching laboratory facilities and animal holding facilities on site. Teaching proposals are reviewed by 2 physiologists and the Learning and Teaching co-ordinator.

Personal licences

Provide the number of your current or previously held ASPA personal licence.
70/123456

Project licences

Provide the number(s) and expiry date(s) of your current or previously held (in the last 5 years) ASPA project licence(s).
60/0000 Expired January 2001 70/0000 Expired January 2006

Continuation of work

If you are seeking authority in this application to continue work under one or more current ASPA project licences, provide the number of the relevant expiring project licence(s) and expiry date(s).

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Duration of project

Under ASPA 5(7), the maximum allowable duration of a project licence is five years

Specify the duration of licence you require if less than five years

HOME OFFICE LIAISON CONTACT (if you have one; this must be someone at your establishment)

a. Name	HOLO
b. Telephone number and extension	
c. Fax number	
d. E-mail address	

In your absence, who may we contact if we have any questions about the management of your project?

a. Name	Dr Stan Din
b. Position held	Reader
c. Telephone number and extension	01234 666 666
d. E-mail address	

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B. PLACE(S)

Under ASPA 5(1), a project licence must specify a place or places (so-called 'availabilities') where the regulated procedures will be carried out.

Primary availability

a. PCD number:	60/0000
b. Name of designated establishment:	Any University

Additional availability (if any)

If you intend carrying out regulated work at more than one additional designated establishment paste in a copy of this section for each establishment. **You should note that the relevant parts of this application must complete the ethical review process at each additional establishment and that the Certificate Holder at each of these must complete a declaration in Part F (3) of this application.**

a. PCD number:	N/A
b. Name of designated establishment:	

Why do you need this additional availability? Please indicate whether you intend to move animals between establishments during the course of a series of regulated procedures and if so describe the reasons for such transfers.
N/A

Who will be responsible for supervising the work at this additional establishment?	
a. Title (e.g. Professor, Dr, Mr, Ms)	
b. Surname	
c. Forename(s)	
d. Address for correspondence *This will normally be the address of the establishment where the supervisor is working and must be within the UK* Post Code	
e. Telephone number and extension	
f. Mobile phone number (optional)	
g. Fax number	
h. E-mail address	

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Places other than a designated establishment (PODEs) (if any)

List any place(s) that is not a designated establishment and where you intend to carry out regulated procedures
N/A

Why do you need to undertake regulated work at this PODE?
N/A

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C. SCIENTIFIC BACKGROUND Section 17

Once the licence is granted, you should only need to amend Part C if you are significantly changing your project's purpose.

The total response to this Part must not exceed **2000 words**

Background

- For research projects: What is the current position in your area of work and how will this project help to advance knowledge or meet a clinical need?
- For testing or screening projects: What are the relevant statutory requirements or regulatory guidelines?
- For service or production projects: What are the likely demands for the service or product in the lifetime of the licence?
- Where applicable, summarise relevant progress under any previous project licence.

This Project Licence will enable undergraduate students in the biomedical sciences to be taught the fundamental physiological and pharmacological principles as they relate to the mammalian cardiovascular system, and provide a unique opportunity to interpret complex and often unpredictable responses to drugs within whole integrative physiological systems, which cannot be achieved using other methods.

In the last 5-10 years, the ability of students to start work quickly within academia and industry has declined. One factor in this may include the reduction in the use of *in vivo* experiments. These skills and experiences are essential prerequisites to the future careers of these undergraduates in biomedical research and the pharmaceutical industry. The proposed in vivo studies form part of fully integrated physiology, anatomy, and pharmacology course (see course syllabus appendix). The *in vivo* studies will be conducted in the final year of a Senior Honours degree program. By this stage in their undergraduate career the students will have successfully completed a lecture course in cardiovascular physiology and basic pharmacological principles. This lecture course will be fully integrated with video presentations, computer simulations, and will follow on from dissection studies using cadavers and artificial models in addition to the lectures, seminars and tutorials.
Before conducting the in vivo studies the students will have successfully completed Modules 1-3 and have been granted personal Licences from the Home Office to permit them to conduct the techniques described under supervision from an experienced tutor and Licensee. Ethical consideration of the use of live animal studies and the application of the 3Rs (Reduction, Refinement, and Replacement) (Russell and Burch) in the design of in vivo studies will be considered in Module 1 and is also an integral part of the lecture series on in vivo physiology.

Participation in practical classes involving living animals provides students with crucial knowledge, experience and a mature appreciation of animal experimentation that they will build upon in their future careers. Students on the course are prime candidates for a career in the pharmaceutical industry (typically 5-10% of graduates). The pharmaceutical industry in the UK, one of the UK's major industries, is clearly keen to recruit sufficient individuals with the necessary *in vivo* knowledge. Academic institutes also have need of such individuals. This course will produce individuals appropriately trained for pharmaceutical companies and physiology and pharmacology departments, who are universally supportive of such courses through funding via the British Pharmacological and Physiological Societies.

Thus this course affords the opportunity to apply the pharmacological and physiological concepts the students learned in lectures and seminars to appreciate the complex, inter-related systems responsible for physiological responses, for example, in the control of blood pressure.

The animal models that have been selected are related to major human health problems, in particular cardiovascular diseases. These will remain areas of significant importance to human health and pharmacological R&D in the foreseeable future and is likely to impinge on the lives and careers of all

students on our courses. For instance, the WHO report (ref) that cardiovascular disease is the leading cause of mortality associated with around 12 million deaths each year. Feedback from students in previous years has illustrated that the students retain a more robust and long-lasting knowledge and understanding of the physiological processes than those who do not undertake *in vivo* experiments, thought to be due to "reinforcement by doing". They also gain invaluable first hand experience of the issues behind variability, requiring interpretation and potential changes in experimental design and statistical treatment of experiments. Specific unique learning experiences encountered in these practical classes that cannot be easily modelled in other ways include basic surgical technique, including live tissue handling, control and monitoring of induction and maintenance of anaesthesia, control of haemorrhage, pre-mortem examination of the *in situ* heart and lungs, and management of "complications" such as ventricular fibrillation or broncho-spasm. With a live animal, neither demonstrator nor student knows precisely what will happen next; for example in the present practical classes intravenous administration of acetylcholine to anaesthetised rats may decrease or increase heart rate or have no effect. Uncertainty thereby teaches a respect for accurate and unbiased experimental observation and illustrates that scientific knowledge is not preordained but comes from measurement, analysis and hypothesis testing.

Work conducted under this Project Licence will be reviewed annually by the local Ethics Committee. This annual review process will consider the continued need for such *in vivo* teaching, bearing in mind what alternatives have been developed, and consider the number of animals used in relation to the number of students trained. It will also take into account feedback from students who have completed the course and any constructive changes incorporated into subsequent years.

Benefits

Under ASPA 5(4), the Secretary of State is required to weigh the likely adverse effects on the animals to be used in the programme against the benefit likely to result from the programme to be specified in the licence.

What are the likely benefits of this project? Why are they worthwhile?

1. Students will acquire improved understanding of the complex processes involved in cardiac physiology and the modulatory effects of known drugs.
2. Provision of bioscience graduates with a thorough appreciation of *in vivo* experimental design, statistical analysis of data obtained.
3. Ensure students gain experience of due ethical consideration of the live animals used in scientific studies, and in the application of the 3Rs.

Future scientists require a sound knowledge and understanding of the normal physiological processes involved in the maintenance of normal cardiovascular physiology and function to enable them to design studies aimed the expansion of physiological knowledge or the identification of novel drugs or therapeutic intervention pathways. The power of using whole animals in experiments is in the integrated response observed as a result of discreet events or stimuli. For example, a drug administered for one purpose can often have other important effects in non-target tissues, which cannot be observed in non-sentient samples. A further benefit of incorporating experiments using animals is that the students will develop an understanding of the strengths and weaknesses of biological experimentation. This will allow them to understand and appreciate the limitations of pharmacological research and development, and the validity of drug discovery. Students will also observe first hand the variability inherent in biological measurements obtained from live animals in experimental settings. Students who have undergone this or similar training should be able more quickly and actively to participate in ongoing research programmes.

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References

List up to 10 key references and/or regulatory guidelines supporting the need for the work and/or benefits set out above and relevant references for any specific models proposed in your programme of work.
Russell and Burch ref - Home Office Supplementary Guidance to Applicants for Project Licences: Projects for Educational Purposes - WHO Report ref - From Guinea pig to Computer Mouse Nick Jukes & Mihnea Chiuia Pub Interniche ISBN 1-904422-000-4

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D. PLAN OF WORK Section 18

The total response to this Part must not exceed **2000 words**

For the purposes of this application, a "plan of work" is defined as a series of steps designed to achieve specified scientific purposes.

Purpose

What are you aiming to achieve, find out, establish, or produce by undertaking this project? Express this either as a single programme purpose, or as an overall aim with one or more key elements. The purpose should be specific to this project, unambiguous, realistic and achievable.
To educate undergraduate students in the biomedical sciences in the field of cardiovascular physiology with an emphasis on the following fundamental areas: 1. Expansion of knowledge and understanding of the physiological and pathophysiological integrated responses in the cardiovascular system. 2. Develop and appreciation of the issues required to successfully undertake well controlled *in vivo* experiments, including ethics, animal welfare and the 3Rs, and legislative requirements. 3. Facilitate the development of the critical interpretation of the integrated physiological responses arising from specific interventions.

Project plan

• Provide an outline of the stages of the plan of work and indicate clearly, by using the protocol numbers, how each protocol will be used to achieve your objectives. Where it would aid clarity, illustrate the steps of the programme using an annotated flow diagram or process map. • Indicate how in vitro and ex vivo work integrates with the in vivo work, the relationship between each component of the project and the sequence of the work. • In broad terms, what data or products are needed to achieve the purpose of the project? • How will those data or products be generated?
Students will have successfully completed a lecture course (including videos and computer simulations of cardiovascular physiology) before commencing the practical classes involving the use of living animals. The classes are staged with progression from isolated preparations to whole living animals to enable the students to effectively build their knowledge up from lecture studies, to in vitro cell cultures of smooth muscles (given earlier in the course – see attached timetable), to *ex vivo* isolated organs, before finally conducting studies on living animals. The latter step reinforces the integrated nature of the mechanisms controlling cardiac and respiratory physiology. Each student will have a note book and will generate unique data sets from the animal. Before conducting the *in vivo* studies the students will have successfully completed Modules 1-3 and have been granted personal Licences from the Home Office to permit them to conduct the techniques described under supervision from an experienced tutor and Personal Licensee. Ethical consideration of the use of live animal studies and the application of the 3Rs (Reduction, Refinement, and Replacement) (Russell and Burch) in the design of *in vivo* studies will be considered in both the training Module 1 and is an integral part of the lecture series on in vivo physiology. Initially students will conduct a practical that will involve heart preparations to demonstrate the direct inotropic and chronotropic effects of agents with known modulatory effects on the isolated heart. The organs will be prepared by experienced Personal Licensees. It is necessary to administer an anticoagulant prior to preparing an isolated heart preparation to ensure clotting does not interfere with the microcirculation. The students will investigate responses by administering the substances via the physiological perfusate to the in vitro preparation. Thereafter all practical classes will use animals that are under terminal general anaesthesia.

The anaesthetic regime will be designed by the tutor and personal licensee in consultation with the NVS, and adequate anaesthesia will be assured by an experienced personal licensee.
Rats have been used in these practical classes for many years as their physiological systems are well characterised, their responses are similar to those of humans, and they are used as experimental models in a number of disease models and efficacy and safety evaluation trials of novel pharmaceutical compounds destined for human use. Physiological conditions in the animal will be maintained with the aid of fluid therapy and heating pads for core body temperature. One or two arteries (including advancement of catheter to the heart) and one or two veins will be surgically cannulated to allow accurate monitoring of blood pressure, administration of test and control substances, and respiration. The trachea may be cannulated to allow artificial respiration and / or monitor airways pressures. Subcutaneous ECG leads will be used to monitor modulations in cardiac electrical activity. Nerves relating to the cardiovascular system may be exposed surgically, and electrodes or topical substances used to stimulate or block. All surgical steps will be conducted by course demonstrators who are experienced Licensees. Using these means it will be possible to accurately assess the effects of exogeneous factors such as known pharmaceutical compounds or electrical impulses to demonstrate the complex mechanisms controlling cardiac physiology. In some animals arterial sampling will be performed to monitor oxygen levels and levels of the substances known to be involved in physiological control of cardiovascular function.
Each entire practical class will last up to 8 hours and during this time the participation of the students will be limited non-surgical techniques such as the administration of well characterised substances and the withdrawal of blood samples. This practical class will instil a thorough knowledge and understanding of the physiological and pathophysiological integrated responses in the cardiovascular system.

The data generated will be analysed by the student, and conclusions drawn, to facilitate the development of the critical interpretation of the integrated physiological responses arising from specific interventions. In groups, the students will share their individual data sets to enable statistical analysis of the data generated and this lead to an improved understanding of experimental design and data analysis. The completed lab books will be marked and the mark will contribute to the final degree
The in vivo practical classes take place after the lecture course and in vitro classes (full time-table attached) the students will be better able to apply the knowledge they have learned to the observations in the *in vivo* classes thus improving their interpretation skills.
The students provide written, anonymised, feedback on the perceived benefits of the practical in vivo classes after the marking process in complete. This feedback is taken into consideration at the annual review of the Project Licence by the local Ethical Review Committee.
Following successful completion of this degree course we request details of the careers that the graduates enter into. We then conduct follow-up careers information after 12 months to determine how many remain in the biomedical and pharmaceutical sectors. Whilst this data is often incomplete, the information is collated and also reviewed annually by the local Ethical Review Committee to give further information on the career paths taken by graduates who have undertaken this course in order to ensure that the animals have been used for adequate benefit.

THE 3Rs

Under ASPA 5(5)(a), the Secretary of State cannot grant a project licence unless he/she is satisfied that the purpose of the programme to be specified in the licence cannot be achieved satisfactorily by any other reasonably practicable method not entailing the use of protected animals.

Under ASPA 5(5)(b), the Secretary of State cannot grant a project licence unless he/she is satisfied that the regulated procedures to be used are those which use the minimum number of animals, involve animals with the lowest degree of neurophysiological sensitivity, cause the least pain, suffering, distress or lasting harm, and are most likely to produce satisfactory results.

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Replacement

- Why is it not possible to achieve the objectives of your project without using animals?
- What alternatives have you considered and why are they not suitable? What alternatives will be used in achieving your objectives?

- Complexity of the *in vivo* systems and responses involved in the maintenance of normal cardiovascular function cannot be fully and accurately reproduced in vitro and the action of drugs on the whole body system requires the use living animals.
- Alternatives have not been rejected but instead form an integral part of the course preceding the in vivo studies described in this Project Licence.
- These will include video presentations, demonstrations on cadavers and use of both in-vitro organs harvested post mortem and plastic models of the heart and blood vessels.
- The effects of some chemicals and drugs on cardiovascular cells, for example smooth muscle cells, will be conducted on cell lines *in vitro*.

Reduction

- What measures have been or will be taken to ensure that the minimum number of animals will be used in this project?
- Explain the principles of experimental design you will use and any sources of advice you will consult e.g. on statistics

- The experiments proposed are built on similar studies that we have performed in practical classes over the past 5 years. The design has been based on studies published in peer reviewed scientific journals and have incorporated advice on experimental design for analysis of class data from a professional biostatistician in our University.
- We anticipate running this course four times for 10 or 20 students at each course.

Numbers of animals used in this project will be reviewed annually as part of our Ethical Review Process.

Refinement

- Explain your choice of species, model(s) and method(s). Explain why they are the most refined for the intended purpose.
- How will you minimise animal suffering in order to achieve your objectives?
- Provide specific justification for any substantial severity protocols

- All experiments are conducted under terminal general anaesthesia to minimise the welfare costs to the animals used.
- We consider that there is not a more refined way to conduct the in vivo training studies described in this Project Licence. We will, however, regularly review the choice of general anaesthetic agent(s), in consultation with the NVS, to ensure that the agent(s) and route(s) used are the ones which will cause the minimum of discomfort and distress to the animals during the induction of anaesthesia without compromising the educational objectives.

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SPECIAL SPECIES

Cats, dogs, primates and equidae

Under ASPA 5(6), a licence cannot authorise the use of cats, dogs, primates or equidae unless no other species is suitable or it is not practicable to obtain animals of another suitable species.

If you intend using cats, dogs, primates or equidae, explain why no other species is either suitable for the purpose or practicably available
N/A

Endangered species

Under ASPA 10(3)(c), no vertebrate of an endangered species may be used unless the Secretary of State considers an exception justified.

If you intend using an endangered species, explain why no other species is either suitable for the purpose or available
N/A

Animals taken from the wild

Under ASPA 10(3)(d), no protected animal taken from the wild may be used unless the Secretary of State considers an exception justified. *Note that animals undergoing work in the wild are <u>not</u> regarded as having been taken from the wild.*

If you intend using wild-caught animals, explain why no other animals are available or suitable for the purpose
N/A

USE OF NEUROMUSCULAR BLOCKING AGENTS

Under ASPA 17, neuromuscular blocking agents may only be used if expressly authorised by the personal and project licences under which the relevant regulated procedure is carried out and may not be used instead of an anaesthetic.

If you intend using neuromuscular blocking agents in any part of this project give details of how they will be used and provide justification for their use.
N/A

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TRANSFER OF ANIMALS – the following gives authority to transfer animals from a previous project to this project, and/or to export / import rodents, normal and genetically altered, genetically altered zebra fish and genetically altered Xenopus sp. Provided these conditions can be met there is no need to seek prior authorisation for such transfers from the Home Office.

Authority is hereby given to acquire rodents (including genetically altered animals), genetically altered zebra fish and genetically altered Xenopus sp. from non-designated establishments and transfer animals undergoing regulated procedures under the licence(s) specified at 'Continuation of Work' in part A to this project for continued use in the relevant protocols.

Export of genetically altered rodents, genetically altered zebra fish and genetically altered Xenopus sp
Genetically altered rodents, genetically altered zebra fish and genetically altered Xenopus sp. bred and/or maintained under the authority of this project may be transferred to scientific establishments outside the United Kingdom only if:
1. The transfer will be made to a recognised scientific research establishment with a scientific requirement for genetically altered animals (or their controls) of that type; and where appropriate veterinary care can be provided as necessary; and
2. Sending tissue, gametes or embryos is not practicable or carries a higher potential welfare cost than moving live animals; and
3. Animals will be transported in accordance with all relevant regulations regarding welfare of animals in transit or the import or export of animals; and
4. Animals will be inspected by a competent person before transfer; and
5. A veterinary surgeon will confirm that he/she is not aware of any reason why these animals might suffer by virtue of the fact of being moved to another recognised scientific establishment.
6. Any transport related problems with the welfare of the animals will be notified to the Home Office promptly.

Acquisition of rodents (including genetically altered animals) genetically altered zebra fish and genetically altered Xenopus sp. from non-designated establishments
Rodents (including genetically altered animals), genetically altered zebra fish and genetically altered Xenopus sp. may be obtained from recognised scientific and breeding establishments outside the United Kingdom for use under this project licence only if:
1. The purpose for which animals are imported is consistent with the programme of work specified on the schedule; and
2. Attempts have been made to obtain the animals from Designated Sources in the UK but they are not available or animals from Designated Sources in the UK are not suitable for the purpose; and
3. Receiving tissue, gametes or embryos is not practicable or carries a higher potential welfare cost than moving live animals; and
4. Animals are transported in accordance with all relevant regulations regarding welfare of animals in transit or the import or export of animals; and
5. Animals will be inspected by a competent person after transfer
6. Any transport related problems with the welfare of the animals will be notified to the Home Office promptly.

Details of each transfer shall be recorded and made available to the Home Office on request. These records should contain the information set out in paragraph 4.30 of the HO guidance, and include the reasons for obtaining animals from non-designated sources.

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E. PROTOCOLS Section 19

Under ASPA 5(1), a project licence must authorise the application of specified regulated procedures to animals of specified descriptions.

The term "protocol" is used to describe a single or a series of regulated techniques applied for a particular experimental or other scientific purpose to a protected animal. In most cases a protocol will involve all regulated procedures applied to the animal until the animal is killed or released from the controls of ASPA. Depending on the complexity of your work you may need one or several protocols. Different protocols are usually needed where different types of experimental procedures are to be used to achieve your objective(s). For example a project licence may have a protocol for the breeding and maintenance of genetically altered animals. These animals may then be transferred to another protocol in which, for example, treatments are evaluated in disease models.

ASPA 5(5)b states that: The Secretary of State shall not grant a project licence unless he is satisfied that the regulated procedures to be used are those which use the minimum number of animals, involve animals with the lowest degree of neurophysiological sensitivity, cause the least pain, suffering, distress or lasting harm, and are most likely to produce satisfactory results.

To add extra lines to the Summary place the cursor at the end of the line and press ENTER

To add extra protocols copy and paste new protocol sheets into the application. Each protocol should start on a new page.

Summary. Section 19a

Protocol no.	Short title	Species of animals	Estimated numbers over the duration of the project	Severity limit
1	Control of heart rate and blood pressure	Rat	80	Unclassified
2	Effects of cardiac drugs	Rat	80	Mild
3	Heart preparation	Rat	40	Mild

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PROTOCOL NUMBER. Section 19b : 1

Title:	Control of heart rate and blood pressure
Species of animals (state if genetically altered):	Rat
Severity limit:	Unclassified

If the animals have been used, bred or surgically prepared under the authority of this or any other project licence, briefly describe what has been done to them and indicate whether the use now proposed represents 'continued-use' or 're-use' - refer to the Home Office Guidance on the Operation of the Animals (Scientific Procedures) Act 1986 and Home Office guidance on Use, Continued Use and Re-use of Animals.

N/A

List each of the steps in this protocol. Note: It is accepted that the order of steps may be varied according to scientific need. Indicate which steps are optional and for each give the anaesthetic code. If appropriate indicate the method of killing, Schedule 1 or non-Schedule 1. Give brief details of non-Schedule 1 methods e.g. perfusion fixation (AC).

1. Induction and maintenance of general anaesthesia (AC).
2. Tracheostomy and tracheal intubation (AC).
3. Cannulation of the femoral and/or carotid artery(ies) (AC).
4. Cannulation of the femoral and/or jugular vein(s) (AC).
5. Optional application or insertion of ECG leads under the skin (AC).
6. Administration of substances with known agonistic or antagonistic effects on arterial blood pressure and heart rate by the subcutaneous, intraperitoneal, intramuscular or intravenous routes. (AC).
7. Optional exposure of vagus and/or cardio-acceleratory nerve(s) and application of electrical or chemical stimulation or block (AC).
8. Optional blood sampling by superficial venepuncture or by previously implanted cannulae (AC).
9. Optional section of the nerve(s) affecting the cardiovascular system (AC).
10. Animal killed by a Schedule 1 method.

Total duration 6-8 hours.

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Fate of animals not killed at the end of the protocol

Indicate the proposed fate of animals which are not killed at the end of the protocol.

- ☐ **Continued use in another protocol under this or another project licence** - give details below and ensure that you give an appropriate cross reference in the protocol sheet under which the continued use will occur.
- ☐ **Kept alive at the designated establishment.** Note that any subsequent re-use must be authorised in the relevant project licence.
- ☐ **Discharge from the controls of the Act at a PODE site** – e.g. setting free in the wild.
- ☐ **Other** – give details below

Adverse effects

List the likely adverse effects of each of the regulated procedures described above. Indicate how you will manage these effects to minimise severity. There is no need to list uncommon or unlikely adverse effects or effects from procedures that cause no more than transient discomfort and no lasting harm, for example intravenous injection. For each adverse effect indicate:

- the likely incidence
- how the adverse effect will be recognised
- the measures you will take to prevent or control occurrence and severity
- practicable and realistic humane end-points.

Transient discomfort during induction of anaesthesia is expected in all animals.
The entire experiment is conducted under terminal general anaesthetic. Risk of death from anaesthesia is estimated to be < 1%. Heating blankets and fluid therapy will be provided throughout the experiment to ensure physiological stability. Depth of anaesthesia will be assessed by experienced licensees throughout the study using appropriate means, eg pulse-oximetry.
The cardiac agents proposed for use are well characterised previously and are not expected to produce any adverse effects.
Risk of major haemorrhage is very rare <0.01% and animals will be killed by a Schedule 1 method if this occurs. Minor haemorrhage will be controlled by pressure or ligation of small blood vessels as required.

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PROTOCOL NUMBER: 2

Title:	Effects of cardiac drugs
Species of animals (state if genetically altered):	Rat
Severity limit:	Mild

If the animals have been used, bred or surgically prepared under the authority of this or any other project licence, briefly describe what has been done to them and indicate whether the use now proposed represents 'continued-use' or 're-use' - refer to the Home Office Guidance on the Operation of the Animals (Scientific Procedures) Act 1986 and Home Office guidance on Use, Continued Use and Re-use of Animals.
N/A.

List each of the steps in this protocol. *Note: It is accepted that the order of steps may be varied according to scientific need.* Indicate which steps are optional and for each give the anaesthetic code. If appropriate indicate the method of killing, Schedule 1 or non-Schedule 1. Give brief details of non-Schedule 1 methods eg perfusion fixation (AC).
1. Optional administration of drug or drug combinations with known effects on cardiac function for up to five days by inclusion in the drinking water (AA). 2. Induction and maintenance of general anaesthesia (AC). 3. Tracheostomy and tracheal intubation (AC). 4. Cannulation of the femoral and/or carotid artery(ies) (AC). 5. Cannulation of the femoral and/or jugular vein(s) (AC). 6. Optional application or insertion of ECG leads under the skin (AC). 7. Administration of substances with known agonistic or antagonistic effects on arterial blood pressure and heart rate by the subcutaneous, intraperitoneal, intramuscular or intravenous routes. (AC). 8. Optional exposure of vagus and/or cardio-accelaratory nerve(s) and application of electrical or chemical stimulation or block (AC). 9. Optional blood sampling by superficial venepuncture or by previously implanted cannulae (AC). 10. Optional section of the nerve(s) affecting the cardiovascular system (AC). 11. Animal killed by a Schedule 1 method. Total duration 6-8 hours.

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Fate of Animals Not Killed at the End of the Protocol

Indicate the proposed fate of animals which are not killed at the end of the protocol.

- ☐ **Continued use in another protocol under this or another project licence** - give details below and ensure that you give an appropriate cross reference in the protocol sheet under which the continued use will occur.
- ☐ **Kept alive at the designated establishment**. Note that any subsequent re-use must be authorised in the relevant project licence.
- ☐ **Discharge from the controls of the Act at a PODE site** – e.g. setting free in the wild.
- ☐ **Other** – give details below

Adverse effects

List the likely adverse effects of each of the regulated procedures described above. Indicate how you will manage these effects to minimise severity. There is no need to list uncommon or unlikely adverse effects or effects from procedures that cause no more than transient discomfort and no lasting harm, for example intravenous injection. For each adverse effect indicate:

- the likely incidence
- how the adverse effect will be recognised
- the measures you will take to prevent or control occurrence and severity
- practicable and realistic humane end-points.

Transient discomfort during induction of anaesthesia is expected in all animals.
The entire experiment is conducted under terminal general anaesthetic. Risk of death from anaesthesia is estimated to be < 1%. Heating blankets and fluid therapy will be provided throughout the experiment to ensure physiological stability. Depth of anaesthesia will be assessed by experienced licensees throughout the study using appropriate means, eg pulse-oximetry.
The cardiac agents proposed for use are well characterised previously and are not expected to produce any adverse effects.
Risk of major haemorrhage is very rare <0.01% and animals will be killed by a Schedule 1 method if this occurs. Minor haemorrhage will be controlled by pressure or ligation of small blood vessels as required.

Version Date	

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PROTOCOL NUMBER: 3

Title:	Heart preparation
Species of animals (state if genetically altered):	Rat
Severity limit:	Mild

If the animals have been used, bred or surgically prepared under the authority of this or any other project licence, briefly describe what has been done to them and indicate whether the use now proposed represents 'continued-use' or 're-use' - refer to the Home Office Guidance on the Operation of the Animals (Scientific Procedures) Act 1986 and Home Office guidance on Use, Continued Use and Re-use of Animals.

N/A.

List each of the steps in this protocol. *Note: It is accepted that the order of steps may be varied according to scientific need.* Indicate which steps are optional and for each give the anaesthetic code. If appropriate indicate the method of killing, Schedule 1 or non-Schedule 1. Give brief details of non-Schedule 1 methods eg perfusion fixation (AC).

1. Optional subcutaneous or intraperitoneal injection of an anti-coagulant (eg heparin) in physiological saline on a single occasion. Volume will not exceed LASA Guidelines. (AA).
2. Induction of general anaesthesia (AC).
3. Thoracotomy and removal of heart whilst still beating (AC).

Version Date	

Applicant to complete version date

PPL No.

Fate of Animals Not Killed at the End of the Protocol

Indicate the proposed fate of animals which are not killed at the end of the protocol.

- ☐ **Continued use in another protocol under this or another project licence** - give details below and ensure that you give an appropriate cross reference in the protocol sheet under which the continued use will occur.
- ☐ **Kept alive at the designated establishment**. Note that any subsequent re-use must be authorised in the relevant project licence.
- ☐ **Discharge from the controls of the Act at a PODE site** – e.g. setting free in the wild.
- ☐ **Other** – give details below

Adverse effects

List the likely adverse effects of each of the regulated procedures described above. Indicate how you will manage these effects to minimise severity. There is no need to list uncommon or unlikely adverse effects or effects from procedures that cause no more than transient discomfort and no lasting harm, for example intravenous injection. For each adverse effect indicate:

- the likely incidence
- how the adverse effect will be recognised
- the measures you will take to prevent or control occurrence and severity
- practicable and realistic humane end-points.

Transient discomfort during induction of anaesthesia is expected in all animals.
The entire experiment is conducted under terminal general anaesthetic. Risk of death from anaesthesia is estimated to be < 1%. Depth of anaesthesia will be assessed by experienced licensees throughout the study using appropriate means, eg pulse-oximetry.
The anticoagulant agents proposed for use are well characterised previously and are not expected to produce any adverse effects at the dose, route, and volumes given.
Risk of major haemorrhage is very rare <0.01% and animals will be killed by a Schedule 1 method if this occurs. Minor haemorrhage will be controlled by pressure or ligation of small blood vessels as required.

Version Date	

Applicant to complete version date

PPL No.

F. DECLARATIONS

1. Declaration by the applicant

I hereby apply for a project licence in respect of the studies described in this application form. To the best of my knowledge and belief all the information I have provided in this application form is correct and complete.

Signature of applicant:

Date:

2. Declaration by the certificate holder at the primary availability

I confirm that this application has completed my establishment's ethical review process.

If licensed, I accept responsibility for ensuring that suitable facilities will be available in accordance with the 'Code of Practice for the Housing and Care of Animals Used in Scientific Procedures'. I am aware of, and will carry out, my responsibilities as set out in the published 'Guidance on the Operation of the Animals (Scientific Procedures) Act 1986 (HC321)'.

Name of PCD holder:

Signature of PCD holder:

Date:

3. Declaration by the certificate holder at the additional availability

I confirm that the relevant parts of this application have completed my establishment's ethical review process.

If licensed, I accept responsibility for ensuring that suitable facilities will be available in accordance with the 'Code of Practice for the Housing and Care of Animals Used in Scientific Procedures'. I am aware of, and will carry out, my responsibilities as set out in the published 'Guidance on the Operation of the Animals (Scientific Procedures) Act 1986 (HC321)'.

Name of PCD holder:

Signature of PCD holder:

Date:

Make further copies of box 3 if you have more than one additional availability. Each additional availability must have a declaration signed by the relevant Certificate Holder.

Version Date	

Applicant to complete version date

PPL No.

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/. Examples of other abstracts can be viewed on this site.

NAME OF APPLICANT

DR E Ducator

DESIGNATED ESTABLISHMENT

Any University

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

Education in cardiovascular physiology

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.

This Project Licence will enable undergraduate students in the biomedical sciences to be taught the fundamental physiological and pharmacological principles as they relate to the mammalian cardiovascular system, and provide a unique opportunity to interpret complex and often unpredictable responses to drugs within whole integrative physiological systems, which cannot be achieve using other methods.

The practical component of the courses requiring whole animals follows lectures courses, video presentations, computer simulations and demonstrations on isolated tissues. The cardiovascular model selected reflects that this is a major human health problem. For instance, the WHO Report that cardiovascular disease is the leading cause of mortality with some 12 million people dying each year. Without increased treatment and research the incidence of this disease is likely to increase in the future. All of the studies involving the use of live animals are conducted under terminal general anaesthesia to minimise the welfare costs to the animals used. The experiments are well characterised and designed to involve the minimum number of animals consistent with achieving statistically significant results. The physiological measurements obtained in the experiments are vital for life and include heart rate, blood pressure, and rate of breathing. Each group of students will generate their own set of data from the experiments allowing them to learn about statistical analysis and experimental design.

Participation in practical classes involving living animals provides students with crucial knowledge, experience and a mature appreciation of animal experimentation that they will build upon in their future careers. Students on the course are prime candidates for a career in the pharmaceutical industry (typically 5-10% of graduates). The pharmaceutical industry in the UK, one of the UK's major industries, is clearly keen to recruit sufficient individuals with the necessary *in vivo* knowledge. Academic institutes also have

need of such individuals. This course will produce individuals appropriately trained for pharmaceutical companies and physiology and pharmacology departments in academic institutions.
(316 words).