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

Multi-PART

Work Package 2 – Dirnagl and Macrae

Deliverables

- D2.1 : Agreement around and definition of a core set of animal models

  D2.2 : Template for designing the structure of a study protocol approved

- D2.3 : Quality Standards Committee established
- D2.4 : Data Monitoring Committee established

- D2.5 : Steering Committee established along with the mechanism for initiating and approving preclinical stroke studies.
- D2.6 : Process for pre-trial information and knowledge exchange on therapy to be established

D2.1 : Agreement around and definition of a core set of animal models

Rodent stroke model SOPs:
Mouse distal diathermy MCAO
Rat distal diathermy MCAO
Mouse intraluminal filament MCAO
Rat intraluminal filament MCAO
Mouse thrombin MCAO

Behavioural testing in mice (β test)
Inversed grid test mouse
Extended neuroscore mouse

Randomisation, blinding & power analysis
Protocols developed within WP 3

Experimental protocol SOPs
Asceptic technique & anaesthesia
Inclusion exclusion criteria
Maximising animal welfare pre & post stroke (includes humane end-points)
CBF monitoring with laser Doppler flowmetry rat
CBF monitoring with laser Doppler flowmetry mouse
TTC staining for infarct size assessment in rat & mouse
Measurement of infarct volume from TTC stained brain slices

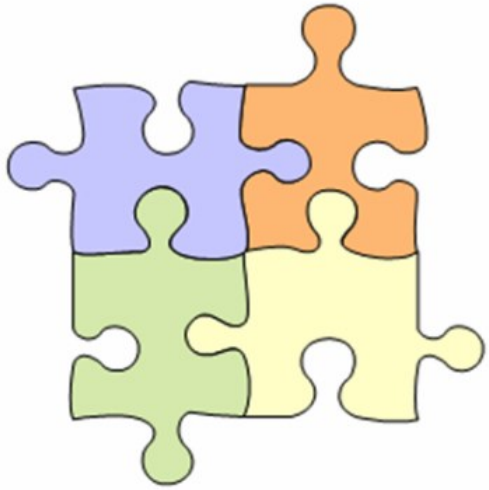
D2.2 Month 6: Template for designing the structure of a study protocol

Proposal: Study protocol will be generated from:

- the portfolio of approved SOPs & protocols

+ new SOPs for any additional stroke models & outcome measures required

+ background data on the therapy under test



D2.2 : Template for designing the structure of a study protocol

Overall study protocol document:
details of models, doses and outcome measures to be generated across all the sites, sample size calculations for planned experiments & detailed plan of statistical analysis

Site-specific study protocol document:
Details of species, strain, sex & age, stroke models, therapy doses, group sizes, randomisation & blinding procedures, outcome measures and reporting instructions specific for each site.

IND/ Investigator's Brochure folder
All prior data available on the therapy under test including any commissioned meta-analyses & systematic reviews.

Site-specific costs

Centre calculates costs for each centre's studies from the costing database.

Centre sends costing agreement document for site PI signature which details the agreed funding plus number of experiments, data sets to be generated & deadline for completion & uploading of data.

Site-specific results summary

Template report form and instructions for a short narrative report on any unexpected findings, problems etc.

D2.2 : Template for designing the structure of a study protocol

- SOPs for rodent stroke models, asceptic technique, animal welfare & humane end-points
- SOPs for confirmation of ischaemic insult (e.g. laser Doppler, MRI or behavioural assessment)
- SOP for therapy/vehicle preparation & administration
- SOPs for outcome measures (e.g. behavioural tests, TTC staining & infarct assessment)
- SOP for inclusion/exclusion criteria & any defined GO/NOGO points.
- SOP for removal & storage of blood or tissues at end of experiment

Reviewing and updating

Multi-PART members:

Continue with current MULTIPART process:

SOPs & protocols are regularly reviewed and further improved, and the whole trial methodology advanced.

Circulation of protocols, SOPs etc., around group as we have done during the last 2 years.

D2.5 : Steering Committee

Structure: [n=5=6]

- Should include clinician(s) external members who are independent of the investigators, their employing organisations, funders and sponsors.
- Can include investigators and a representative of the sponsor (if there is one).
- The chair should not be involved in the trial.

Remit:

- Decide if there are sufficient positive data to authorise a multi-site study
- Select participating laboratories.
- Monitor trial progress and conduct and advise on scientific credibility.
- Decide on amendments to the protocol, consider and act, as appropriate, upon the recommendations of the Data Monitoring Committee (DMC) or equivalent and ultimately carry the responsibility for deciding whether a trial proceeds, and/or needs to be stopped on grounds of animal welfare or efficacy.
- Responsible for designing the study, maintaining the quality of study conduct, ethical review, ongoing monitoring and writing study publications.

Powers:

- Can delay (until sufficient +ve data are available), halt or stop a study altogether (animal welfare, futility)
- Exclude centers that violate protocol or are not adhering to guidelines.

D2.3 : Quality Standards Committee

D2.4 : Data Monitoring Committee

Do we need these ?

Combine both within a single committee ?

D2.4 : Data Monitoring & Quality Control Committee

Structure of DM&QCC:

- Appointed by the steering committee
- Potential conflicts of interest must be considered.
- 5 members experienced in animal stroke studies, not involved in the study external representative and include a clinician, vet/animal welfare representative, & statistician.
- Must operate under a written charter that includes well-defined SOPs.

Remit:

- Animal welfare, 3Rs: check for futility or excessive mortality with power to halt the trial also in cases of a clear benefit ?

Monitoring:

- DM&QCC members perform site/monitoring to assure high quality trial conduct. Perform "on site" monitoring of individual experiments, assess adherence to protocols, ensure the ongoing implementation of appropriate data entry and quality control procedures, and in general assess adherence to good laboratory practices.
- These monitors will remain blinded to study arm assignment.

Powers:

- The DM&QCC, in consultation with the SC, can delay, halt or stop a study altogether (animal welfare, futility)
- Exclude centers that violate protocol or are not adhering to guidelines

D2.6 : Establish a process for pre-trial information and knowledge exchange on therapy

- All available data on the candidate drug/therapy (chemistry, in vitro and in vivo data including all PK, PD & Tox data) collected & loaded onto the multi-PART site in the form of an IND.
- Follow up of corresponding authors to ask for any additional data (e.g. negative or neutral data) which could be made available
- Include search of Dryad and Figshare databases for any additional data.
- In vivo studies given a quality score.
- Option to commission a meta-analysis / systematic review [Multi-PART publication]
- Multi-PART members send any comments to Steering Committee charged with making the final decision on whether or not to proceed with a multi-centre trial
- A report is prepared providing the evidence on which the decision was based (which could also be used in applications for funding).

Funding for personnel to search & collect data, prepare IND, reviews and reports included in multi-site study costings