# **Multi**centre **P**reclinical **A**nimal **R**esearch **T**eam

Multi-PART

**Work Package 3 – Experimental Design**

Hanno Würbel, Denis Vivien

# WP 3

## Purpose of WP 3 – Experimental design

- to develop strategies to maximise both the internal and external validity of the studies performed within Multi-PART or other multi-centre research consortia

# WP 3

## Topics to discuss

- Database issues
- Experimental design issues

# WP 3 – Database issues

## Experimental variables

| | | | |
|---|---|---|---|
| Drug under investigation | | Intervention under investigation | text |
| | drug/vehicle/saline | | |
| | Weight | | |
| | Age | | |
| Strain | | Strain | text |
| Sex | | Sex | text |

## Study descriptors

| | | | |
|---|---|---|---|
| Filter Top | | Filter Top | Yes/No |
| Food Deprivation | | Food Deprivation | Yes/No |
| Food Deprivation Schedule | | Food Deprivation Schedule | Text |
| Handling | | Handling | Text |
| Health Check | | Health Checks | Yes/No |
| Health Check Frequency | | Health Check Frequency | Number |
| Lid Brand | | Lid Distributor | Text |
| Lid Type | | Lid Type | Text |

# WP 3 – Database issues

## Variables listed in the database

| | | | |
|---|---|---|---|
| Acclimatization Period | | Acclimatization Period | Number |
| Acoustic Background | | Acoustic Background | Text |
| Additional Species in Lab | | Additional Species in Lab | Yes/No |
| Additional Species in Building | | Additional Species in Building | Yes/No |
| Bedding Material | | Bedding Type | Text |
| Cage Brand | | Cage Distributor | Text |
| Cage Type | | Cage Type | Text |
| Cage Size | | Cage Size | Number |

## Variables not listed in the database

| | | | |
|---|---|---|---|
| Pets held by care takers | | Pets held by care takers | Text |
| Color of lab walls | | Color of lab walls | Text |
| Lab coat colour | | Lab coat colour | Text |
| Water bottle brand, size, … | | Water bottle brand, size, … | Text |
| Cage rack material, hight, …. | | Cage rack material, hight, …. | Text |
| … | | … | … |

# WP 3 – Database issues

**The listing fallacy** (Würbel 2002 Genes Brain Behav)

- There exist many more variables than are listed
- Selection of listed variables is arbitrary
- Many variables are unknown and unlistable
- Listed variables are no more likely to explain results than unlisted variables

# WP 3 – Database issues

**The listing fallacy** (Würbel 2002 Genes Brain Behav)

*"Such lists may in fact divert attention away from highly relevant factors that were not considered, were considered to be irrelevant, were too difficult to assess, or simply cannot be listed."*

- Therefore, such lists may induce interpretation bias

# WP 3 – Database issues

**What should be listed?**

- Experimental design variables
- Descriptors to be reported in the papers' methods section
- Variables relevant for meta-analyses

**However**: All "variables" not varied within studies are confounded with "study" (i.e. with all other fixed aspects – listed or unlisted – of that study)

# WP 3 – Database issues

## Revision of database

Include variables only if they are:

- Potential experimental design variables
- Relevant descriptors of the study method
- Variables relevant for meta-analyses

# WP 3 – Experimental design issues

## Main factors of the experimental design

- Surgery (surgery, sham surgery, no surgery)
- Intervention (drug, saline, vehicle)
- Stroke Model (intraluminal filament, distal MCAO electrocoagulation, …)
- Animal Species (rat, mouse, macaque, ….)
- Lab (Macrae, Dirnagl, Planas, ….)
- Conditions (standardised or heterogenised)

(**Animals** (strain, age, sex, comorbidities, …), **Housing & Care** (group size, cage size, enrichment, …), **Procedures** (test protocol)

# WP 3 – Experimental design issues

## Template for the experimental design

| Surgery | Intervention | Stroke Model | Animal Species | Lab | Conditions |
|---|---|---|---|---|---|
| Yes | drug | Model 1 | rat | Macrae | standardised |
| Sham | vehicle | Model 2 | mouse | Dirnagl | heterogenised |
| No | saline | Model 3 | macaque | Planas | |
| … | … | Model 4 | … | Vivien | |
| | | Model 5 | | Howells | |
| | | Model 6 | | Abc | |
| | | …. | | Def | |
| | | | | Ghi | |
| | | | | … | |

# WP 3 – Experimental design issues

## Experimental design 1: Multi-lab study

| Surgery | Intervention | Stroke Model | Animal Species | Lab | Conditions |
|---|---|---|---|---|---|
| **Yes** | **drug** | Model 1 | **rat** | **Macrae** | **standardised** |
| **Sham** | **vehicle** | Model 2 | mouse | Dirnagl | heterogenised |
| No | saline | **Model 3** | macaque | **Planas** | |
| | | Model 4 | | **Vivien** | |
| | | Model 5 | | **Howells** | |
| | | Model 6 | | Abc | |
| | | | | **Def** | |
| | | | | Ghi | |

# WP 3 – Experimental design issues

## Experimental design 2: Multi-model study

| Surgery | Intervention | Stroke Model | Animal Species | Lab | Conditions |
|---|---|---|---|---|---|
| **Yes** | **drug** | **Model 1** | **rat** | Macrae | standardised |
| **Sham** | **vehicle** | Model 2 | **mouse** | Dirnagl | **heterogenised** |
| No | saline | **Model 3** | macaque | Planas | |
| | | Model 4 | | **Vivien** | |
| | | Model 5 | | Howells | |
| | | Model 6 | | Abc | |
| | | | | Def | |
| | | | | Ghi | |

# WP 3 – Experimental design issues

## Experimental design 3: Multi-lab-multi-model study

| Surgery | Intervention | Stroke Model | Animal Species | Lab | Conditions |
|---|---|---|---|---|---|
| Yes | drug | Model 1 | rat | Macrae | standardised |
| Sham | vehicle | Model 2 | mouse | Dirnagl | heterogenised |
| No | saline | Model 3 | rat | Planas | |
| | | Model 4 | macaque | Vivien | |
| | | Model 5 | mouse | Howells | |
| | | Model 6 | rat | Abc | |
| | | | | Def | |
| | | | | Ghi | |

# WP 3 – Experimental design issues

**Optimise experimental design**

- Use existing data to analyse different designs
- Model trade-offs between variation of different factors
- Model trade-offs between sample size and external validity

# WP 3 – Experimental Design

## Deliverables

- **Month 12:** Preliminary solutions for randomisation and blinding for further discussion and refinement
- **Month 18:** Preliminary solutions for sample size calculation and systematic variation for further discussion and refinement
- **Month 24:** Final report describing the most appropriate design of future preclinical trials (randomisation, blinding, sample size calculations, systematic variation)