Multi-PART
Rationale & Purpose

Emily Sena
Centre for Clinical Brain Sciences, University of Edinburgh

Why do we need to change *in vivo* research?

- Translation is failing (in human stroke, MS, AD, glioma)
- Reports of animal experiments seldom report measures to reduce the risk of bias
- Experiments at risk of bias give overstatements of treatment effects
- Secondary analyses of *in vivo* data suggest substantial publication bias and selective outcome reporting bias
- Investigators are often unable to replicate published findings

Clinical trials and *in vivo* studies

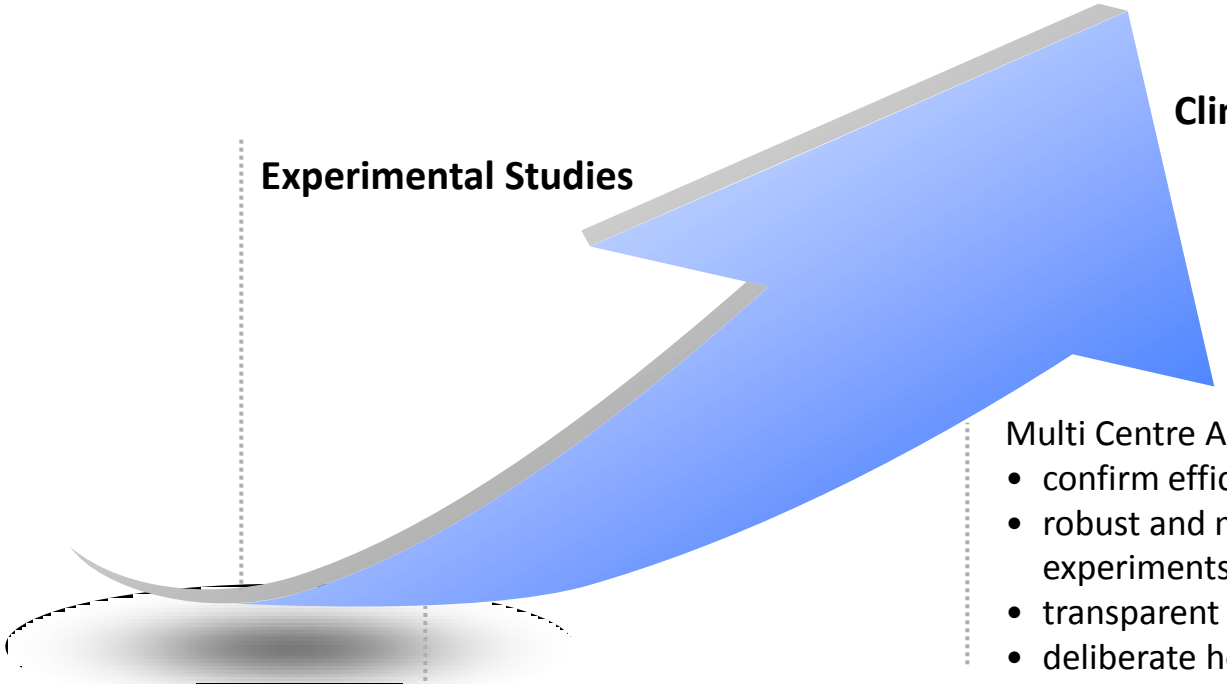
- Differences that potentially could be reduced to develop "*phase III preclinical studies*"
  - Number of centres
  - Time-response
  - Sample size
  - Outcomes
    - Functional, death…..
  - Publication bias
  - Data sharing
  - Regulatory & ethical processes

Bath *et al IJS* 2009

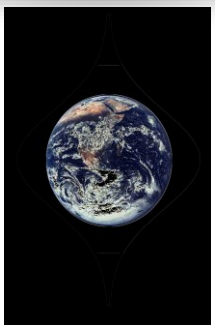
The place of multicentre studies in the pipeline

- It is neither appropriate nor desirable that every *in vivo* study be conducted as part of a multicentre programme
- Hypothesis-generating/testing experiments can and should remain as single-centre studies
- For confirming efficacy in robust and intensively monitored experiments with transparent analysis and reporting.

Evidence based translational medicine



Multi Centre Animal Studies
- confirm efficacy
- robust and monitored conduct of experiments
- transparent analysis and reporting
- deliberate heterog



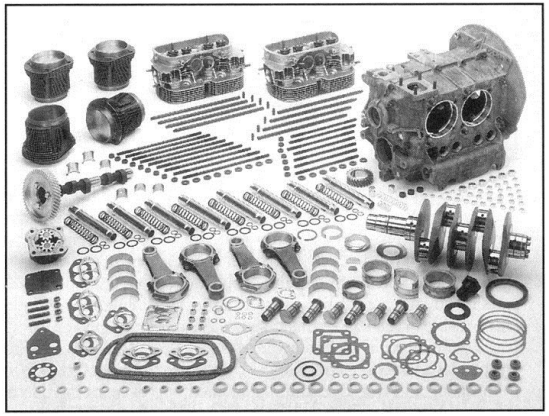
Systematic review and meta-analysis
- how powerful is the treatment?
- what is the quality of evidence?
- what is the range of evidence?
- is there evidence of a publication bias?
- What are the conditions of maximum efficacy?

Multi-PART

- Consortium to establish a framework for multicentre animal trials
- EU FP7 funded 24 month project
- 10 participants from 7 countries
- Using stroke as a worked example
- This will inform the design and conduct of adequately powered multicentre animal studies with improved internal and external validity.

Multi-PART

- WP1: Project management, training and dissemination
- WP2: Scientific coordination
- WP3: Experimental design
- WP4: Regulation & Ethics
- WP5: Data management
- WP6: Statistical analyses



Each work package will be jointly led by:

- Expert in the theme
- *In vivo* practitioner

WP1: project management, training and dissemination

The Practical aspects of organising multicentre studies

Deliverable: Model consortium agreement and costing model for multicentre animal studies

Milestones: Policy documents

- Requirements for Multi-PART study sites
- Recruiting and approving Multi-PART sites

Bart van der Worp and David Howells

WP2: scientific coordination

A framework for the scientific coordination of potential studies

Deliverable: Mechanism for initiating and approving studies, including process for pre-trial knowledge exchange on therapy

Milestones:

- Agreement & definition of a core set of models
- Template for designing the structure of a study protocol
- Quality standards committee
- Data monitoring committee

Uli Dirnagl and Mhairi Macrae

WP3: experimental design

To develop strategies to maximise internal and external validity

Deliverable: Report describing the most appropriate design of future preclinical trials

Milestones:

- Procedure to establish the most appropriate experimental design – randomisation & blinding

Denis Vivien and Hanno Würbel

WP4: regulation and ethics

To define the ethical and regulatory environments

Deliverable: Seek approval from regulatory authorities for ethical review roadmap

Milestones:

- Identify relevant regulatory authorities and approval processes across participating countries
- Establish prototype ethical review roadmap for Multi-PART studies

Stuart Allan and Nathalie Percie du Sert

WP5: data management

To establish specifications for a distributed data management system

Deliverable: Demonstration web based data management system available

Malcolm Macleod and Anna Planas

WP6: statistical analysis

To develop statistical approaches

Deliverable: Statistical analysis guide

Milestones:

- Establish datasets in which to test approaches to statistical analysis

Philip Bath and Joan Montaner

External Advisory Committee

- To provide guidance on the applicability and generalisabilty of our recommendations with a formal review ~ 12M
  - Andrew Rice, Imperial College London (Pain)
  - David Baker, University of London (MS)
  - Kathy Ryder, UK Home Office (Regulation & Ethics)
  - Terry O'Brien, University of Melbourne (Epilepsy)
  - John Steeves, University of British Columbia (SCI)
  - Shai Silberberg & Francesca Bosetti (NINDS)
  - Manoj Lalu (Anaesthesiology)

Surveys

- It is important for us to engage the wider stroke modelling community
  - Broaden applicability
  - Validity
- 3 Surveys
  - WP1: Characteristics of Study Sites (Delphi)
  - WP2&5: Capacity & database design
  - WP6: Statistical Analysis

WP2&5: Capacity & database design

- Identify stroke modelling capacity within the group
- Use the data collected to inform the development of the database
- The NC3Rs has recently convened an expert working group to apply the 3Rs to animal models of stroke.
  - Anonymised data related to the animal care package will be shared with the NC3Rs and working group members in confidence for analysis and review, and provide an evidence base for identifying 3Rs opportunities.
- WP3 will also use the husbandry data to look into variation between laboratories & internal validity

WP2&5: Capacity & database design

- 32 Responses (54%)
  - 8 from within the current consortium
  - Questions:
    - Animals
    - General Anaesthesia
    - Aseptic techniques
    - Internal validity
    - Monitoring success of blood vessel occlusion
    - Model of focal ischaemia
    - Drug administration
    - *In vivo* real time assays
    - Housing
    - Pre & post-op care
    - Outcomes
    - Termination
    - *In vitro* models
- Will make a report of the results available

General comments to the survey

- It was long/tedious vs general gratitude
- Confusion between “lab” and “centre”
- Some questions didn’t account for labs performing multiple models or allow multiple answers
- Concerns about privacy
- Would be useful to share the complications learnt by ‘trial and error’
- Harmonisation desperately needed

Meetings

Across the two years series 5 of face-to-face meetings:

- Utrecht: 12 March 2015
- Brussels: 3 September 2015

Dates and information can be found on our website:

www.multi-part.org

Purpose of meeting

- Update of progress
- Assessment of where we are against our milestones

What we want from you about what we propose?

- Feedback
- Suggestions
- Comments

- How can we test this using real experiments (α-test)?

Agenda

1015-1045 **Lessons from the CD49 & IL1-RA trial** Andre Rex & Stuart Allan

Work Package Sessions: Update on WP objectives followed by group discussion

1045-1130 **Delphi Results** – Bart van der Worp

1130-1150 Coffee break

1150-1235 **SOPs & Survey Results** - Uli Dirnagl & Mhairi Macrae

1235-1330 **Heterogeneity** – Hanno Würbel
MRI protocols – Xenios Milidonis

1330-1430 Lunch

1430-1515 **Mock Ethics Application** – Stuart Allan

1515-1545 **Database development** - Jing Liao & Anna Planas

1545-1615 Coffee break

1615-1700 **Statistical Update** - Philip Bath & Joan Montaner

1700-1800 **Reflection from guests and Meeting Conclusions** – Uli Dirnagl

2100 **Dinner - La Camarga, Carrer d'Aribau, 117, 08036 Barcelona, Spain**