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Stage 1 proposal content (maximum 6 pages for section 1 and 2 together)

1: Scientific and/or technical quality, relevant to the topics[1] addressed by the call

1.1 Concept and objectives

The overall objective of Multi-PART (**Multi**centre **P**reclinical **A**nimal **R**esearch **T**eam; www.multi-part.org) is to develop the capacity to undertake international multicentre animal studies to improve the validity and generalisability of current preclinical research. We propose a paradigm shift to perform experimental studies with the same rigour, driven by the same centralised coordination, as is the case for multicentre phase-III randomised controlled clinical trials (Bath et al. 2009;Dirnagl and Fisher 2012).

(i) Problems with the current translational paradigm

Developing new drug treatments for human disease is challenging, and the number of new drugs coming to market continues to fall. This is particularly true for diseases of the central nervous system, such as dementia, epilepsy, depression and stroke. Although large numbers of novel treatment strategies for these diseases are being developed in laboratories each year and are shown beneficial in animal models, very few are ultimately proven effective in patients (van der Worp et al. 2010). Reasons for this translational failure include limited validity, poor generalisability, and inadequate sample size of many animal studies. The failure to translate drug efficacy in stroke from animal studies to clinical trials (Sena et al. 2007) is probably the best studied example, but the problem is widespread (Perel et al. 2007;van der Worp et al. 2010). Translational research is approaching a crisis, and the enthusiasm within pharmaceutical companies for neuroscience research in general and stroke research in particular continues to wane.

Over the last three decades, more than 500 putative neuroprotective interventions have reported efficacy in animal models of ischaemic stroke, but despite many clinical trials not one of these has been demonstrated to be effective in man (O'Collins et al. 2006). At present, no systematic or evidence-based criteria inform the decision to venture from preclinical testing into clinical development. In most prior translational stroke research programmes the decision to proceed was based on limited experimental evidence and personal opinions of stakeholders in the process. We propose that preclinical research should learn from the experience of clinical trialists by seeking firmer evidence to inform the process of translation.

(ii) Animal studies may be confounded by bias

Animal experiments testing the efficacy of potential treatments are central to the process of progressing to clinical trial. The outputs from these preclinical studies need to be reliable and valid in order to improve human health. The applicants have been at the forefront of detailing the limits of preclinical research (Dirnagl 2006;Perel et al. 2007;Macleod et al. 2008;van der Worp et al. 2010;Landis et al. 2012). Our systematic analyses of preclinical data used to justify clinical trials, for a range of drugs tested in models of ischaemic stroke, have revealed substantial overestimates of treatment effects as a result of compromised internal and external validity of these experiments. This was attributable to inappropriate study designs (Macleod et al. 2008), and to publication bias (Sena et al. 2010). In addition, animal studies in this and other fields are in general too small to detect reliably the effects they purport to observe (Vesterinen et al. 2010); and groups may use models which are highly sensitive to the phenomena being studied (i.e. designed explicitly to show large effect sizes) at the expense of the generalisability of their conclusions.

Adequate sample size, and hence statistical power, is fundamental to the usefulness of preclinical research findings. Sample size calculations based on published data for effect size and variance suggest that experiments should be substantially larger than reported in the literature. Indeed, the typical focal ischaemia study is powered at only 30% - that is, even if the effect being sought is present, there is a 70% chance that it will not be detected. We have shown - at the bench and in systematic review - that animals with co-morbidities (e.g. diabetes, hypertension) yield smaller treatment effects. Given the prevalence of co-morbidity in patients with stroke this has important clinical implications. Most animal studies are therefore underpowered to detect potentially important treatment effects under tightly defined conditions in healthy young animals, let alone to detect smaller but nonetheless potentially important effects in less tightly controlled conditions in older animals with relevant co-morbidities.

Taken together with empirical evidence of a substantial publication bias (Sena et al. 2010), it is likely that for many stroke drugs tested in animals, true biological efficacy in those models is substantially lower than that suggested by the published literature (O'Collins et al. 2011). For some drugs, the size and direction of these various biases is such that the apparent benefits may be due purely to bias, and the agent itself may be inert.

These limitations in experimental validity are not unique to ischaemic stroke studies and have been identified across a range of disease models; most experiments do not report the measures to avoid bias that might improve their validity (table 1). The impact of selection bias (eliminated by randomisation), of performance bias (eliminated by blinded conduct of the experiment) and of measurement bias (eliminated by blinded outcome assessment) should be familiar to the clinical investigator; it is widely

recognised that in clinical trials certain aspects of study design can introduce bias that usually leads to overestimations of drug efficacy. This has resulted in clear standards for good clinical practice in clinical trials, and to the development of ethical, regulatory, funding, reporting and methodological standards to ensure the validity of conclusions drawn from clinical studies. At present clear standards such as these do not exist for most preclinical research, and the reporting of measures to avoid bias is uncommon.

Table 1: Reporting of measures to avoid bias in preclinical neurological research

Disease modelled		Number of Publications	Sample Size Calculation (%)	Random Allocation to Group (%)	Blinded conduct of experiment (%)	Blinded Assessment of Outcome (%)
Alzheimer's Disease		428	0	16	n/a	22
Multiple Sclerosis		1117	<1	9	n/a	16
Parkinson's Disease		252	<1	16	n/a	15
Intracerebral Haemorrhage		88	0	31	8	49
Pain		160	0	12	n/a	26
Focal Ischaemia	NXY 059	9	22	33	56	44
	Hypothermia	101	0	36	4	38
	Erythropoietin	19	0	37	21	42
	Tirilazad	18	0	67	6	72
	Alteplase	113	7	37	20	21

(iii) Differences between animal and human studies

In addition to the unavoidable difference between species, equally fundamental differences exist between animal studies and clinical trials in the way such studies have previously been designed. These avoidable differences (table 2) are likely to impact on the value of translation of animal data to human studies and may explain much of the disparity between the results of animal and human studies. The key underlying point is that animal studies are performed in a poorly coordinated manner: there is no central management of participating laboratories; of what species, models, or animal co-morbidities are used; or what dose and timing of intervention are used. In general, laboratories are autonomous and follow their own protocol, often performing easier experiments (with shorter times to treatment, in animals without co-morbidity) because these are more likely to be positive and therefore be published. This biases the total dataset for interventions towards less rigorous protocols and less taxing conditions for the intervention to succeed in. Regulatory bodies such as the European Medicines Agency (EMA) and its United States equivalent the Food and Drug Administration (FDA) have only moderate input into preclinical studies, and this input often occurs when most of these preclinical studies have been completed.

In contrast, clinical trials (especially commercial ones) are highly regulated; are usually coordinated from a company or university that designs the trial, manages local recruiting sites (in a hub-and-spoke model), provides a central randomisation service, and ensures that sites comply both with the protocol and with relevant regulations. This difference in the standardisation and organisation of experimental conduct also explains other differences between animal studies and clinical trials, such as the use of sample size calculations and the blinded assessment of outcome.

Table 2: Similarities and differences between preclinical studies and clinical trials (from Bath 2007).

	Animal / preclinical studies	**Clinical trials**
Centres	Many single-centre studies	1 or 2 large multicentre trials
Staff	Academic / laboratory	Academic / clinical
Dose-response studies	Variable	Common
Time-response studies	Variable - most assess early administration	Uncommon
Size	Small (10s)	Large (100s, 1000s)
Outcomes: functional outcome	Uncommon	Common
Outcomes: death	Animals sacrificed and death not reported	Common
Publication bias	Common	Uncommon
Publication quality	May be limited	Moderate
Data sharing	Limited	Moderately common
Systematic reviews based on summary (group) data	Uncommon (except by the applicants)	Common
Regulatory involvement	Minimal, often towards end of preclinical development	Considerable, throughout clinical development
Ethical review	Common, may be institutional	Common, usually external

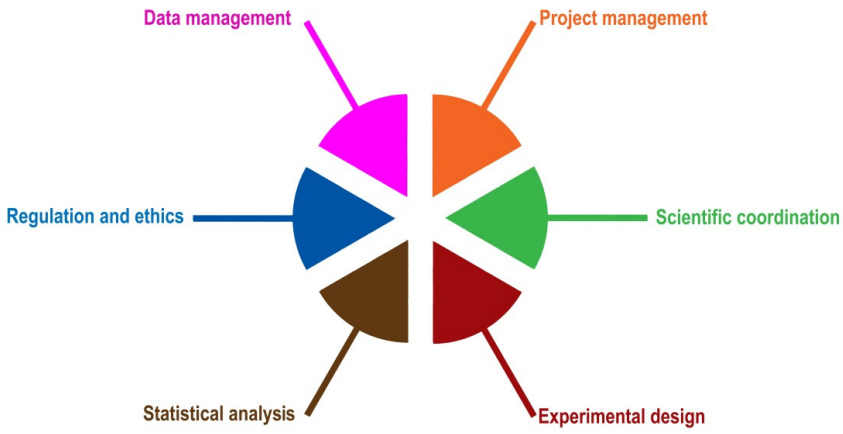
(iv) Purpose

Multi-PART will establish a platform with the potential to transform preclinical animal research across the life sciences, similar to the tremendous improvements in clinical research that occurred through the introduction of multicentre clinical trials. Through a "worked example" of animal modelling of ischaemic stroke, our consortium will define the elements of a successful multicentre animal trial and will describe the tools (technical, regulatory, organisational) that will allow such studies to be conducted, either by Multi-PART or by other consortia. This will inform the design and conduct of adequately powered multicentre animal studies with improved validity and greater generalisability, not just in stroke but also for other disease models.

Multi-PART fulfils the challenge of this FP7 call by proposing a coordinated effort involving key European players in *in vivo* stroke modelling (**Allan, Macrae, Planas, Montaner, Vivien, Dirnagl, Sena**); experimental validity and biostatistics (**Würbel, Bath, Sena, Macleod**), the 3Rs (**Percie du Sert** from the UK's National Centre for the Replacement, Refinement and Reduction of Animals in Research), European collaborative projects (**Planas, Montaner, Vivien, Dirnagl**, **van der Worp, Allan, Bath, Macleod) and SMEs** (**Sanysis**), coming together to develop a strategy to support competitive, high-impact, targeted health research. The inclusion of **Howells** from Australia will ensure we address the applicability of Multi-PART in an international capacity – a key requirement for our success.

The applicants have substantial experience in working together in laboratory, translational and clinical research consortia. The European Stroke Network (ESN: www.europeanstrokenetwork.eu) is a collaborative effort of the European Union's Seventh Framework Program (led by Dirnagl) that brings together researchers (including applicants Planas, Vivien, Montaner, Allan), government, industry, the non-profit sector, and patient group associations. It coordinates preclinical as well as clinical stroke research efforts of 29 institutions in 13 countries. Applicants Macleod, Howells, Sena, Bath, van der Worp and Dirnagl form the core of the Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies (CAMARADES; www.camarades.info), which has been at the forefront of developing an evidence-based approach to translational medicine. Applicants van der Worp, Macleod, Montaner, Bath and Dirnagl collaborate in the EuroHYP-1 trial, an FP7 funded pan-European, open, randomised, phase III clinical trial which assesses the benefit of therapeutic cooling in adult patients with acute ischaemic stroke (http://www.eurohyp1.eu).

Collectively we recognise that it was the progression from small to large studies and from the independent investigator to the research consortium which transformed the science and conduct of clinical trials over the last 30 years. If we thought that it would be a straightforward matter to organise multicentre preclinical studies we would be applying for funding to do those experiments, rather than for the development of a research infrastructure. However, we believe that there are a number of important dimensions to this challenge that must be addressed before we can proceed; and that an organised, strategic approach is more likely to provide a platform for sustained success. We will engage with all partners (academic, pharmaceutical, legal, ethical, institutional, regulatory) to build consensus around the desirability, feasibility, structure, composition and operation of consortia for multicentre animal studies. We propose a series of themed work packages and meetings involving the applicants and other key stakeholders, addressing specific issues including the role of industry and regulators; the capacity to deliver these studies; the statistical analysis plans to be used; and ethical, legal and governance issues. We will seek to appoint a Scientific Advisory Board including individuals with experience in the pharmaceutical industry and of injury models other than stroke; and extend our international dimension to include North America and Asia.



1.2 Quality and effectiveness of the support mechanisms, and associated work plan

There are six work packages covering (1) project management, training and dissemination, (2) scientific coordination, (3) experimental design, (4) data management, (5) statistical analysis, and (6) regulation and ethics. Each work package will be jointly led by an individual with expertise in the theme and an *in vivo* practitioner who can ensure the practicality of solutions developed. Six consortium members will work in each theme, with involvement of external experts as required. Because individuals will work in more than one work package there will be good coordination across work packages. Progress will be overseen by a consortium steering committee (Sena, Macleod, Howells, Allan and Dirnagl) and coordinated by Sena.

(1) Project management, training and dissemination: Led by **van der Worp, Howells** and **Sanisys,** this work package will deal with the practical aspects of organising multicentre studies. These include (i) defining the requirements for study sites;

(ii) establishing a framework for recruiting and approving new sites; (iii) development of training materials – including online training materials – to support the accession of new sites; (iv) a framework for financial management of such consortia; (v) establishing a model Consortium agreement (based e.g. on the Development of a Simplified Consortium Agreement model) to deal with the particular circumstances of multicentre animal studies; (vi) a framework to attribute intellectual property arising from a multicentre animal study. A dissemination strategy will include not only conventional publications, but also engagement (at least in part) with the applicants' extensive network of international collaborators who work in other disease models (i.e. the EUROPAIN consortium, MS-STOP) to guide us on the validity of our approach in their domain.

(2) Scientific coordination: Led by **Dirnagl** and **Macrae,** the purpose of this theme is to establish a framework for the scientific coordination of potential studies. Key deliverables will include (i) a mechanism for initiating and approving studies; (ii) the structure of a study protocol; (iii) agreement around and definition of a core set of animal models; (iv) agreement around a standard set of inclusion and exclusion criteria; (v) agreement around primary and secondary outcome measures; (vi) the development of standard operating procedures for study procedures; (vii) provisions for monitoring standards of laboratory practice and compliance with the protocol and quality control; and (viii) responsibilities and operating procedures for a study data monitoring committee.

(3) Experimental design: Led by **Vivien** and **Würbel,** the purpose of this theme is to develop strategies to maximise the internal and external validity of studies. We will define strategies to minimise bias including (i) centralised randomisation, (ii) blocked randomisation strategies where appropriate, (iii) blinding during the experiment (including the possibility of central (blinded) drug supply); (iv) blinded assessment of outcome (including off-site assessment of structural or functional outcomes); and (v) a priori sample size calculations. Rather than attempting to create identical experimental conditions in each study centre we will exploit these differences to increase the generalisability (external validity) of findings. However, the way this is dealt with in the study design will require that these differences should be identified and defined so that they can be accounted for in the blocked randomisation strategy. This theme will also define additional deliberate variations (for example in environmental enrichment) which might be varied between sites. This work will include some simulation studies based on existing outcome data held by the participants.

(4) Regulation & Ethics: Led by **Allan** and **Percie du Sert,** we will engage with national and institutional regulators and EU institutions to explore the different regulatory environments. Specifically, we will explore whether a single or common application for regulatory approval might be developed; the views of regulators to giving approval to an experiment which is conducted in part outside their jurisdiction; and whether there is scope for multicentre animal studies to have a single sponsor within the EU with a single ethical application. This will involve consultation with relevant stakeholders (the EMA, FDA and national and regional organisations implementing directive 2010/63/EU across Europe). Further, we will engage with other stakeholders (including the Laboratory Animals Science Association and the Royal Society for the Prevention of Cruelty to Animals) to consider the ethics of multicentre rather than single-centre animal studies.

(5) Data management: Led by **Macleod** and **Planas,** we will establish specifications for a distributed data management system which would allow (i) site management and approvals; (ii) randomisation service; (iii) central data management; (iv) uploading of outcome data (numbers, text, images, video) and sending to blinded outcome assessors for scoring; (v) central statistical monitoring; (vi) provision of data for interim and final analysis; (vii) providing reports of activity and of missing data.; and (viii) provisions for external data sharing. Once specified, the system will be developed, and will be tested by potential users. This process will include testing the feasibility of off-site outcome scoring by blinded assessors using real data, and an assessment of the optimal number of scorers for each category of outcome.

(6) Statistical analyses: Led by **Montaner** and **Bath,** we will develop statistical approaches for (i) sample size calculations for the various outcomes used; (ii) blocked randomisation; (iii) interim analyses for efficacy or futility; (iv) primary and secondary outcome analyses; (v) possibility of adjusting outcomes for observed baseline differences; and (vi) approaches for central statistical monitoring to ensure compliance with the study protocol. Once established, these approaches will be tested using the data used to pilot (5) above.

Meetings: Across the twenty-four months proposed, we intend to schedule an initial start-up meeting, a series of themed meetings and a final consolidation meeting. The initial meeting will be a face-to-face meeting that all participants will attend. Further themed work package meetings will be directed by work package leaders but will be open to all participants and attended by other relevant stakeholders depending on subject and expertise. Work package meetings will consist of three face-to-face meetings (every 6 months) and eight teleconferences (every 2 months). Due to the overlap in participation across work packages, the face-to-face meetings will occur in series over three days in one location. The final consolidation meeting will take place during month twenty-four in Brussels and will be attended by all participants, and other relevant stake holders; appropriate persons from the commission will be invited.

2. Impact

Improving the quality and methodology of preclinical studies is likely to reduce the number of ineffective interventions being taken forward to clinical trial, and thereby to improve research efficiency. This will reduce potential harm to trial participants and

ultimately benefit patients in Europe and beyond. The economic and social costs of translational failure are substantial. Stroke is the second cause of death in Europe, with over 500,000 deaths each year. Annually, immediate healthcare costs and long-term disability costs in the developed world have been estimated at between €202.4bn and €790.1bn. It currently costs around €11bn to bring one successful stroke drug to market, and it has been estimated that the introduction of multicentre animal studies would reduce this by €1.4bn (Howells et al. 2012). In human terms the impact of developing an effective intervention has been estimated at around 15 patients saved from death or dependency per 1000 strokes (Gilligan et al. 2005), equivalent to 22,250 persons per year in Europe, and twice the potential benefit of thrombolysis.

Preclinical multicentre trials will have a substantial 3Rs impact, primarily in refinement and reduction. The traditional assumption is that standardisation of experimental conditions and procedures guarantees reproducibility and the external validity of results. However, environmental homogeneity within laboratories together with unavoidable environmental differences between laboratories (e.g. staff, room architecture and noise) has been shown to lead to spurious results with limited external validity (Richter et al. 2009). By incorporating environmental variability in the experimental design, multicentre trials provide more robust findings (Richter et al. 2009), and there is now good evidence supporting systematic heterogenisation between animal studies (Richter et al. 2010). Improving the validity of data from animal experiments is likely to reduce the requirements for animal use in research; for any given number of animals, a small number of adequately powered and externally valid studies are likely to be more informative than a large number of small underpowered studies. Further, the use of systematic randomised block design to account for environmental heterogeneity will improve precision and statistical power without requiring larger sample sizes (Wuerbel and Garner 2007).

Establishing rigorous experimental designs and procedures requires resources (intellectual and other) not available in a single country or programme; for this reason, a European consortium is required. Our approach will allow smaller laboratories with limited personnel and experience to contribute to high-quality research. Central provision of study platforms (randomisation, data management, outcome adjudication, statistical analysis) will reduce costs for national funding agencies and will allow new centres (and new countries) to join the field in a supported, mentored and monitored way. In this way, Multi-PART will increase high-quality research capacity by reducing entry costs. This approach might be characterised as the national equivalent of pre-competitive partnership, creating tools to bring about health gains for all.

Addressing the huge and completely unmet medical needs of patients with neurological diseases poses tremendous commercial opportunities. Demonstrating neuroprotection or neurorepair in stroke, a prototypical acute CNS disorder, would have substantial implications for the development of treatments in many other acute and chronic neurological and neuropsychiatric diseases. Furthermore, such a trial paradigm could serve as a blueprint to overcome similar translational roadblocks in other disease areas.

2.1 Expected impacts listed in the work programme

Multi-PART will establish the capacity for central randomisation, outcome adjudication, and monitoring of laboratory practice; planned variation of experimental conditions between sites to increase generalisability; and the capacity to deliver large studies in a short timeframe. Our data will be more reliable than those obtained from isolated research groups, reducing the need for further animal studies; and because clinical trials will be founded on better evidence the chance of benefit to patients participating in clinical trials will be higher, and their risks lower. We will establish frameworks for data sharing. Finally, multicentre animal studies offer the real prospect of providing the route for the development of effective treatments for diseases of substantial public health and economic importance.

Multi-PART clearly meets the expectations of the FP7 call:

(1) **Brain research** is a work programme priority. Developing the capacity to undertake multicentre preclinical studies has the potential to deliver **effective** agents that **translate** to patients with ischaemic stroke and will act as a blueprint for other neurological disorders and beyond.

(2) We request support for **coordination** between **key European** academics, and a **SME;** and we have a strategy to involve industry partners that are currently exiting the field of stroke research.

(3) This proposal is **driven** by the **demand** to reduce **health care costs** of ischaemic stroke and the need to transform translational stroke research, currently characterised by a failure to translate the effects from the bench to the bedside.

(4) The coordination of this project has the potential to increase the **standard** of research undertaken by participant sites and will **widen participation** by smaller and less experienced laboratories, with appropriate levels of support and supervision to undertake research with a rigour that would otherwise not be possible.

(5) Multi-PART will engage regulators to define the **regulatory needs** and ethical considerations for multicentre preclinical studies.

(6) Multi-PART is a **translational network** that supports the **innovation** of **novel** translational research paradigm that is **open** and **actively collaborative**.

(7) **International cooperation**, both within and outwith Europe, is a key objective of Multi-PART. The inclusion of an Australian participant contributes to the **innovative potential** of the proposal by demonstrating validity outside of Europe. The US

NIH/NINDS is considering calling for preclinical phase III type trials, potentially in collaboration with the EC, Canada, and Australia. Our programme will be able to provide the conceptual basis for such international trials, and allow swift action.

(8) **Diversity of the research workforce:** The consortium has reasonable gender and ethnic balance, and importantly extending the possibility of research activity to institutions not currently active in world will also promote diversity of the research workforce.

(9) **Public understanding of science:** The applicants' extensive experience will ensure **media and general public engagement**. Macrae is a registered Science, Technology, Engineering and Mathematics (STEM) Ambassador who participates regularly in school events designed to get pupils interested in science. Macrae and Allan also contribute to the Glasgow and Manchester Science Festivals respectively, Brain Awareness Week and regularly give secondary school pupils work experience in their laboratories. Macrae has given talks on stroke research to the general public (e.g. NEXXUS Scotland), has given a seminar on stroke research to the general public overseas and has been interviewed on "Women in science". Allan has successfully run stroke patient-carer workshops and regularly speaks on the use of animals in research. Macleod was integral to the successful media coverage of the EuroHYP trial (see www.eurohyp1.eu).

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