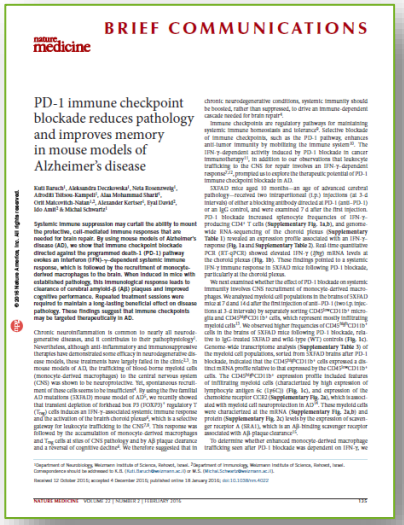
The European Quality in Preclinical Data Consortium

Data Quality in Preclinical Research

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 777364. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.

A “Typical” Scenario


BRIEF COMMUNICATIONS

nature medicine

PD-1 immune checkpoint blockade reduces pathology and improves memory in mouse models of Alzheimer's disease


RESEARCH HIGHLIGHTS

NEURODEGENERATIVE DISEASE

Immunotherapy opportunity emerges for Alzheimer disease


GLIA

WILEY

RESEARCH ARTICLE

Systemic immune-checkpoint blockade with anti-PD1 antibodies does not alter cerebral amyloid-β burden in several amyloid transgenic mouse models

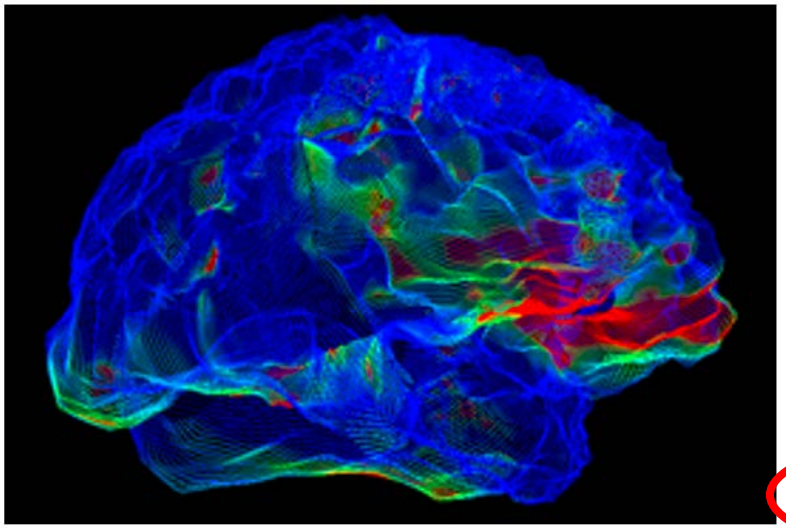
Exciting finding → **Enthusiasm in the field** → **Sobering news**

CHEMISTRY

Why Alzheimer's Drugs Keep Failing

Drug candidates have a 99.6 percent failure rate, and poor early detection methods make clinical trials difficult and costly

By Maria Burke, Chemistry World on July 14, 2014



Areas of cell loss are in red on this brain scan of an older person with Alzheimer's disease. *Credit: NIH*

Challenges

- Understand disease pathophysiology and disease heterogeneity
- Diagnose early
- Get timing of treatment right
- Generalizability / translatability of animal models
- Robustness and reliability of preclinical data

What is EQIPD?

First IMI consortium completely dedicated to improving preclinical data quality

Joint undertaking by Big Pharma, CROs, Academia, Technology Provider, and Scientific Associations

Proof of concept in Neuroscience and Safety, facilitated by a Quality Management System

Expand R&D-wide if successful

Our Vision

Robust data and scientific rigor in animal studies will impact on the 3Rs, enhance the pace of knowledge gain and shorten the time needed to make new drug treatments available to patients

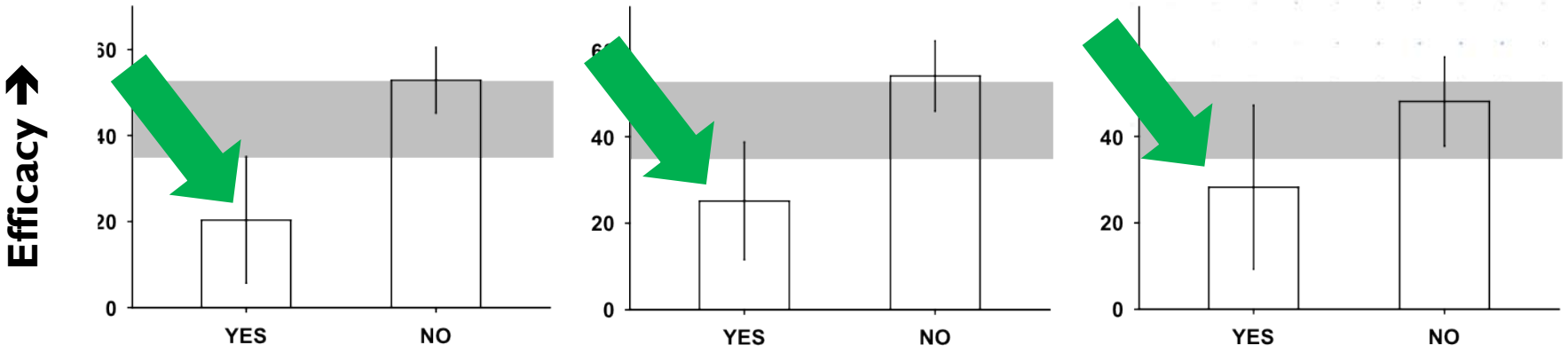
Internal Validity

Animal studies not using RDN or BLD much more likely to be positive (n = 290)

BLD - / RND - vs
BLD + / RND +

odds ratio **5.2** (95% CI 2.0-13.5)

Bebarta et al., Acad Emerg Med, 2003

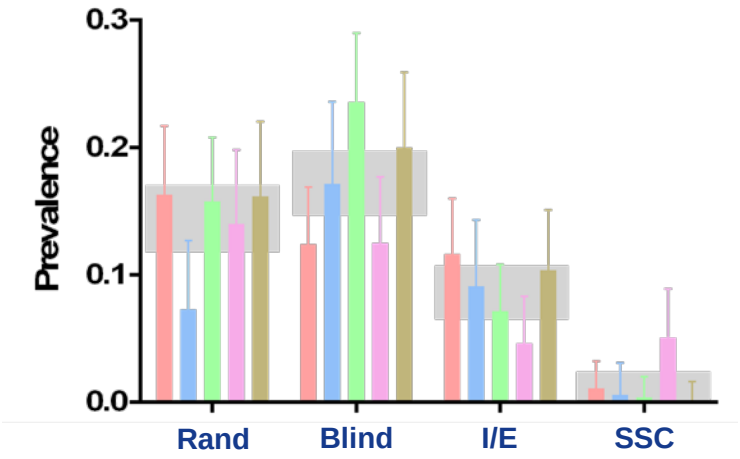


Randomisation

Blinded conduct of experiment

Blinded assessment of outcome

Prevalence of risks of bias



Evidence-based Preclinical Medicine
Open Access
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SYSTEMATIC REVIEW

From a mouse: systematic analysis reveals limitations of experiments testing interventions in Alzheimer's disease mouse models

K.J. Egan,[1] H.M. Vesterinen,[1] V. Beglopoulos,[2] E.S. Sena[1] and M.R. Macleod[3*]

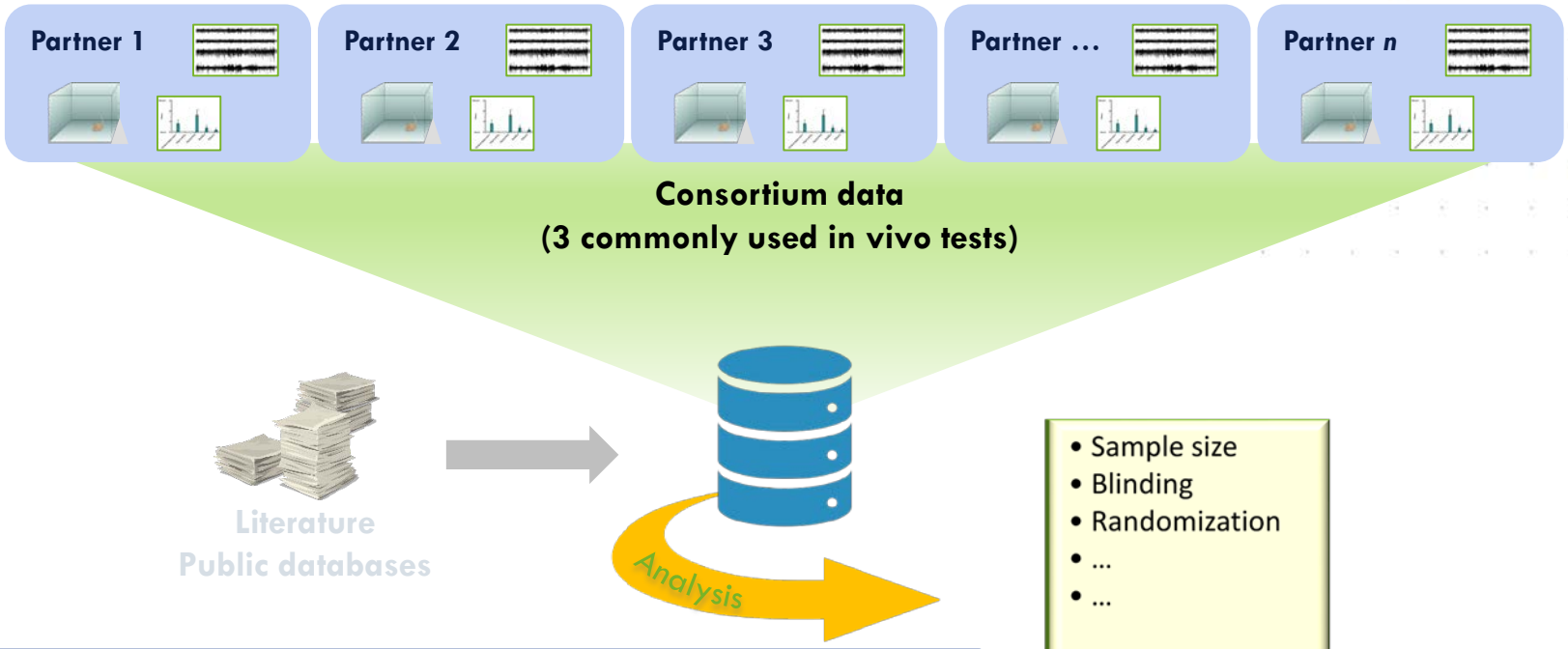
Random allocation to group	67/427	16
blinded assessment of outcome	95/427	22%
sample size calculation	0/427	0%

reported efficacy was

- 3.4% higher in nonrandomized
- 5.8% higher in non-blinded studies

Historical Data Analysis

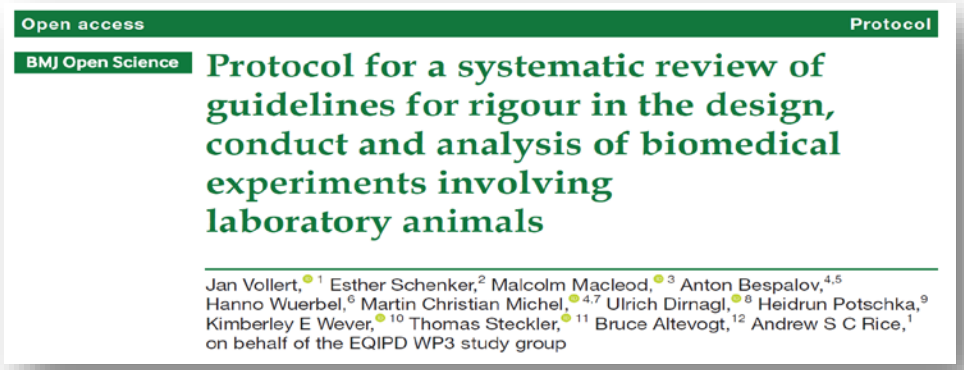
Aim: Define variables of internal and external validity in experimental design, conduct and data analysis that are determinants of outcome in preclinical studies



Open Field: 200 studies; Irwin: 18 studies; EEG: 401 studies

Research Guidelines

Aim: Develop guiding principles and criteria governing rigor in experimental design, conduct and analysis of preclinical studies


Open access Protocol

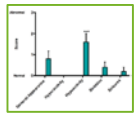
BMJ Open Science

Protocol for a systematic review of guidelines for rigour in the design, conduct and analysis of biomedical experiments involving laboratory animals

Jan Vollert,[1] Esther Schenker,[2] Malcolm Macleod,[3] Anton Bespalov,[4,5] Hanno Wuerbel,[6] Martin Christian Michel,[4,7] Ulrich Dirnagl,[8] Heidrun Potschka,[9] Kimberley E Wever,[10] Thomas Steckler,[11] Bruce Altevogt,[12] Andrew S C Rice,[1] on behalf of the EQIPD WP3 study group

- 13,863 papers screened
  - 62 papers finally included
  - 58 items extracted
- 2 Delphi rounds
- Consensus meeting
  - 33 items finally included

Evidence from validation studies



Hx DATA ANALYSIS

- Sample size
- Blinding
- Randomization
- ...
- ...

EQIPD Quality System: Overview

Aim: Support the essential processes, procedures, responsibilities and cultural aspects relevant to implement the guiding principles that improve robustness of preclinical studies (using animals)

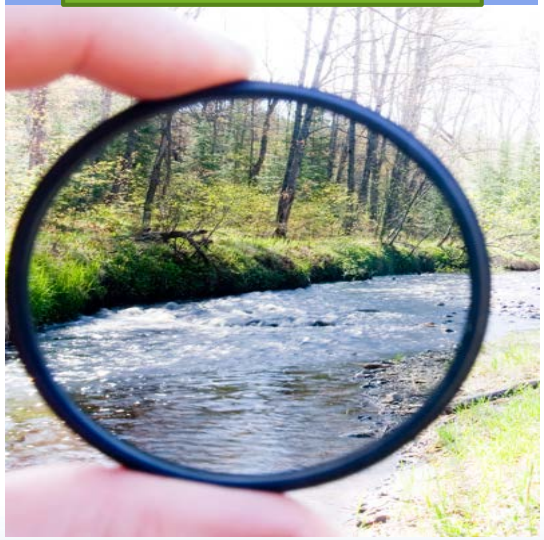
TOOLBOX

All information

- Everything related to research quality that a scientist may need to know about or have access to
- Created and maintained by EQIPD

PLANNING TOOL

Filter

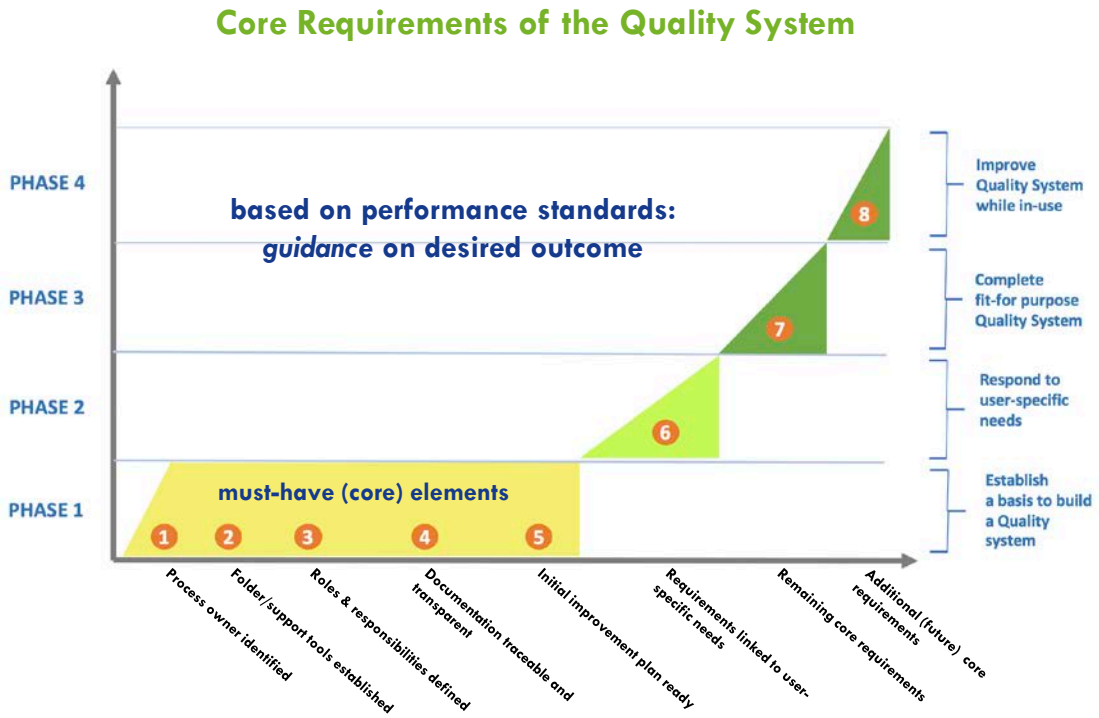


DOSSIER

Relevant information

- Quality-related items, such as protocols and training records, that were developed by a research unit as solutions to challenges specific to their needs

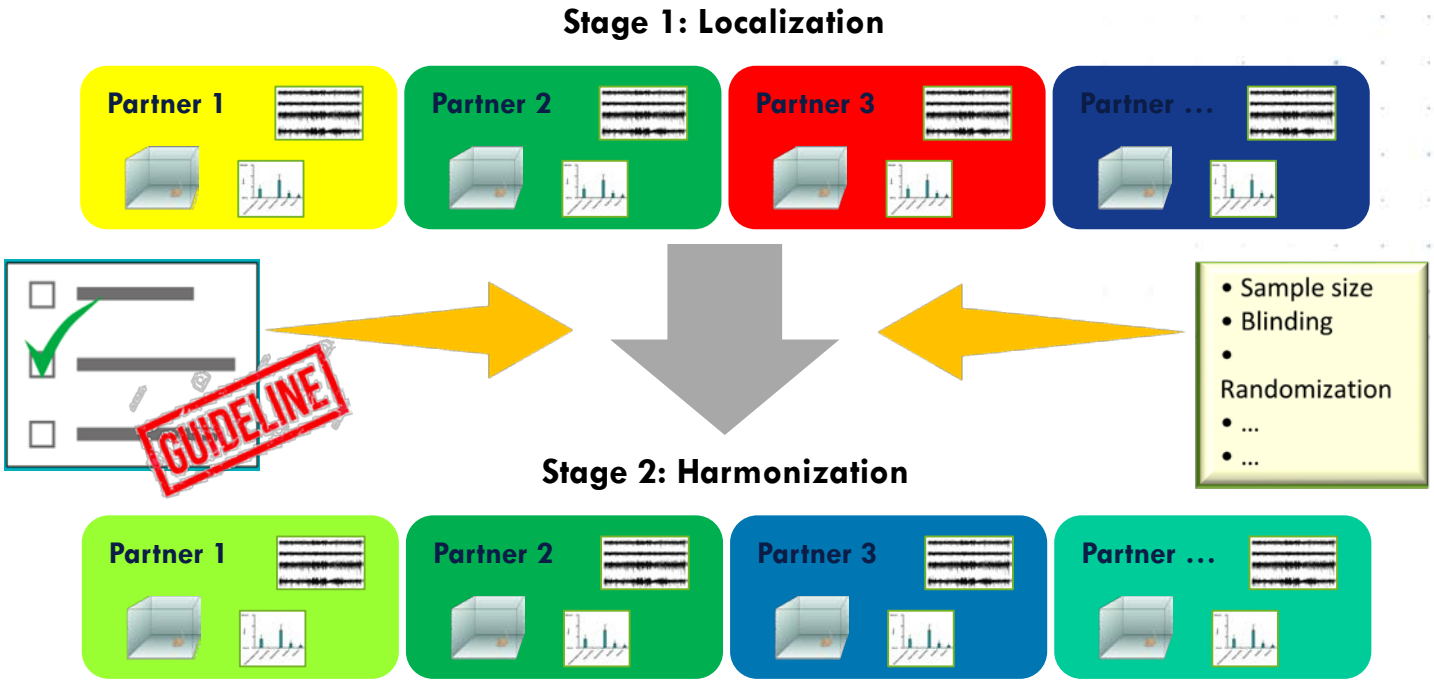
Lean and Fit-for-Purpose System, Easy to Use Tools



Version 1 rolled out May 2019

Cross-site Validation

Aim: Validate the principles and research models that improve robustness and data quality in preclinical studies (using animals)



Effect of reduced inter-lab variability?

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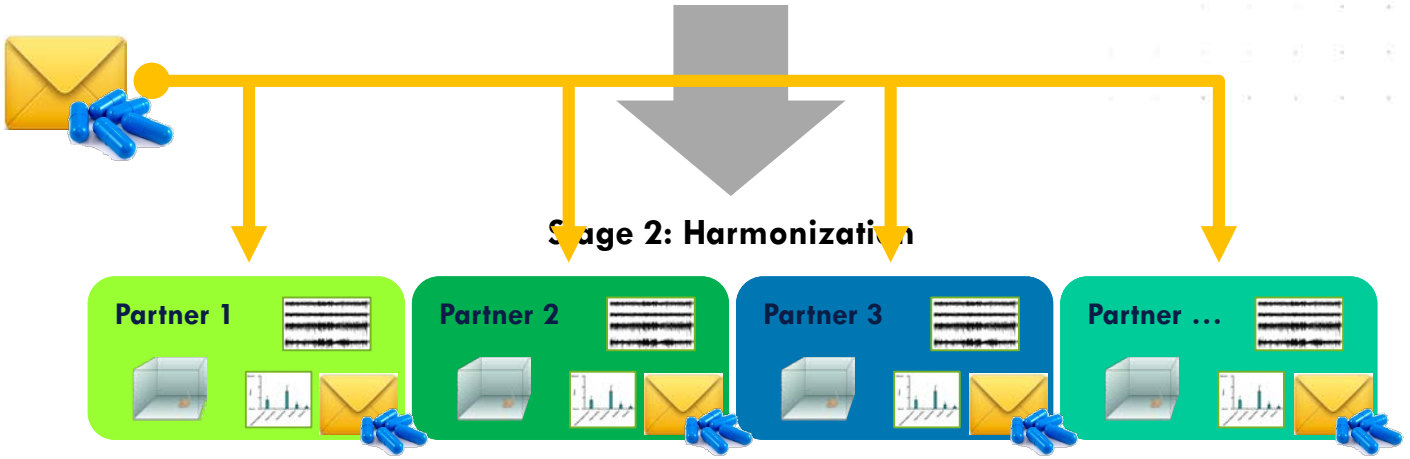


Effect of blinding of test item

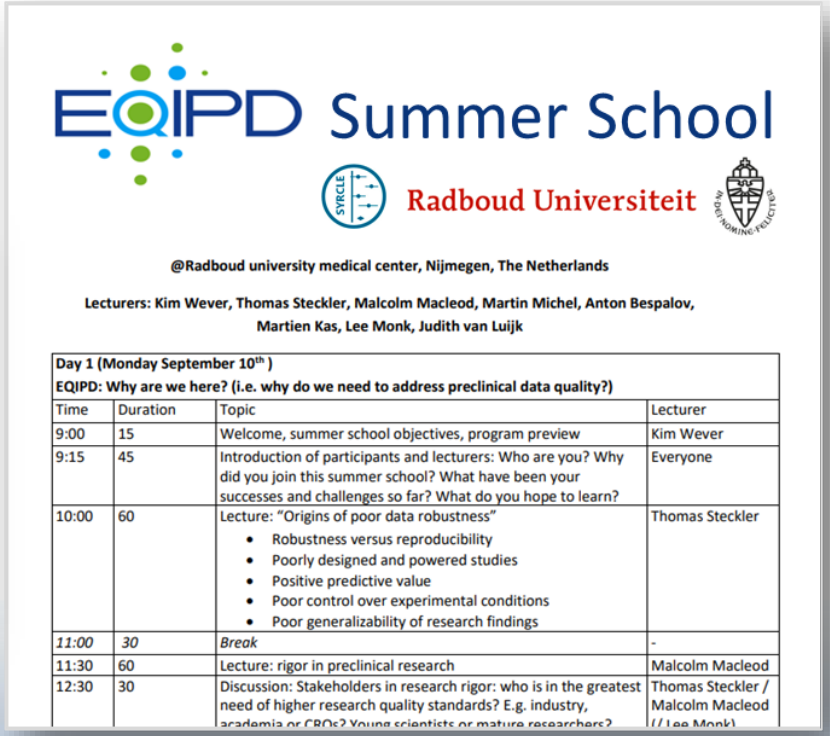
Training Platform

Aim: Maximize sustainability and impact of the EQIPD Quality System by development of an engaging learning environment to ensure research community wide expansion of knowledge about the EQIPD principles

- Evaluation of existing training modules
- User requirements identified
- Potential service providers to host the platform contacted

Table 1: evaluated materials and included materials per module

Module	# materials evaluated	# materials suitable for inclusion
Scientific integrity	0	0
Experimental design	3	2
Validity	7	5
Ethics and animal welfare	5	1 (+ 3 potential)
Data handling	1	1
Statistics	5	4
Transparent reporting	3	3
Systematic review of animal studies	1	1
Data governance and data integrity	0	0
Set up of industry/academia collaborations	0	0
Implementing QMS in discovery research	0	0
Total	25	17 (+ 3 potential)



EQIPD Summer School

Radboud Universiteit

@Radboud university medical center, Nijmegen, The Netherlands

Lecturers: Kim Wever, Thomas Steckler, Malcolm Macleod, Martin Michel, Anton Bespalov, Martien Kas, Lee Monk, Judith van Luijk

Day 1 (Monday September 10th)
EQIPD: Why are we here? (i.e. why do we need to address preclinical data quality?)

Time	Duration	Topic	Lecturer
9:00	15	Welcome, summer school objectives, program preview	Kim Wever
9:15	45	Introduction of participants and lecturers: Who are you? Why did you join this summer school? What have been your successes and challenges so far? What do you hope to learn?	Everyone
10:00	60	Lecture: "Origins of poor data robustness" • Robustness versus reproducibility • Poorly designed and powered studies • Positive predictive value • Poor control over experimental conditions • Poor generalizability of research findings	Thomas Steckler
11:00	*30*	*Break*	-
11:30	60	Lecture: rigor in preclinical research	Malcolm Macleod
12:30	30	Discussion: Stakeholders in research rigor: who is in the greatest need of higher research quality standards? E.g. industry, academia or CROs? Young scientists or mature researchers?	Thomas Steckler / Malcolm Macleod (/ Lee Monk)

Assets

1. “Living” systematic review identifying primary research in AD
   - ~26,000 publications identified
2. Systematically curated guidelines for the conduct of animal experiments
3. Individual animal data from multi-site experiments
4. Ontology for describing animal experiments
   - Allows FAIR data sharing
5. Training platform and materials
   - Including materials from 2 Summer schools
6. The EQIPD Quality System

Acknowledgements

WP1

Thomas Steckler, Janssen
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Kathleen Wuyts, Janssen

WP2

Emily Sena, U Edinburgh
Karsten Wicke, Abbvie

WP3

Jan Vollert, Imperial College
Andrew Rice, Imperial College
Esther Schenker, Servier

WP4

Martien Kas, U Groningen
Sylvie Ramboz, Psychogenics

WP5

Anton Bespalov, PAASP
Anja Gilis, Janssen

WP6

Rene Bernhard, Charite
Uli Dirnagl, Charite

WP7

Kim Wever, U Nijmegen
Lee Monk, UCB

WP8

Maarten Loos, Sylics
Tom Van de Casteele, Janssen

WP9

Javier Guillen, AAALAC
Hanno Würbel, U Basel

Arlenda, Boehringer Ingelheim, Roche, LMU, Noldus, Novartis, Orion, Pfizer, Porsolt, Sanofi, Science Exchange, ECNP, Synaptologics, U Tübingen, U Mainz, U Aberdeen