WP 2 Scientific coordination

Aim:

To establish:

- the structures and procedures which allow a consortium of trialists to agree on specific investigational drugs or therapeutic principles worth testing by the group

- the models, experimental design, and protocols to be used.

Hanno's slides

- Internal validity:
- Randomisation
- Blinding
- Sample size
- Inclusion / Exclusion criteria
- selective reporting
- statistical design

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Specifically, to establish

1. a core set of stroke models
2. SOPS and structure of study protocol
3. a system for monitoring standards of SOPs, protocols
4. the structure, remit, membership, powers of a *data monitoring committee*
5. the structure, remit, membership, powers of a *steering committee*
6. a process to exchange information on new therapy to be tested (incl. commissioning systematic review)

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Core set of stroke models

1. Species? Strain?
2. Type, method of occlusion (ischaemia, haemorrhage, filament, thrombus, photothrombosis, etc.?)
3. Permanent or transient focal ischaemia? Survival interval?
4. Endpoints?
5. Comorbidities, gender, aging, diet etc. (external validity)
6. All related to type of therapy: neuroprotection, neuroregeneration

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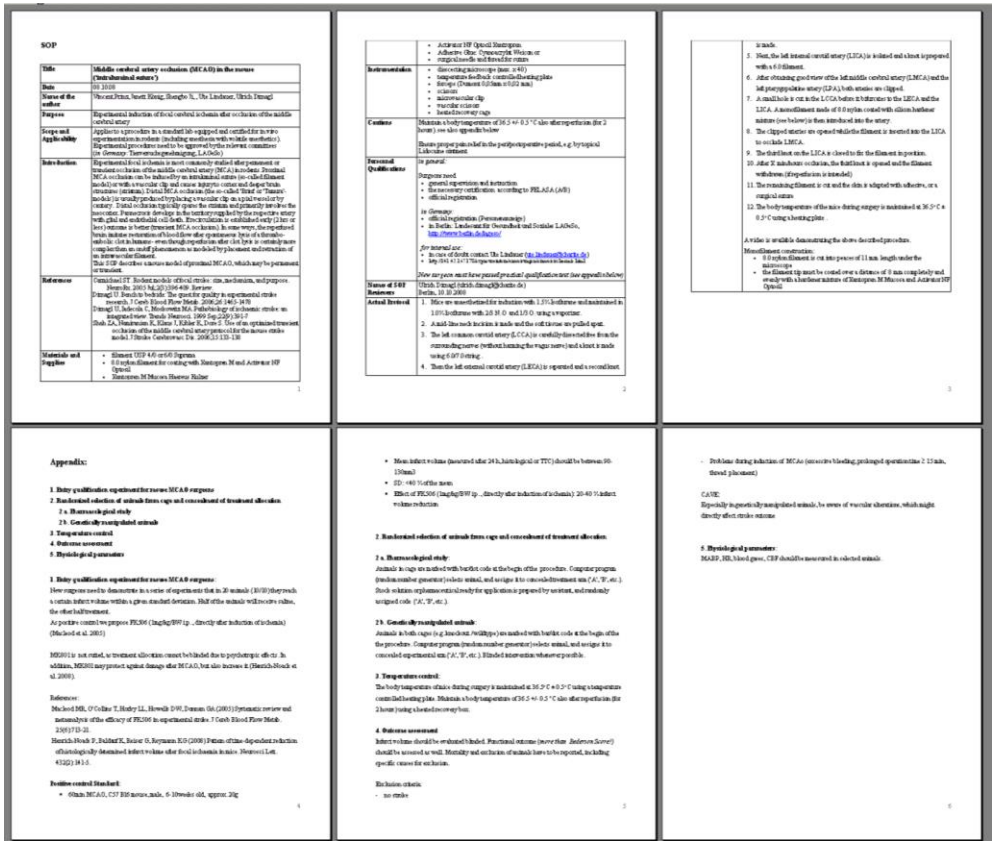
SOPS and structure of study protocol

1. 'Internal' validity
2. Inclusion/exclusion criteria
3. Randomization, blinding
4. Anesthesia
5. Primary & secondary outcome criteria, timing
6. Group sizes, dosages,etc.

Example: Berlin Mouse filament MCAO SOP



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A system for monitoring standards of SOPs, protocols

1. 'Quality and standards committee'
2. Training
3. Round robin tests?
4. Site visits?

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Structure, remit, membership, powers of a data monitoring committee

1. Templates from clinical stroke trials?
2. ....

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Structure, remit, membership, powers of a steering committee

1. Templates from clinical trials?
2. Conflicts of interest?
3. ....

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Process to exchange information on new therapy to be tested :

- Decide upon a process for effective data sharing.

  For example, facilitate information exchange through a central web location (e.g. drop box). All available data for candidate therapy (in vitro, in vivo, safety, tox, PK, etc.) stored in a single location for consortium access.

  Individual consortium members then take responsibility for writing up detailed reports on a specific data set. The collection of reports would cover all information needed to decide on progressing to clinical trial.

- Decide upon a process for GO/NOGO decision on pre-clinical trial

  For a candidate therapy: establish the process by which the consortium decides, on the basis of the pre-clinical data package & reports, whether or not to proceed with a multi-centre pre-clinical trial.

WP 2 Scientific coordination

General issues

1. By which process do we establish the mechanisms/structures of this WP? Delphi process? Email - telecon?
2. How much information do we need to collect before we start to get into details?
3. How much flexibility do we allow in our modelling & procedures (2 examples: use of LDF during filament occlusion: obligatory, or optional? Only one species and strain, or do we allow diversity, e.g. rat/mouse)
4. Many of our decisions will make changes in local protocols necessary: Loss of expertise, regulatory issues!

Reserve slides

Draft of categories to populate Skills Set Database

1. Species Rat, mouse, other - details of strains and sex

2. General anaesthetics (GA) - details (O2, nitrous oxide , medical air ?)
fasted or non-fasted, oral intubation or free breathing on face mask

3. Monitoring & maintaining under GA – BP, HR, body temp, brain temp, blood gases, blood glucose ? Use of heparin,atropine & dose ?

4. Asceptic technique – details (e.g. instruments autoclaved, hot beads, etc. wear greens , gloves & mask ? etc.)

5. Quality Control – a)Randomisation yes/no and how?
b) Allocation concealment during surgery, handling,
c) Blinded assessment of outcome measures – infarct size, behaviour etc.

6. Monitoring success of blood vessel occlusion -
Laser Doppler flowmetry ?
Bring animals round when filament is in place & test for deficit?
MRI for CBF (ASL) and DWI ?
Inclusion/exclusion criteria used?

7. Models of focal ischaemia
Permanent or transient & method of vessel occlusion (filament, embolic, rose Bengal, clip)
Duration of ischaemia ± secondary insult (e.g. uni- or bilat CCA, hypotension)

8. Routes of drug administration: iv (tail vein, femoral), ip sc, icv, osmotic minipump, oral gavage

9. In vivo real time assays - details - e.g. in vivo microdialysis for glutamate, oxidative stress etc., in vivo confocal imaging of vasculature

10. Post-op care package – details (e.g. special diet, subcut fluids, single housing, local anaesthetics, pain relief?)
Recovery questionaire to record animal condition?
Frequency of body weight recording ? Other signs monitored ?

11. Outcome measures _

a. Infarct size - details – (e.g. TTC, histology, MRI) How many coronal levels, Rostro-caudal extent covered, correction for brain swelling used?

b. Behavioural outcome details - period post-stroke you record behaviour
neurological score
specific sensorimotor tests used

c. Brain tissue assays used - details (e.g. western blotting, mRNA analysis miRNA analysis Elisa, biochemical assays , HPLC-MS, etc.

12. Brain processing - Perfusion fixation - yes/no
Brain sectioning - cryostat fresh frozen
cryostat fixed and sucrose impregnated
paraffin embedded & cut on microtome
any other ? Immunohistochem, double/triple labelling ?

13. In vitro models which complement in vivo ? –details (e.g. cells in culture, organotypic slices hypoxic chamber, OGD , glutamate toxicity etc.)