Multicentre **P**reclinical **A**nimal **R**esearch **T**eam

WP4: Regulation and Ethics

Tasks

✓1. Identify relevant regulatory authorities across countries

? 2. Examine existing ethical approval processes across participating countries

✓3. Establish ethical review process for Multi-PART studies

4. Co-ordinate with WP2 Task 1 (Stroke models)

✓5. Explore the potential to establish a single point of contact and approval for preclinical studies

6. Explore the role of other regulatory bodies

Task 4.2 Examine existing ethical approval processes across partners

Question	Barca (AP)	Barca (JM/AR)	Berlin	Caen	Glasgow	Man	Melbourne	Nottingham
1. Do you need regulatory approval for conducting stroke studies?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Do you need ethical approval for conducting stroke studies?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Do you obtain approval for your stroke studies from the same body?	No	Yes	Yes	No	No	No	Yes	No
4. If yes, who gives this approval:	n/a	Institutional EC	State Office of Health and Social Affairs Berlin (State government of Berlin)	n/a	n/a	n/a	Austin Health Animal EC	n/a
5. If no, who gives regulatory approval?	EC of CSIC	n/a	n/a	Lap approved by veterinary agency/Specific study protocols by French Ministry for Research	UK Home Office	UK Home Office	n/a	UK Home Office
6. If no, who gives ethical approval?	EC of the University of Barcelona (CEEA), following approval of our local Government 'the Generalitat de Catalunya'	n/a	n/a	Lab approved by veterinary agency/Specific study protocols by French Ministry for Research	Local Animal and Welfare Ethical Review Board (AWERB)	Local Animal and Welfare Ethical Review Board (AWERB)	n/a	Local Animal and Welfare Ethical Review Board (AWERB)

Task 4.2 Examine existing ethical approval processes across partners

Question	Barca (AP)	Barca (JM/AR)	Berlin	Caen	Glasgow	Man	Melbourne	Nottingham
7. Could you do a MultiPART study right now i.e. is it covered by your current approval for stroke studies?	No	No	No	Possibly (minor approval only)	Possibly	Possibly	Possibly.	No
8. If not, why not, and what would be required?	Requires renewal & some modification of recent protocol for participation in the multitrial Natalizumab study (~2 months).	Require a new protocol for each new study.	Direct experiment-related approvals and personal licenses are required by law for every study	Need description of the protocol, including a rationale for the study, expected results etc	Would alert HO inspector and AWERB to make sure	Would alert HO inspector and AWERB to make sure	Using a different drug would require a project specific application.	Would need to make an amendment to include the particular drug in question, and its potential adverse events - must fit background of licence.
9. On average, how many pages does an application for conducting a stroke study contain, and how long does it take to put an application together (in total if several applications needed)?	About 10 pages. We normally have stroke protocols ongoing. Something new with minor modifications would take about 2-3 months for CEEA approval.	Between 12 and 15 pages. We follow an official template from our institution. Does not take too long.	45-50 pages, one-two weeks	Not defined	Current licence 91 pages. Valid for 5 years. Amendments~1 page.	Current licence 49 pages. To prepare new licence would take~2 months.	On average, the ethics applications are 40-60 pages following a template provided by EC.	A new application might take couple of months to write.
10. On average, how long does it take to obtain full approval for a stroke study from the time of submission?	Up to 6 months	1-2 months	4-6 months	Approx 2 months - though often no formal decision received which is just taken as a yes.	Amendments probably <2 months.	Amendments probably <2 months. Full application could take up to 1 year.	The EC holds bimonthly meetings to review ethics submissions. Whole process 6-8 weeks.	For an amendment 1-2 months. For a full licence – could be up to 1 year.
11. Can you make an application ad hoc or are there annual deadlines?	Ad hoc	Ad hoc but there is monthly deadline. If too many applications have to wait till next month.	Ad hoc	Lab approval covers 5 years. Ad hoc submission of study protocols.	Ad hoc - but AWERB only meets certain times and needs application 2 weeks in advance.	Ad hoc - but AWERB only meets certain times and pre-approval of application required.	An original application can be prepared at any time; however, it will only be seen by The Committee at the bimonthly meetings.	Ad hoc

Task 4.5 Potential to establish single point approval

- Aim: to provide ‘example’ common application
- Based on survey of regulatory approvals needed based this on UK Project Licence application (PPL)
- Extracted information from existing Glasgow, Manchester & Nottingham PPLs

Knowledge, Skills, Background

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.

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?

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.

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

Plan of work

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.

Objectives

The procedures listed under section 19 of this licence have been designed to enable our research programme to fulfil the following objectives:-

- To provide a service of multicentre preclinical stroke trials of high quality and design
- To design in covariates which should contribute to maximising the likelihood of translation to clinical benefit
- To measure efficacy of potential therapeutic products for stroke
- To provide definitive evidence of non-efficacy in potential therapeutic products

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?

The 3Rs

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?

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

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

Protocols (Section 19)

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.

Protocols (Section 19)

Protocol no.	Short title	Species of animals	Estimated numbers over the duration of the project	Severity limit
1	Drug administration	Rats/Mice	Rat, numbers? Mouse, numbers?	Moderate
2	Characterisation of co-morbid rodents	Rats/Mice	Rat, numbers? Mouse, numbers?	Moderate
3	MCAO intraluminal filament	Rats/Mice	Rat, numbers? Mouse, numbers?	Substantial
4	Distal MCAO by electrocoagulation	Rats/Mice	Rat, numbers? Mouse, numbers?	Substantial
5	Proximal MCAO by electrocoagulation	Rats/Mice	Rat, numbers? Mouse, numbers?	Substantial
6	Distal MCAO be electrocoagulation	Rats/Mice	Rat, numbers? Mouse, numbers?	Substantial
7	MCAO by compression	Rats/Mice	Rat, numbers? Mouse, numbers?	Substantial
8	Embolic stroke, blood clot	Rats/Mice	Rat, numbers? Mouse, numbers?	Substantial

19b1: Drug administration

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).

Purpose: The main purpose of this procedure is to investigate the pharmacokinetics of drugs and their effect on the brain and circulation of a conscious rodent (in the absence of brain injury or stroke)

1. * MR Scanning **(AB-G)** Animals will be anaesthetised in order to undergo MR scanning, prior to, during or following drug treatment. The duration of anaesthesia and the maximum number of scans to be performed in a given time period, etc. are detailed in Local Appendix 6

2. *Behavioural Testing **(AA)** Animals may be subjected to behavioural, testing (e.g. sensorimotor, or cognitive tests) some of which require training/acquisition of the task prior to drug administration. See Local Appendix 1.

3. *Drug treatment: **(AA,AB-G)** Routes of administration, maximum volumes administered and their frequency are detailed in Local Appendix 2.

*Optional

19b1 Drug administration

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.

Death from anaesthetic accident: up to 1%.

Death from surgical complications: up to 5%.

19b2 MCAO intraluminal filament

Purpose: The main purpose is the induction of focal cerebral ischaemia in the anaesthetised animal.

1. General Anaesthesia (AC-G). Induction and maintenance of general anaesthesia with agents suitable for the species and the duration of the procedure. Followed by:

2. *Drug treatment. A pharmacologically active substance or its vehicle may be administered under the guidelines in Local Appendix. Drug treatment may be started prior to ischaemia, during or after the induction of ischaemia and maintained to cover the period under investigation.

3. * Hypothermia. Body temperature may be reduced to 32˚C or any value intermediate between 32-38˚C, by withdrawing heat support under anaesthesia and/or actively cooling down the animal (e.g., using an air current, and, if desired temperature is not reached, spraying fur with alcohol). Core body temperature will be monitored via a rectal probe. Hypothermia may be started at any point following the induction of general anaesthesia and maintained for the duration of general anaesthesia or shorter periods.

4. *Surgical Interventions. Surgical tracheostomy or endotracheal intubation may be performed for artificial respiration. Polythene catheter(s) may be inserted into a suitable artery (s) and/or vein(s).

19b2 MCAO intraluminal filament

5. * Microdialysis or ICP monitoring Animal is inserted into a stereotaxic frame, the scalp exposed and burr holes drilled for placement of up to 2 microdialysis probes (for sampling of endogenous substances (e.g. neurotransmitters) in the extracellular fluid and/or infusion or recovery of a pharmacological substance or its vehicle, or intracranial pressure (ICP) probes/ for measurement of intracranial pressure and to induce changes in ICP).

6. * Stem Cell Delivery may be carried out by one of the methods described in Local Appendix 5. Stem cells alone or containing overexpression of proteins for MRI tracking, may be administered.

7. *Laser Doppler Flowmetry Measurement of Cerebral Blood Flow (CBF).
   i)* Animal may be put into a stereotaxic frame.
   ii)* The scalp is incised and the surface of the skull exposed.
   iii)* Up to a maximum of 4 burr holes may be drilled.
   iv)* Laser Doppler flow probes may be positioned on the surface of the skull, on the dura or into the brain parenchyma to allow monitoring of doppler signal either continuously or at pre-defined intervals.

8. *CSF Sampling. Insertion of an intracisternal or intraventricular cannula for the withdrawal of CSF samples. See Local Appendix 2 for specific details.

19b2 MCAO intraluminal filament

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19b2 MCAO intraluminal filament

9. *Conditioning stimuli. Administering periods of brief non-lethal ischaemia (control group, no ischaemia) to the brain or in a distant tissue before, during and/or following induction of focal cerebral ischaemia.

10. Induction of focal cerebral ischaemia.(or a sham procedure to provide a control group) will be carried out by one of the methods described in Local Appendix 4, under the limitations described to prevent and control any adverse effects.

11. *Reduction in collateral blood flow Collateral blood supply to the middle cerebral artery territory may be reduced by a) Mean arterial blood pressure reduction down to, but not less than 40 mmHg by withdrawal of blood or by pharmacological means (e.g. increased halothane/isoflurane concentration) to induce hypotension;
or b) Uni- or bilateral carotid occlusion

12. *MRI Scanning Under the same anaesthetic, animals may be transferred to the magnet bore for MRI scanning. Guidelines for MRI scanning are detailed in Local Appendix 6

*Optional

Adverse effects

Next stage

- Liaise with WP02 regarding SOPs
- Distribute draft application to partners
- Partners to feedback on what information missing that they would require
- Finalise draft in consultation with Kathy Ryder (with appendix covering additional info if any)