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Bio

Disclosures – Thomas Steckler

- Employee of Janssen Pharmaceutica / Johnson & Johnson
- EFPIA Project Lead EQIPD IMI consortium
- Co-chair ECNP Preclinical Data Forum
- AAALAC ad-hoc specialist
- BMJ Open Science Associated Editor

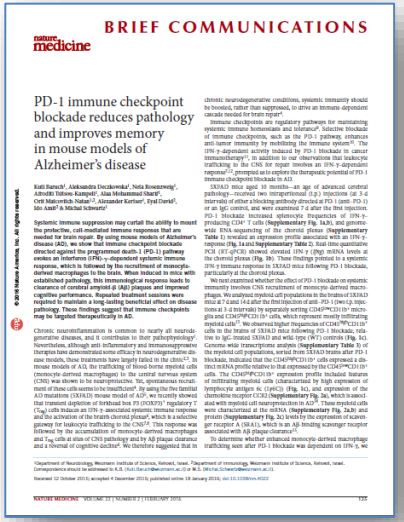
Data Quality and Reproducibility in Neurosciences Research An Industry Perspective

Thomas Steckler

Janssen Pharmaceutica NV

The views expressed in this presentation are solely those of the individual author, and do not necessarily reflect the views of his employer

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

RESEARCH ARTICLE

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

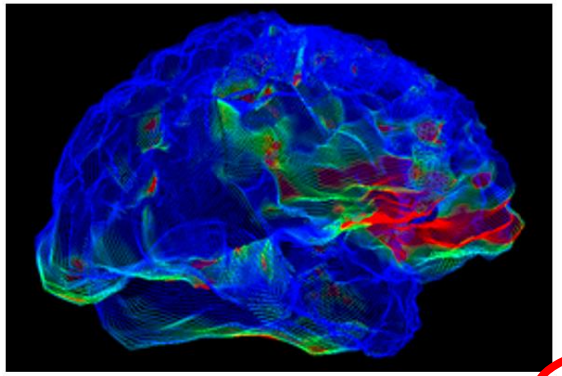
Exciting finding → Enthusiasm in the field → Sobering news

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

Growing External Investment by Pharmaceutical Industry…

CROs and academic organizations

primary outsourcing partners for pharmaceutical companies and biotech

$19.2bn

spent by pharmaceutical industry in 2016 for outsourcing the discovery of pharmaceutical drugs

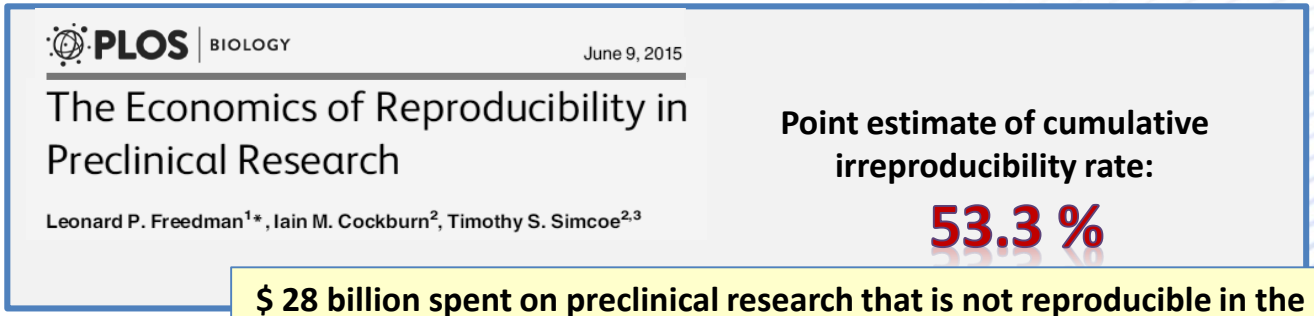
$43.7bn

expected rise by 2026 due to outsourcing in drug discovery

News Medical, Feb 2018

https://www.news-medical.net/whitepaper/20180212/Market-Highlight-The-Outsourcing-of-Pharmaceuticals.aspx

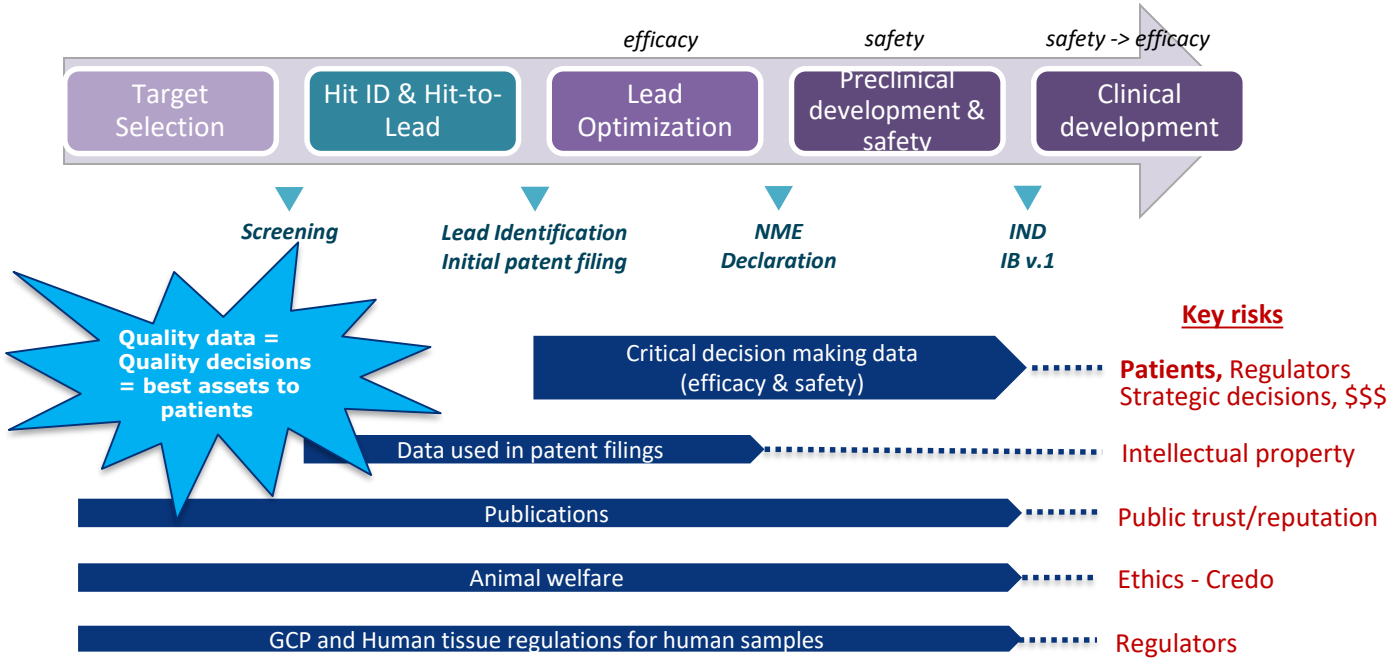
…Could Translate in Large Costs for Non-Reproducible R&D



$ 28 billion spent on preclinical research that is not reproducible in the US

Approx. $ 10 billion spent on outsourcing discovery work that was not reproducible in 2016 ?
Could more than double by 2026

Risks Related to Discovery Data



FACTS AND FIGURES

Full project title:	European Quality In Preclinical Data
Start date:	01 Oct 2017
Duration:	3 years
Participants:	29 institutions from 8 different countries
IMI funding:	4.5 million € (4,495,523.00 €)

https://quality-preclinical-data.eu/

What is EQIPD?

First IMI consortium completely dedicated to improving preclinical data quality

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

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

Expand R&D-wide if successful

The EQIPD Consortium

<u>29 Institutions from 8 different countries</u>

- **11 EFPIA companies**
- **10 Universities**
- **7 CROs**
- **1 Scientific society**

6 External advisors

8 Associated collaborators

~100 Stakeholders

Our Vision

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

Our Objectives

Within animal study design and data analysis, define the variables that influence the outcome of preclinical research conducted in industry and academia

Define the components that will make up the EQIPD Quality Management System and formulate consensus quality recommendations

Validate the feasibility of the quality management system in prospective animal studies conducted by our partners

Deliver an online educational platform providing certified education and training in the principles of quality management and rigor

Progress Today

Systematic Review on Alzheimer's Disease animal models under way

- Systematic search of 3 online database completed
- 265,258 hits detected, 4,000 studies screened, 347 studies included
- To be complemented with historical data from consortium partners

First version of Quality Management System for non-regulated R&D developed

- Roll out for beta-testing May 2019

Guiding Research Principles identified through systematic review of existing guidelines

- Informed development of the QMS and planning for the harmonisation stage of prospective studies

Preliminary scope for E-learning program determined

- E-learning materials have been gathered

Key to Success


Strong collaborative effort


Broad buy-in and support


Very systematic approach, wide coverage


Evidence based, from scientists for scientists

Acknowledgements

WP1 **Malcolm Macleod**, U Edinburgh
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- **Kathleen Wuyts**, Janssen Pharmaceutica

WP2 **Emily Sena**, U Edinburgh
- **Yulia Mordashova**, Abbvie

WP3 **Jan Vollert**, Imperial College
- **Andrew Rice**, Imperial College
- **Esther Schenker**, Servier

WP4 **Martien Kas**, University Groningen
- **Sylvie Ramboz**, Psychogenics

WP5 **Anton Bespalov**, PAASP
- **Anja Gilis**, Janssen, Pharmaceutica

WP6 **Rene Bernhard**, Charite
- **Uli Dirnagl**, Charite
- **Sabine Grote**, Abbvia

WP7 **Kim Wever**, U Nijmegen
- **Lee Monk**, UCB

WP8 **Maarten Loos**, Sylics
- **Tom Van de Casteele**, Janssen Pharmaceutica

WP9 **Javier Guillen**, AAALAC International
- **Hanno Würbel**, U Basel

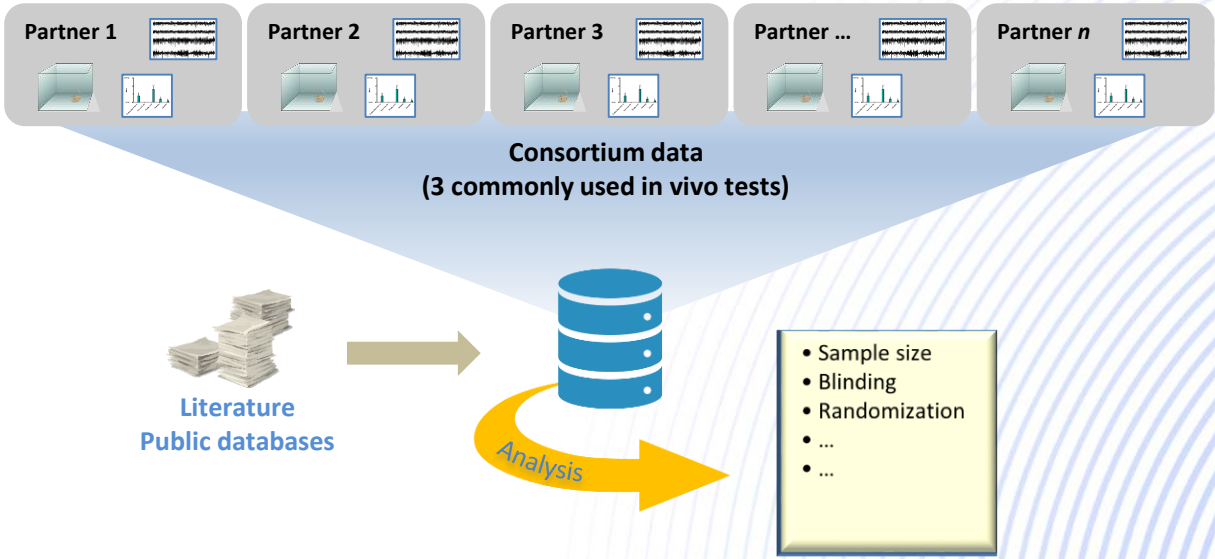
Arlenda, Boehringer Ingelheim, Roche, LMU, Noldus, Novartis, Orion, Pfizer, Porsolt, Sanofi, Science Exchange, ECNP, Synaptologics, U Tübingen, U Mainz, U Aberdeen

The project leading to this application 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.

Backups

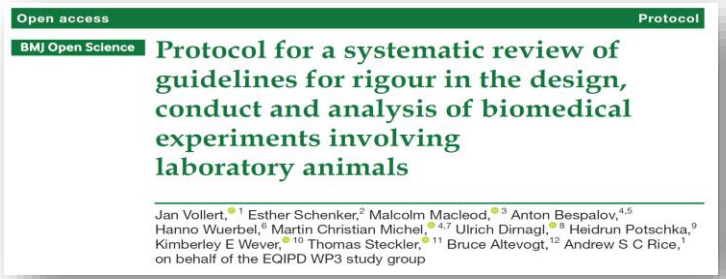
Historical Data Analysis

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



Research Guidelines

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



Open access Protocol

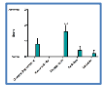
BMJ Open Science

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
- Recommendations for prospective studies

Evidence from WP4

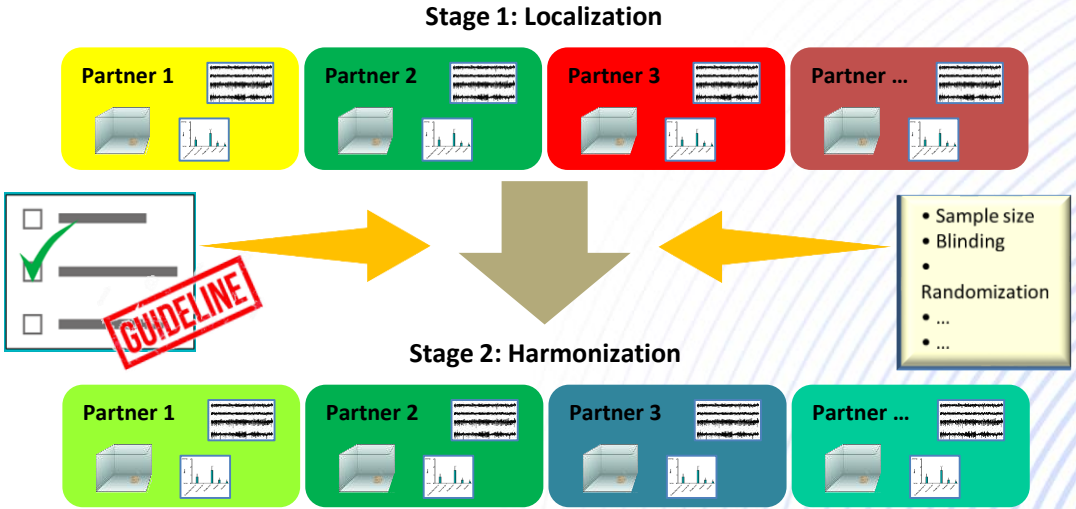


WP2 ANALYSIS

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

Cross-site Validation

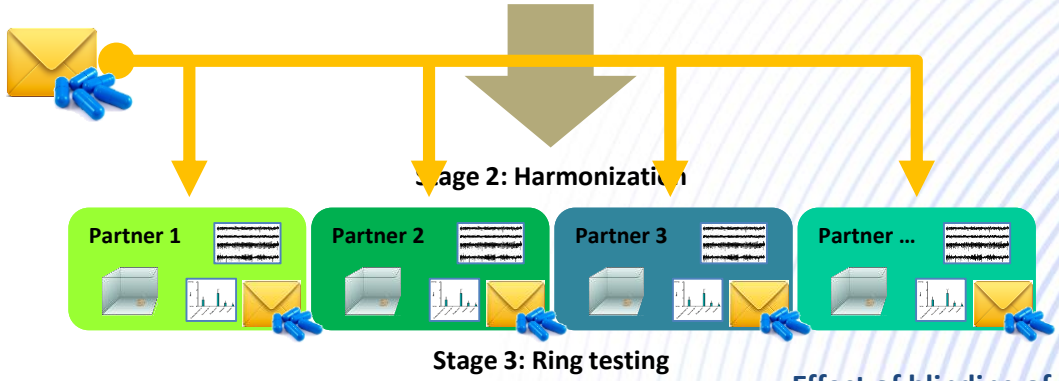
Aim: Validate the principles and research models that improve robustness and data quality in preclinical studies



Effect of reduced inter-lab variability?

Cross-site Validation

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



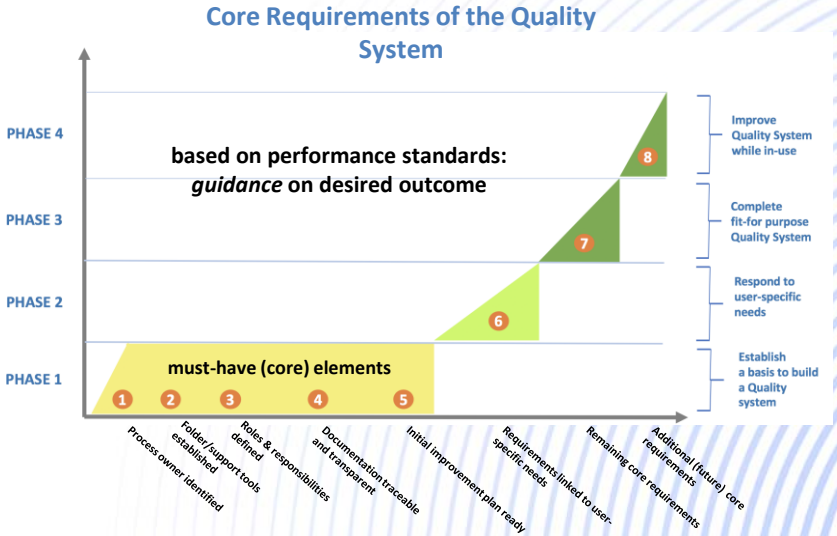
Stage 3: Ring testing

Effect of blinding of test item

Quality Management System for Emerging and Classical Technologies

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

- ✓ Analysis of the current use of research quality principles, best practices and challenges
- ✓ Identification of key principles using a Delphi process
- ✓ Fine-tuning following stakeholder feedback (ongoing)



QMS Maintenance and Assessment

Aim: Generate critical, high-level processes to ensure efficient governance of the new quality system

- **Internal governance:** Develop tools for self-assessment
- **External governance:** Can we learn from AAALAC?
- On-site or remote assessments (e.g. questionnaires)
- Establish an accreditation system?
- Review of existing quality systems

Quality Systems Evaluated

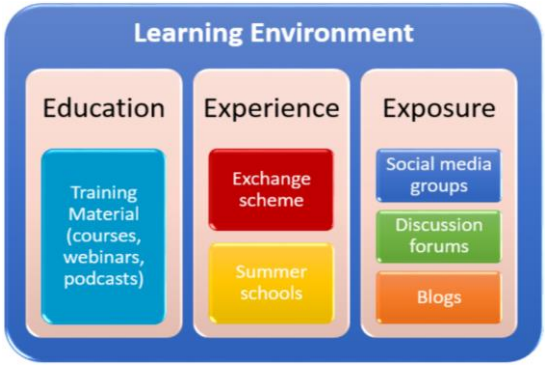
- ISOx3
- AAALAC
- RQA
- BBSRC
- ASQ
- GLP
- Janssen
- Novartis

Governance Building Blocks

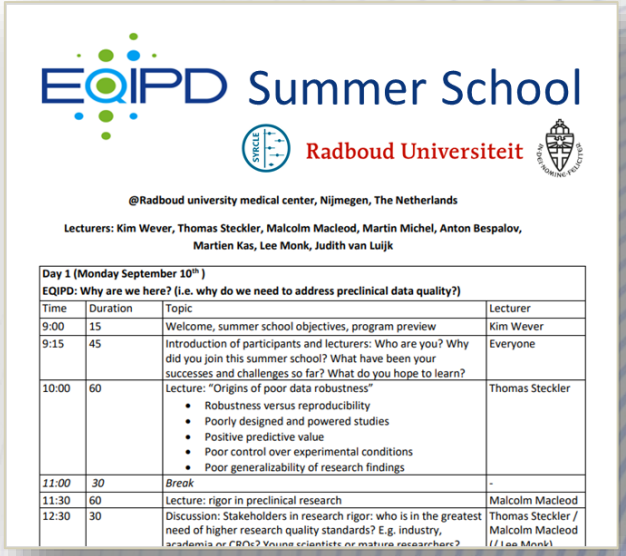
- Roles and responsibilities
- Management of resources
- Conflict of interest
- Control and improvement
- Auditing
- Certification
- Sustainability
- Training

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



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)