Animals (Scientific Procedures) Act 1986

Non-technical summaries for project licences granted during 2016

Volume 31

Projects with a primary purpose of: Higher education or training for the acquisition, maintenance or improvement of vocational skills.

Project Titles and keywords

1. **Undergraduate and Postgraduate Education and Training in Integrative Physiology and Pharmacology**
    - Vocational training, *in vivo* skills, animal models, drug development, capacity building

2. **Cardiac Injection Training in Terminally Anaesthetized Pigs**
    - Pigs, training

3. **Training of Practising Surgeons in Microsurgery**
    - Microsurgery, training

Project 1	**Undergraduate and Postgraduate Education and Training in Integrative Physiology and Pharmacology**	
Key Words (max. 5 words)	Vocational training, *in vivo* skills, animal models, drug development, capacity building	
Expected duration of the project (yrs)		
Purpose of the project as in ASPA section 5C(3) (Mark all boxes that apply)		Basic research
		Translational and applied research
		Regulatory use and routine production
		Protection of the natural environment in the interests of the health or welfare of humans or animals
		Preservation of species
	X	Higher education or training
		Forensic enquiries
		Maintenance of colonies of genetically altered animals
Describe the objectives of the project (e.g. the scientific unknowns or scientific/clinical needs being addressed)	The objective of this license is to provide advanced education and training for undergraduate and postgraduate students. Providing this comprehensive education will enable students to gain a balanced and well informed training in animal procedures.	
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)?	This educational programme will provide students with specialist education in *in vivo* research techniques, the principles behind carrying out whole animal procedures and legal and ethical issues associated with experiments involving a living animal. Alternatives to the current proposed whole-animal experiments have been considered and will continue to form a large component of the practical classes, however, to achieve academic excellence, a component of whole animal studies is felt to be essential because alternatives cannot replace first hand education. Our own experience has been that student are much more able to engage with the ethical issues around experiments when they are working with living animals. Specifically, this license will enable the School to continue to provide tissue for *ex vivo* studies, *in vivo* demonstrations and intensive training courses for undergraduate and postgraduate students. A steady flow of new, suitably qualified and experienced researchers is crucial for medical research and drug	

	development. The potential benefits of these courses are both short (immediate educational outcomes, appreciation of the theoretical and practical aspects of *in vivo* research) and long-term (strengthening UK capacity in *in vivo* skills, sustaining UK research excellence).
What species and approximate numbers of animals do you expect to use over what period of time?	Adult rat – 150 Adult mouse – 600 Guinea pig – 10
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 selected protocols for this educational programme have all been used previously meaning unexpected adverse events are unlikely. Some adverse effects are expected as part of the procedures. For the three protocols using conscious procedures, the animals will experience some stress and mild discomfort associated with the drug administration procedure but this is minimised by good technique. A very small risk of haemorrhage is associated with the injection but this is low and animals are carefully monitored after injection and killed if signs of bleeding are seen. No adverse effects of the drug treatments. These protocols are all mild. The remaining protocols are all non-recovery and animals will only experience transient suffering associated with induction of anaesthesia. There are potential risks associated with general anaesthetic but these are low level (premature recovery <1%, overdose <2%) and mitigated by careful monitoring of the animal. The length of the protocols and associated drug treatments can result in death of the animals before the end of the experiment (<15%). The animals will remain anesthetised throughout and therefore will not experience any suffering. At the end of the experiments, all animals will be killed by a schedule one method, usually anaesthetic overdose.
Application of the 3Rs	
1. Replacement State why you need to use animals and why you cannot use non-animal alternatives	The overall aim of this licence is to provide training for students undertaking study in Biomedical Science degrees to gain experience and training in whole animal pharmacology and the experimental procedures associated with such experiments. This can only be achieved using animals. The *in vivo* work is supported by a large sections of the course

	which use *in vitro* techniques. The species, which have been chosen, represent the most appropriate species for each model. The choice of the models and therefore the species that have been included in this licence application was made based on achieving the specific learning objective. The inclusion of the three different rodent species will also enhance the understanding of the students in terms of animal research, as they will be learning about the advantages and disadvantages of using a particular species for a specific experimental objective. The majority of practical classes (~95%) use alternative methods including computer simulations and human volunteer experiments. Over the last year, we have initiated a programme to develop on-line learning resources to support the in vivo course. This has enabled us to replace some of the protocols and animals used under the previous educational PPL. We will roll this out over the next two years so that more *in vivo* education can be delivered without increasing the use of living animals.
2. Reduction Explain how you will assure the use of minimum numbers of animals	The numbers of animal that will be used annually to achieve the educational objectives of this licence are small relative to the educational value that will be achieved. The number of procedures that will be used as demonstrations has been limited to the minimum consistent with the learning objectives, normally using less than 8 animals per year, 40-60 Biomedical science students will gain first-hand experience of *in vivo* pharmacology and physiology. The design of the *in vivo* course has considered the 3Rs. The choice of species has been restricted to rodents as these are the lowest sentient mammalian species and are also the most widely used species in biomedical research. Alternative species, from lower classes would not be suitable for education in mammalian biology. The number of procedures used and the number of animals used for each procedure has also been minimised. Biostatistics have not been involved in the design of these experiments as the overall numbers used are dependent on the number of students taking the practical. Students will usually work in pairs or small groups to enable them to gain experiential learning

	but without the requirement for one animal per student. The number of animals used in the conscious experiments has been further reduced by organising the students to carry out different parts of the experiment with collation and discussion of the data at the end. For the demonstration sessions, students work in small groups, usually 5-10 and a single set-up is used for ~6 demonstrations. Data from each year are retained and collated so that students can be shown the pooled data and undertake analysis of an appropriately powered data set. Overall numbers will be dependent on the number of students educated each year, expected ~30 undergraduates and up to 20 post-graduates.
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.	These protocols and the choice of species are based on achieving the objectives of providing experiential learning for biomedical science students in systems physiology and pharmacology. The students are primarily learning about human physiology and pharmacology and therefore require experiments using mammalian species. One protocol involves the use of a pre-drug treatment to prepare uterine tissue for *ex vivo* experiments. Without this drug treatment, the number of viable preparations which can be obtained is reduced. The conscious studies use the mouse which is the lowest sentient mammalian species. For the cardiovascular practical we have requested permission to use rats as these are more reliable in terms of the surgical set-up and arising data, mainly due the greater size for cannulation and better anaesthetic stability. Use of mice for these protocols would potential lead to more failures. The guinea pig is necessary for the respiration experiment as it provides a better model of human respiration. The animal models chosen are mild or non-recovery and will provide data that meets the objectives with the minimum suffering. Wherever possible, terminal anaesthesia will be used and only where there is an educational justification for the use of a conscious animal will this protocols been used. All procedures use methods and include end points which ensure they are non- recovery or have a severity limit of mild. A non-mammalian species would not be appropriate for these objectives, as the work needs to correlate directly with the mammalian biology.

Project 2	**Cardiac Injection Training in Terminally Anaesthetized Pigs**	
Key Words (max. 5 words)	Pigs, training	
Expected duration of the project (yrs)	5 years	
Purpose of the project as in ASPA section 5C(3) (Mark all boxes that apply)		Basic research
		Translational and applied research
		Regulatory use and routine production
		Protection of the natural environment in the interests of the health or welfare of humans or animals
		Preservation of species
	x	Higher education or training
		Forensic enquiries
		Maintenance of colonies of genetically altered animals
Describe the objectives of the project (e.g. the scientific unknowns or scientific/clinical needs being addressed)	The purpose of this application is to allow medical cardiologists to train on anaesthetized pigs to develop the skills required to safely inject stem cells into the inside of the heart. Stem cells are undifferentiated cells that develop into specialized tissue when implanted in damaged organs. The potential growth of specialized heart tissue after stem cell injection into hearts damaged by infarction (heart attacks) is exciting because normally, the heart tissue damaged during heart attacks heals imperfectly, and so fails to function effectively. Effective training will allow human cardiologists to apply stem cells more safely to humans and permit a more efficient appraisal of this new 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)?	Effectively training cardiologists to accurately and safely inject stem cells into the hearts of pigs will allow them to go on to study the full benefits of stem cell treatments in humans. The cardiologists will access the heart via the large blood vessels that flow into the heart, as they would in a human patient.	
What species and approximate numbers of animals do you expect to use over what period of time?	Pigs 27 over 5 years	
In the context of what you propose to do to the animals,	All the animals will be anaesthetised only once and will be killed under anaesthesia without being allowed	

what are the expected adverse effects and the likely/expected level of severity? What will happen to the animals at the end?	to recover. They will not experience anything more unpleasant than a single injection in their muscles to sedate them in preparation for general anaesthesia.
Application of the 3Rs	
1. Replacement State why you need to use animals and why you cannot use non-animal alternatives	Before being allowed to use pigs, approved trainees will practice using the equipment on a plastic (non-animal model) of the heart and blood- vessels. This model is plastic and inert, so lacks the "feel" of a real-life patient with a constantly beating heart. Training will also occur using hearts collected from pigs killed for other purposes. Only after showing competence using models will they be allowed to conduct this technique on the beating heart of an anaesthetised pig. Learning to make injections into the beating heart of a human who has recently suffered a heart attack can only be done in the whole human or an animal of similar size, which in this case is an anaesthetised pig.
2. Reduction Explain how you will assure the use of minimum numbers of animals	People to be trained will undergo a rigorous screening process and will be trained in a way that ensures the minimum number or animals will be required to ensure that their competency (or otherwise) can be identified. Each animal will be used to train two cardiologists. The training schedule is explicit, demanding and comprehensive and has been designed by the company which developed the cell delivery system. Experienced trainers will be present at all training sessions; and will certify whether trainees have successfully completed the strict, training protocol. Whilst anaesthetized, the animals will be managed in ways as close as possible to the methods used to look after human patients.
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	The anaesthetic techniques that will be used in this work are in widespread use and are of proven efficacy. All animals will be anaesthetized for all studies, from which they will not be allowed to recover. Consequently, they will typically experience nothing more unpleasant than a single injection that in some pigs may cause mild and momentary discomfort.

Project 3	Training of Practising Surgeons in Microsurgery
Key Words	Microsurgery, Training
Expected duration of the project	5 year(s) 0 months

Purpose of the project (as in ASPA section 5C(3))

Purpose

Yes (f) higher education or training for the acquisition, maintenance or improvement of vocational skills;

Describe the aims and objectives of the project (e.g. the scientific unknowns or scientific/clinical needs being addressed):

The Microsurgical Training programme provides a week of hands on experience for qualified surgeons to learn microvascular anastomoses of blood vessels as small as those of the finger. This service is needed as surgeons are now expected to be able to attach severed hands, fingers and arms and to reconstruct body parts after disease or injury. The microsurgery expertise required to do this cannot be learnt adequately on human subjects.

Previous trainees have become extremely specialised microsurgeons (these include cleft palate repair, hand reconstruction, free-flaps, ear reconstruction and facial reanimation techniques) and this is of great benefit to their patients.

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 benefit of the course is that it enables the surgeons to acquire the safe and speedy application of microsurgical skills to applications in such fields as plastic surgery, maxillo-facial surgery, hand surgery, ENT etc. It also produces surgeons with the confidence and skill to carry out these microsurgical procedures when working on clinical cases. Some surgeons, after completing the courses, recognise the need for research into this area and take 2 years out to do research. These surgeons return to the clinical world as accomplished microsurgeons.

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

Each surgeon uses up to 6 rats for training purposes over a five day workshop. Over the five year period of this licence, it is expected that there will be up to 80 participating surgeons per year using a maximum of 3000 rats.

In the context of what you propose to do to the animals, what are the expected adverse effects and the likely/expected levels of severity? What will happen to the animals at the end?

All animals are maintained under anaesthesia for the entire procedure and are then painlessly euthanased. The anaesthetic regime is very reliable and no animals are expected to wake so even in the unlikely event that a rat should, for example, lose too much blood, it will never be aware of the adverse effects.

Application of the 3Rs

Replacement

It is the nature of animal laboratories that progress in the knowledge required to perform their various tasks is constantly sought in the scientific press, meetings and conferences as well as personal communications between laboratories. A non-animal alternative has yet to be devised that satisfies the requirements of the training of surgeons in microsurgery.
Simulated tissues and tubings can be used for very basic exercises and these are used at the start of our workshops to establish each participants' competency in the use of a micrscope and the small surgical instruments and sutures along with the correct surgical technique before they progress to animal work. It is important, however, to be able to develop a feel for live tissue and learn how to deal with the problems of haemorrhage, blood clots and the way that real blood vessels behave during handling.
A living animal is therefore essential and the rat is chosen as it is the smallest animal in which this work can reasonably be performed.

Reduction

Simulated tissues and tubings are used for initial manual dexterity acquisition which reduces the number of animals required. We have also recorded our own instructional videos which have removed the need for live demonstrations thus further reducing the number of animals used.
Small animal anaesthetic technology has improved considerably over the last 20 years resulting in less animals dying prematurely (rats can now be safely anaesthetised for up to 7 hours) which reduces the number of animals needed.

Maximising the number exercises carried out on each animal have also minimised the number utilised.

Refinement

Rats are easily anaesthetised and provide easily accessible vessels of a similar diameter to human finger vessels. When repaired, these vessels can be assessed for viability of the anastomosis up to a few hours post-operatively.

We have also taken note of the way other microsurgical courses are run, and their types of refinement, both in this country and abroad and where applicable have introduced new ideas. Through our experience we have been able to structure the courses such that the maximum number of exercises is carried out in each animal used. This has come in part from refinement of instructional technique and in part from refinement of exercises.

Anaesthesia is induced and maintained by skilled assistants, all of whom have been assesed as competent by the Home Office and have been issued licences. The depth of anaesthesia is assessed frequently and body temperature is maintained by heat from bench lamps and by covering the rats with a small surgical drape. Local anaesthetic is applied topically throughout the exercises (on advice from the veterinarian). Fluids are applied topically via the wound site, to ensure hydration of the animal and to ensure care of the operative field. The named Veterinary Officer and the Named Animal Care and Welfare Officer may also periodically monitor animals throughout the course to ensure animal welfare compliance.