Increasing robustness of preclinical research towards successful translation:

An assessment of the evolution of protocols from exploration to confirmation

María Arroyo Araujo, Clarissa F. D. Carneiro, Sophia Rotter, Natascha Drude, Ulrich Dirnagl, Ulf Toelch

BIH-QUEST Center for Responsible Research, Berlin Institute of Health,
Charité Universitätsmedizin Berlin

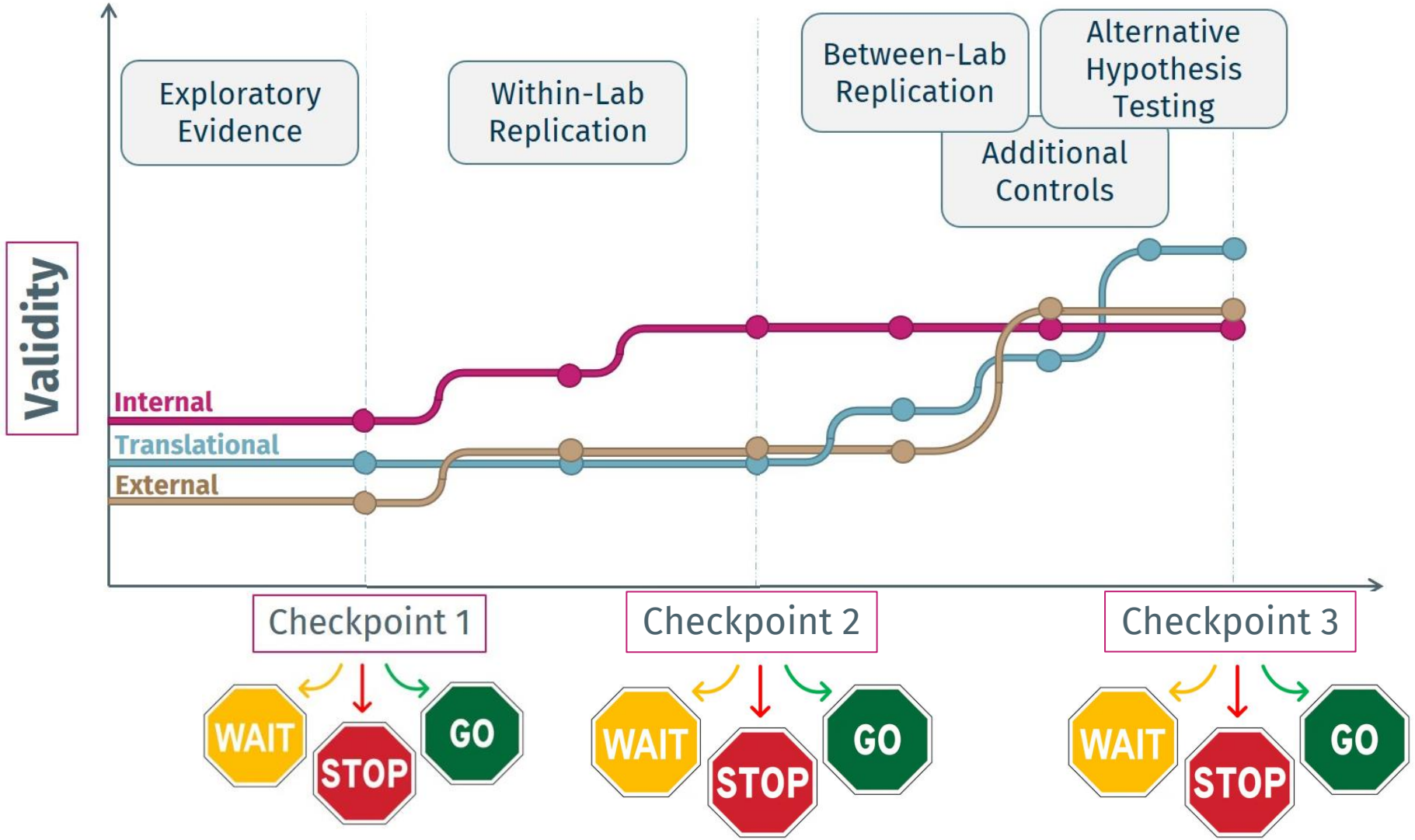
05.06.2024

BIH QUEST
Center for Responsible Research

GEFÖRDERT VOM
Bundesministerium
für Bildung
und Forschung

BIH Berlin Institute of Health @Charité

The preclinical pathway



How can we be confident about these decisions?

Modified from Drude et al., eLife 2021

BIH QUEST Center for Responsible Research

DECIDE - Decision-Enabling Confirmation of Innovative Discoveries and Exploratory Evidence

The accompanying project for the funding call:

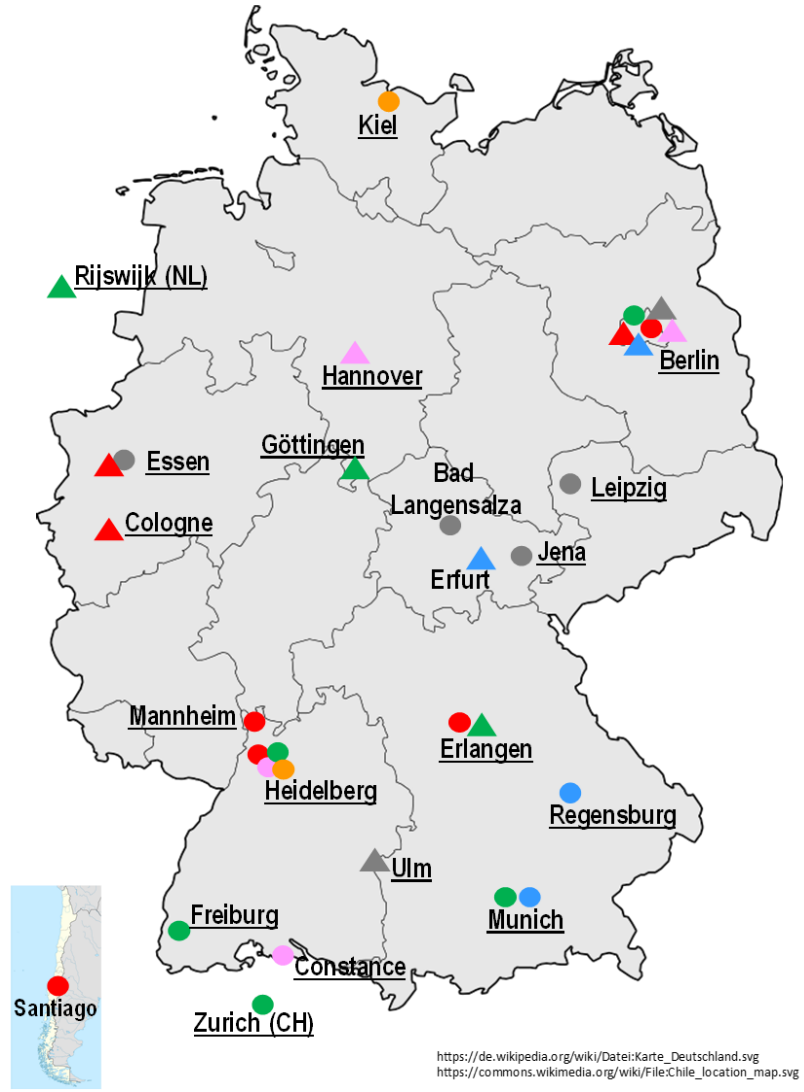
Confirmatory Preclinical Studies and Systematic Reviews

Research practices relevant for study design validity and reliability

DECIDE team @ QUEST

Multi-lab consortia

- ~1MEUR/consortium
- 1-10 labs
- National involvement
- Diverse disease models
- **1 exploratory finding to confirm**

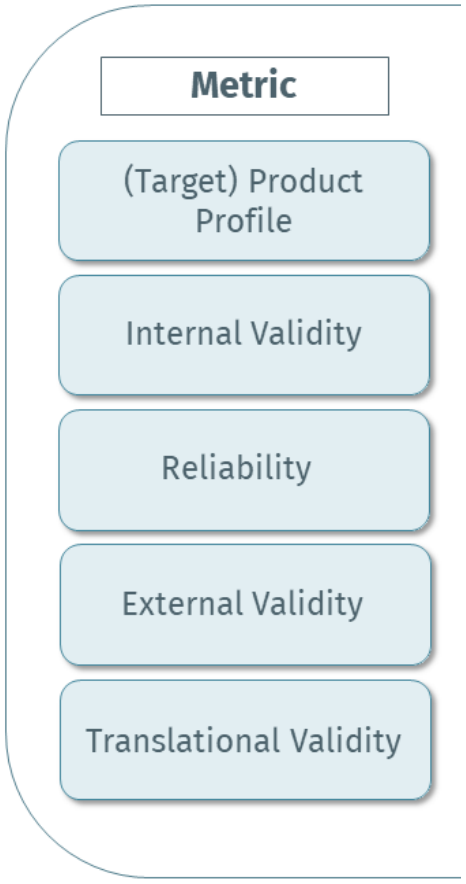


https://de.wikipedia.org/wiki/Datei:Karte_Deutschland.svg
https://commons.wikimedia.org/wiki/File:Chile_location_map.svg

BIH QUEST Center for Responsible Research

Robustness framework
Responsible PreckiniX



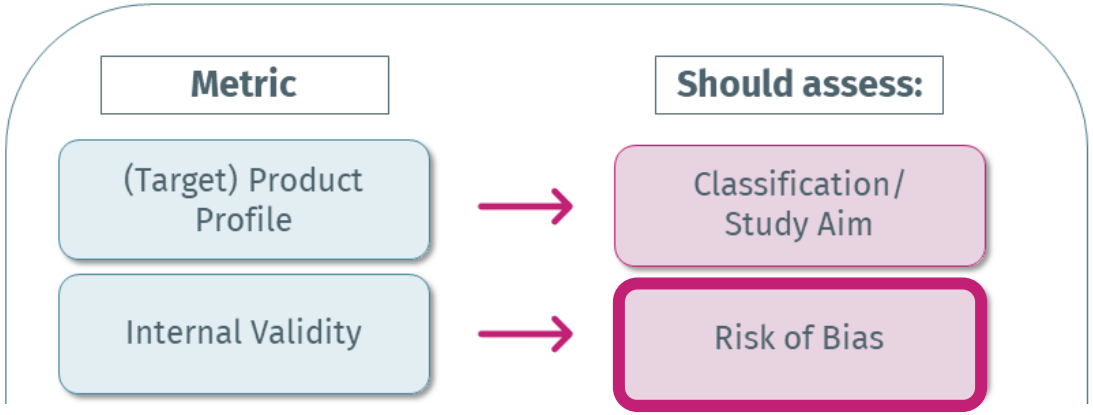
47 items based on

- existing guidelines (e.g., ARRIVE)
- (systematic) reviews
- exchange with research groups (feasibility)

Constantly refined based on interaction with research groups

BIH QUEST Center for Responsible Research

Robustness framework
Responsible PrecliniX



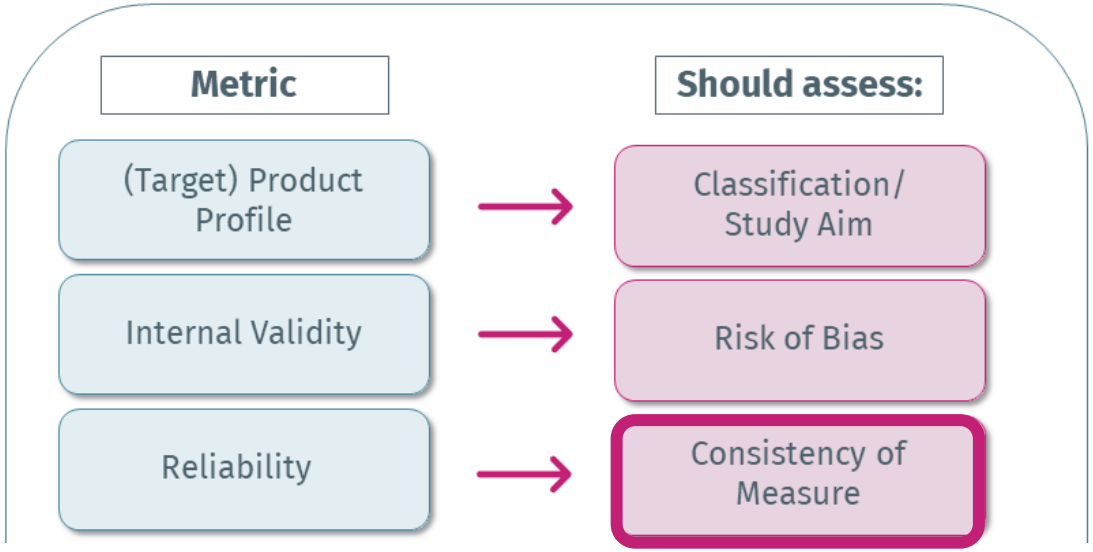
- Blinding
- Randomization
- Inclusion/exclusion criteria
- Control conditions
- Primary outcome

} Pre-registration

- Experience: training/protocols/DMP
- Data availability/ analysis pipeline

BIH QUEST Center for Responsible Research

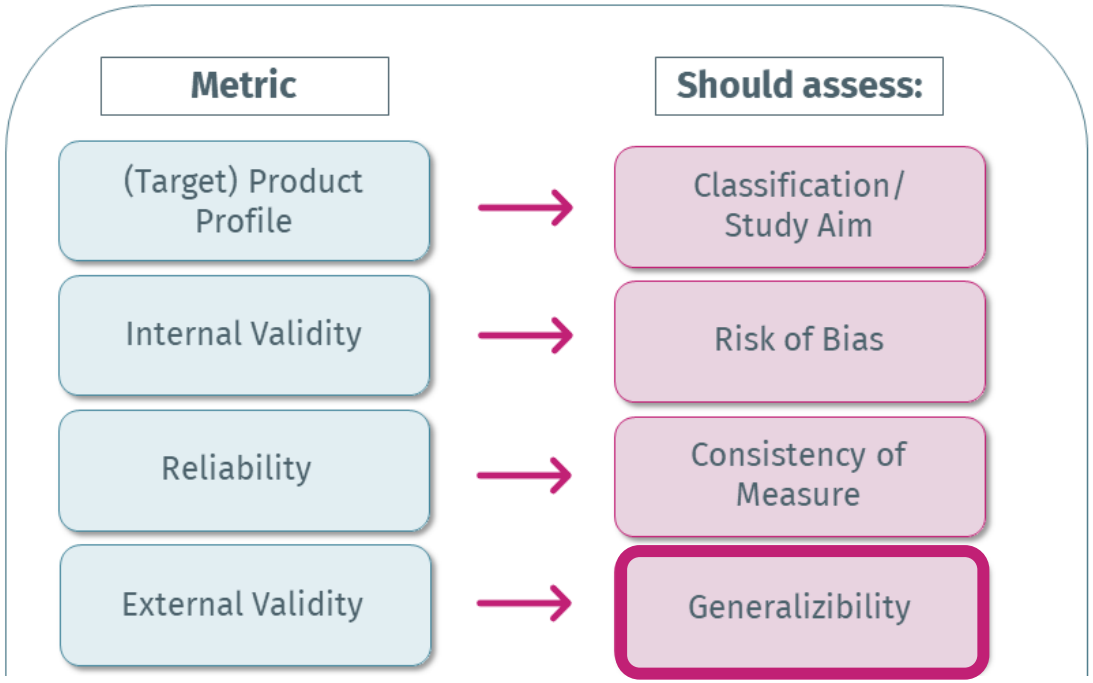
Robustness framework
Responsible PrecliniX



- Statistical analysis plan
- Statistical analysis transparency
- Experimental unit definition
- Power calculation/ sample sizes
- Effect size
- Confounding variables
- Collider bias

BIH QUEST Center for Responsible Research

Robustness framework
Responsible PrecliniX



- Replication in-house
- Different batches
- Replication across laboratories

- **Systematic heterogenization** (both sexes, comorbidities, strains, …)

- **Triangulation**
- Converging evidence
- Discriminant evidence
- Consideration of alternative hypothesis

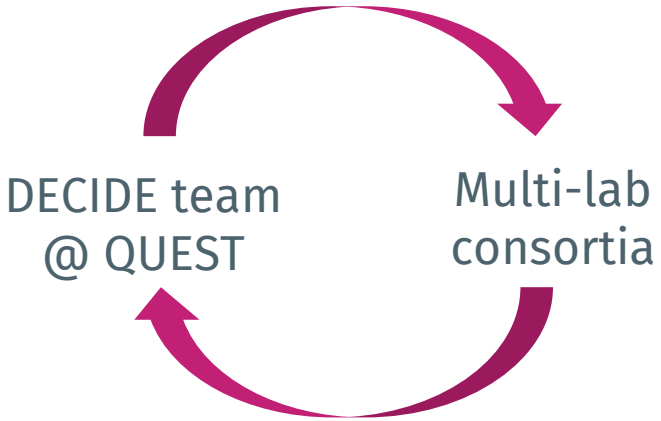
BIH QUEST
Center for Responsible Research

DECIDE - Decision-Enabling Confirmation of Innovative Discoveries and Exploratory Evidence

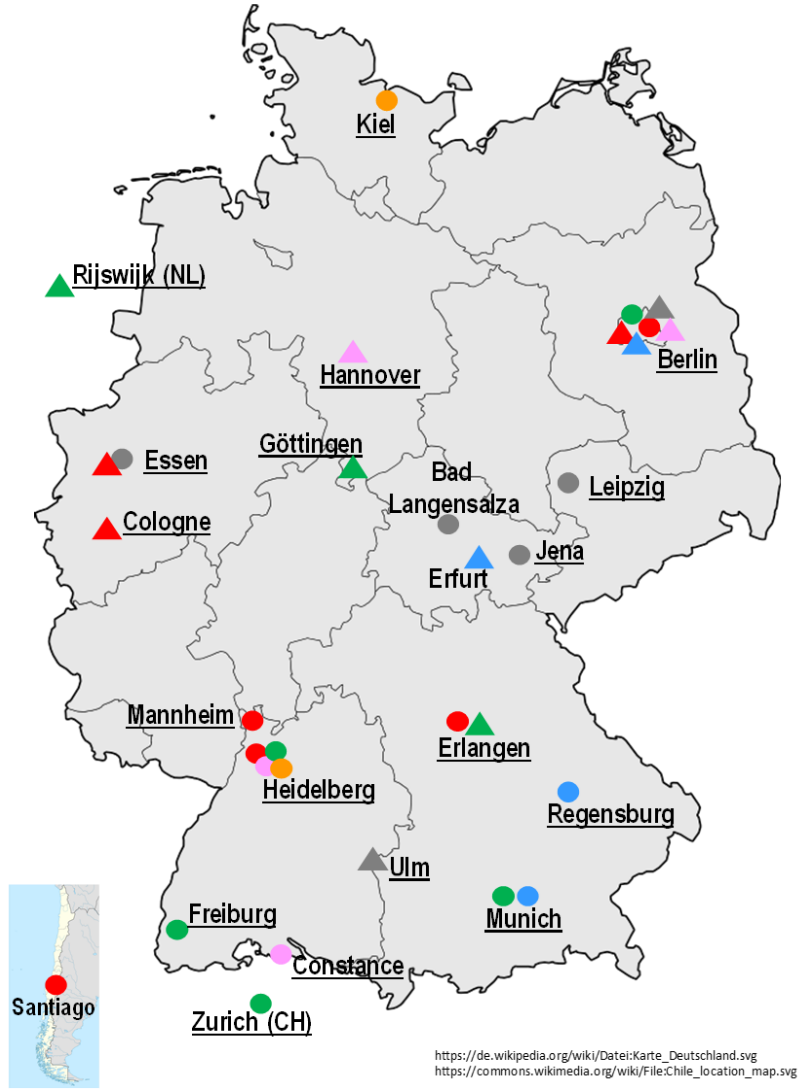
The accompanying project for the funding call:

Confirmatory Preclinical Studies and Systematic Reviews

Research practices relevant for study design validity and reliability



- Feasibility to implement research practices
- Access to study plans, protocol and results



https://de.wikipedia.org/wiki/Datei:Karte_Deutschland.svg
https://commons.wikimedia.org/wiki/File:Chile_location_map.svg

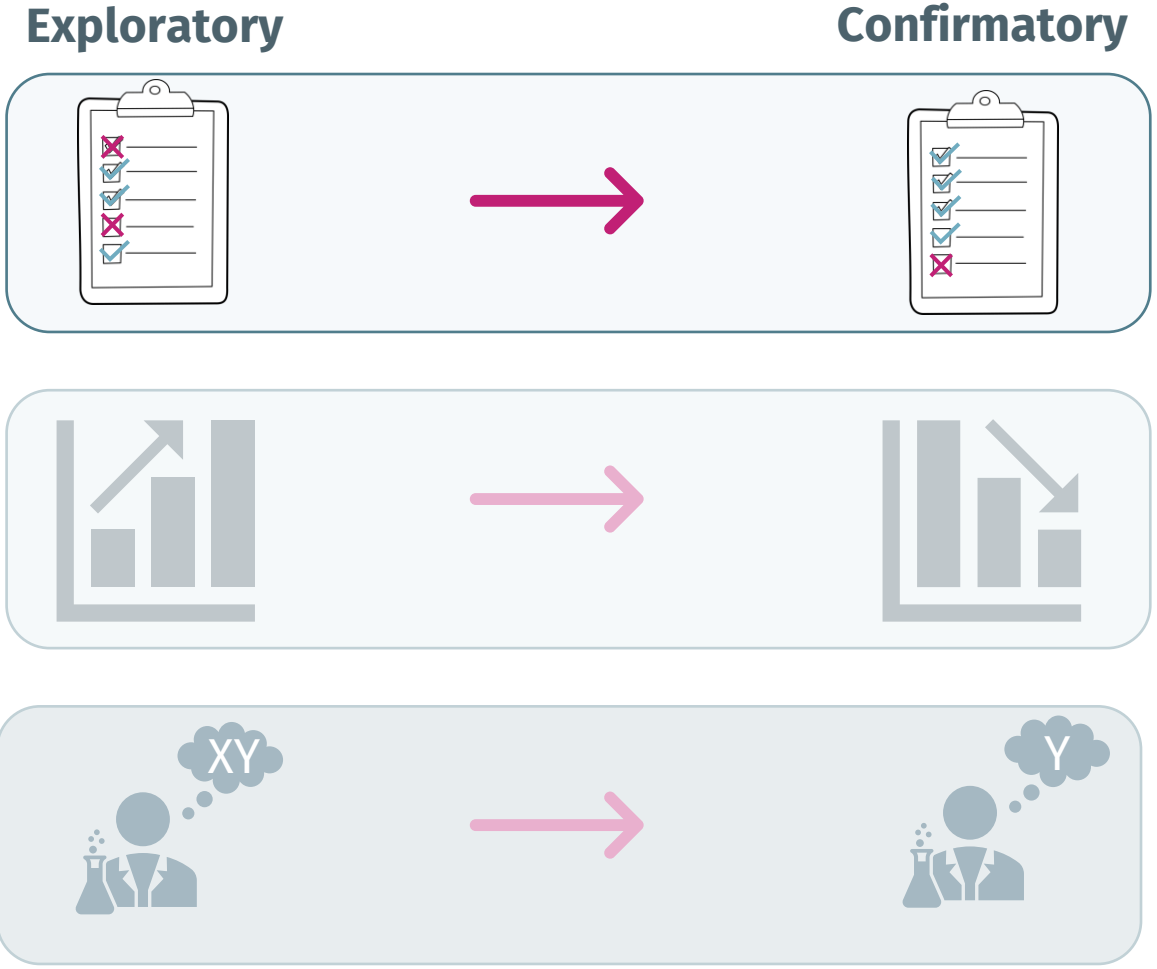
BIH QUEST
Center for Responsible Research

Meta-research: Exploratory vs. Confirmatory studies

A. Protocol comparison

B. Results replicability

C. Knowledge-claim update



i. Exploratory study
ii. Pre-registration
iii. Confirmatory study

BIH QUEST Center for Responsible Research

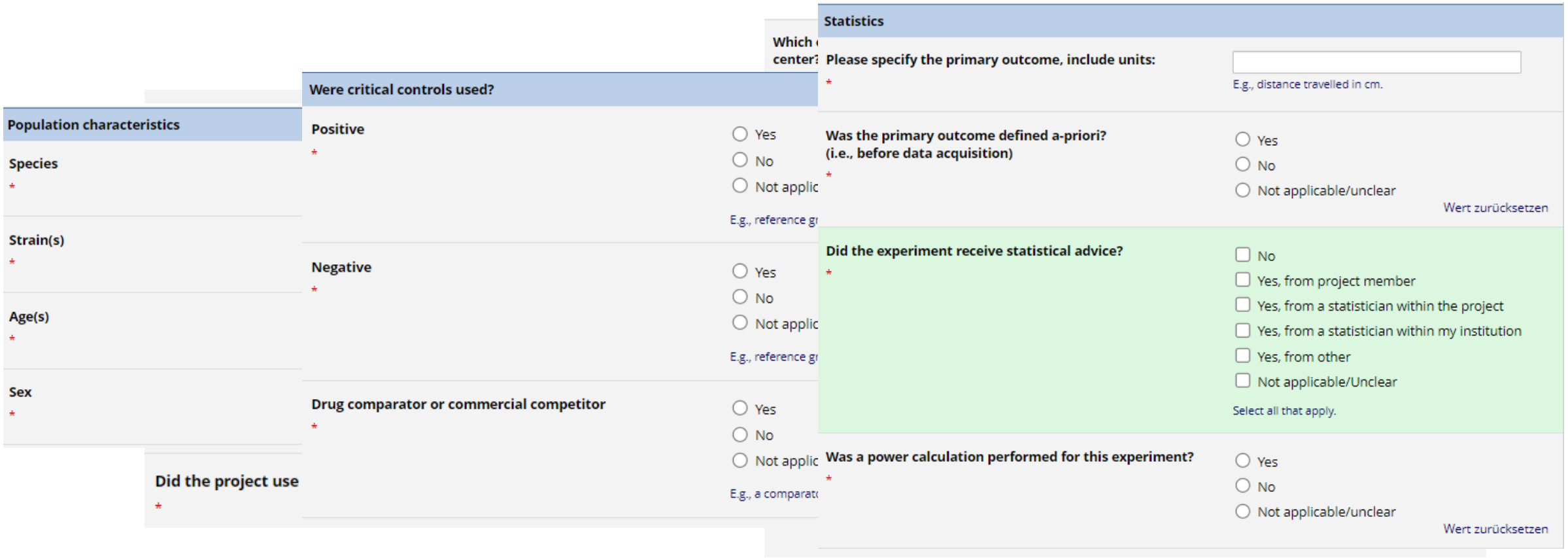
Comparison of protocols

Step 1: List relevant information to extract

- Robustness framework items
- Population-Intervention-Comparators-Outcomes items

Step 2- collecting data from consortia (ongoing)

- **REDCap surveys: Project level and experiment level**



BIH QUEST Center for Responsible Research

Step 3- Experts' elicitation

Example

Condition: Alzheimer's Disease

Animal model: 3xTg-AD mice, 12 months old, male and female

Control groups: Negative control

Intervention: Daily intraperitoneal injections for 2 weeks

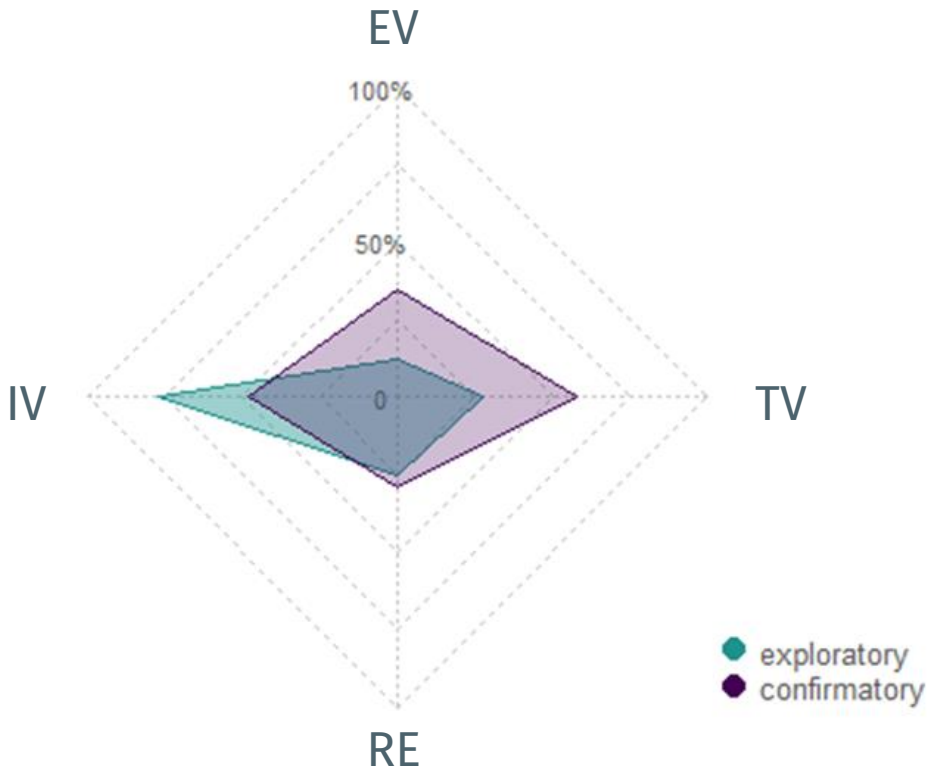
Outcome: Classification of plaque formation in the hippocampus (low, high)

Questions related to:

- Human condition
- Model physiology
- Model pharmacology
- Model disease
- Reproducibility

Storey, J., Gobbetti, T., Olzinski, A., & Berridge, B. R. (2021). A Structured Approach to Optimizing Animal Model Selection for Human Translation: The Animal Model Quality Assessment. *ILAR Journal*, *62*(1–2), 66–76.

Protocol comparison outcome



EV: External validity
IV: Internal validity
TV: Translational validity
RE: Reliability

not real data

BIH QUEST Center for Responsible Research

Limitations and take-home message

- **We offered advice/guidance but the projects decided whether to take it or not**

- **Not all guidance was feasible to implement even when it was welcomed by the groups**

-> To increase the confidence in decision-making we need research made fit-for-purpose

DECIDE team

Prof. Dr. Ulrich Dirnagl

PD Dr. Ulf Tölch

Dr. Natascha Drude

María Arroyo Araujo, PhD

Looking for 1 postdoc @ AG Toelch

XXXX

Clarissa F. D. Carneiro, PhD

Anja Collazo, MSc

Dr. Charlotte Klein

Dipl. Biochem. Claudia Kurreck

Dr. Lorena Martinez Gamboa

Meggie Danziger, MSc

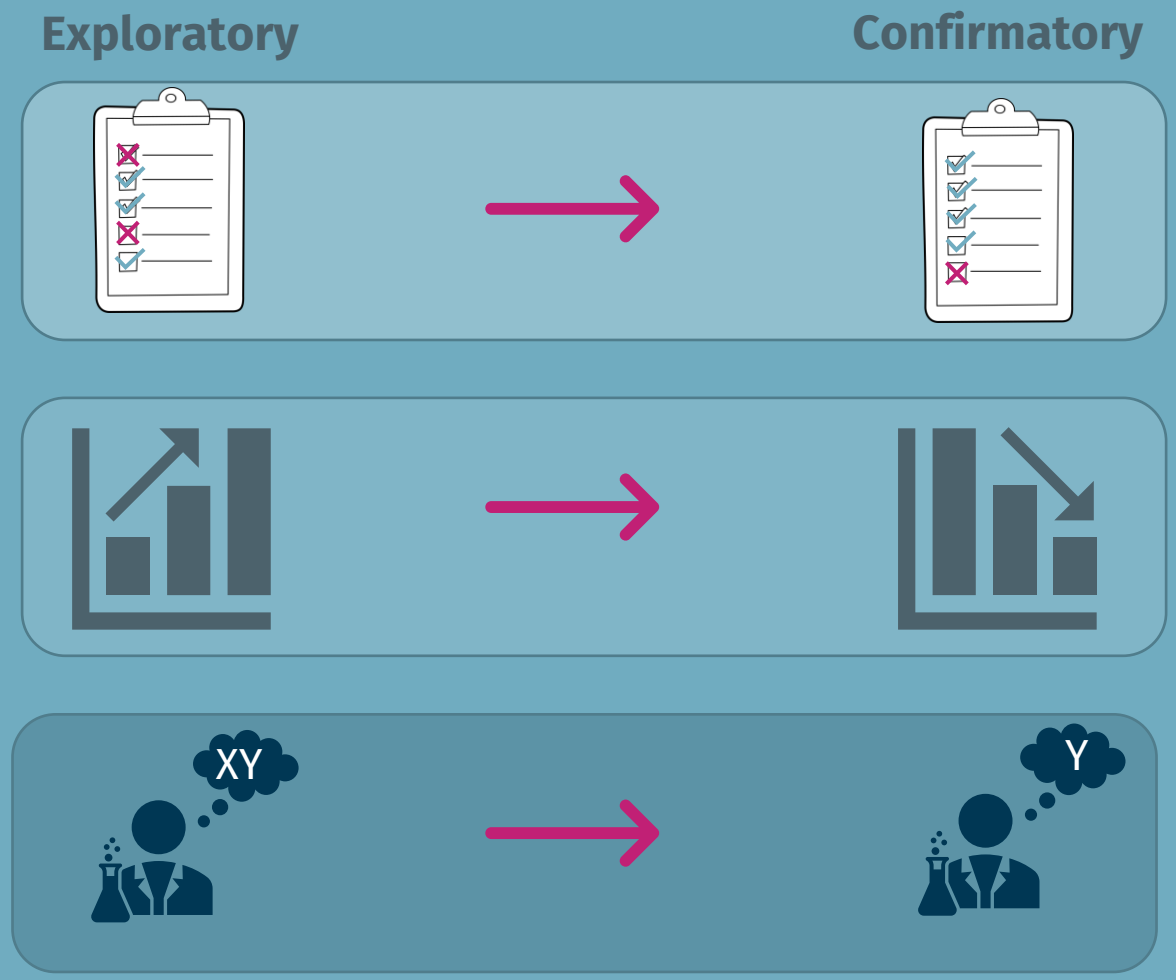
Silke Kniffert, MSc

Dr. Maren Hülsemann

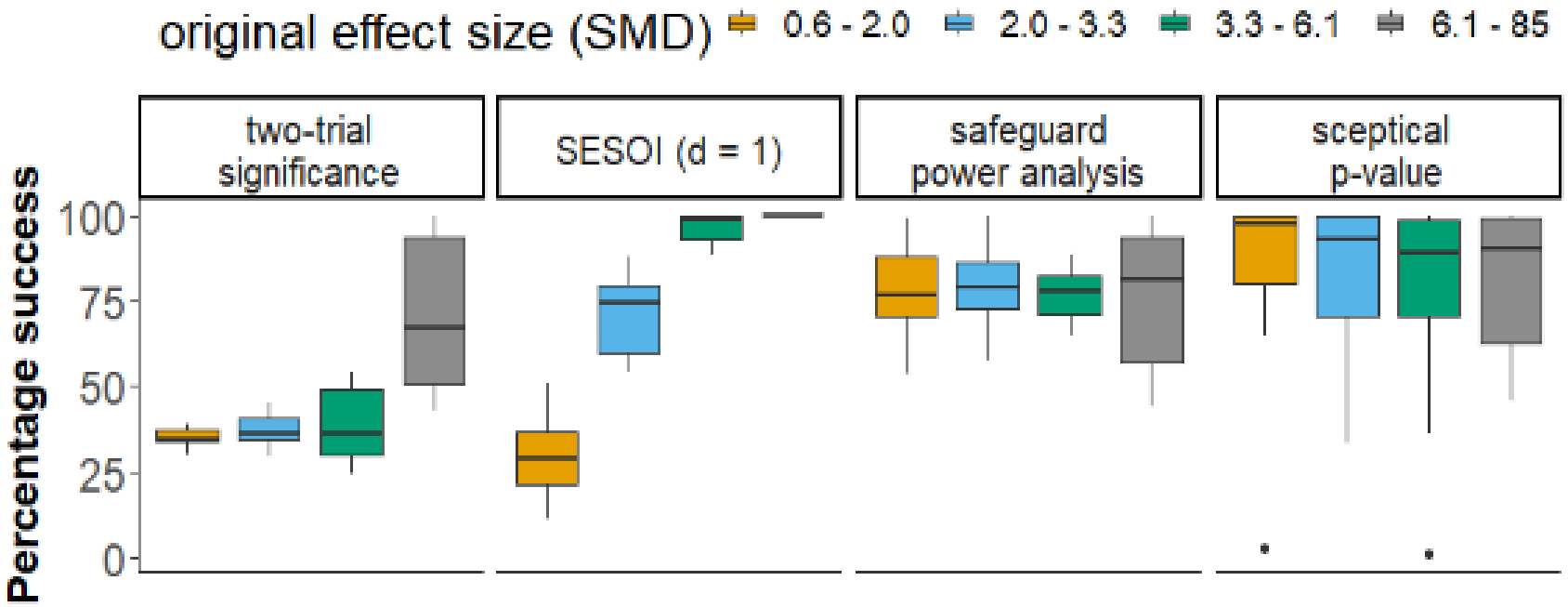
Sophia Rotter, MSc

Contact: decide@charite.de

Thank you!



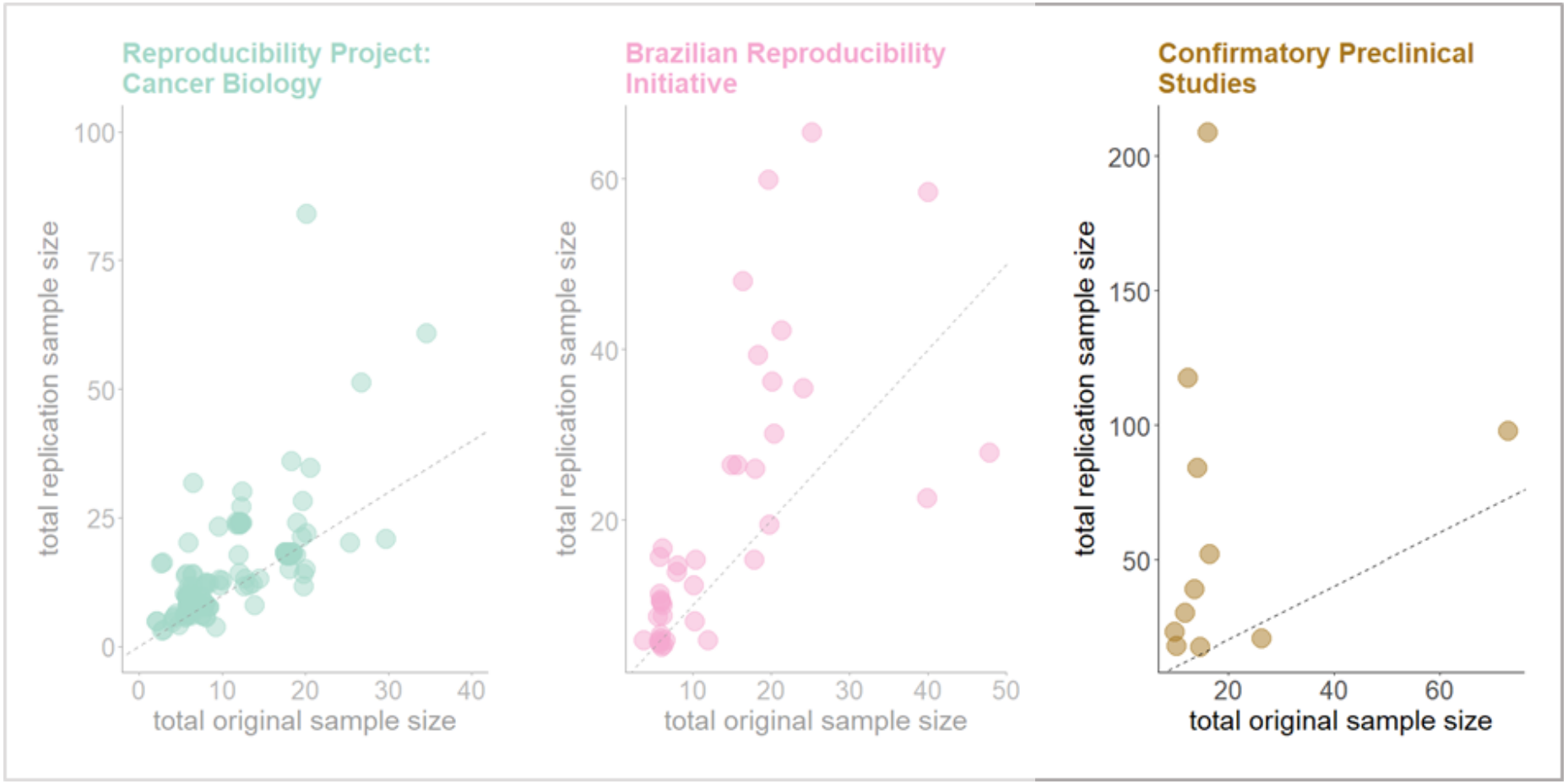
Meta-research:
Sample size calculation methods influence the replication success



Collazo et al, in preparation

BIH QUEST Center for Responsible Research

Sample sizes used in the different groups

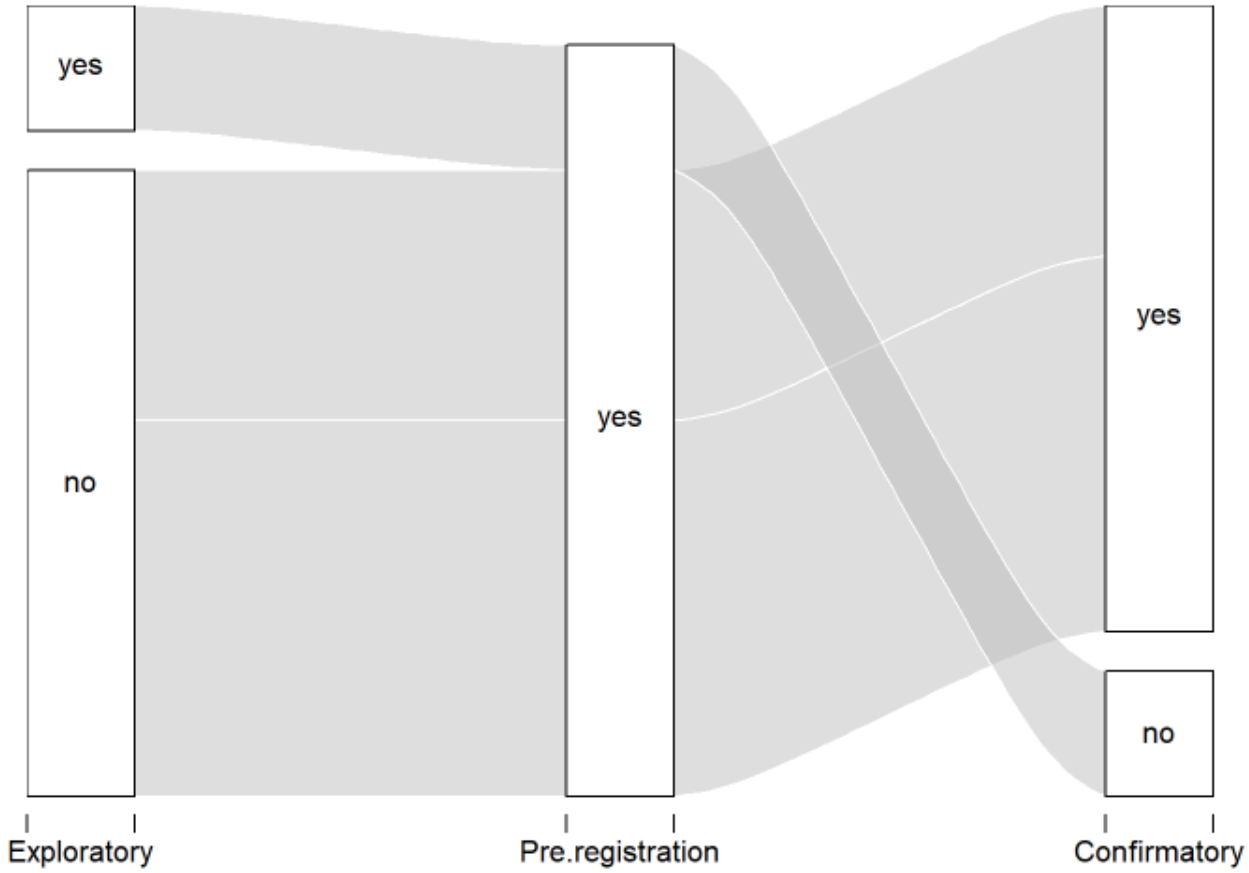


Collazo et al, in preparation

BIH QUEST Center for Responsible Research

Transition of protocols from exploratory to confirmatory

Blinded outcome assessment



**not real data*

BIH QUEST Center for Responsible Research

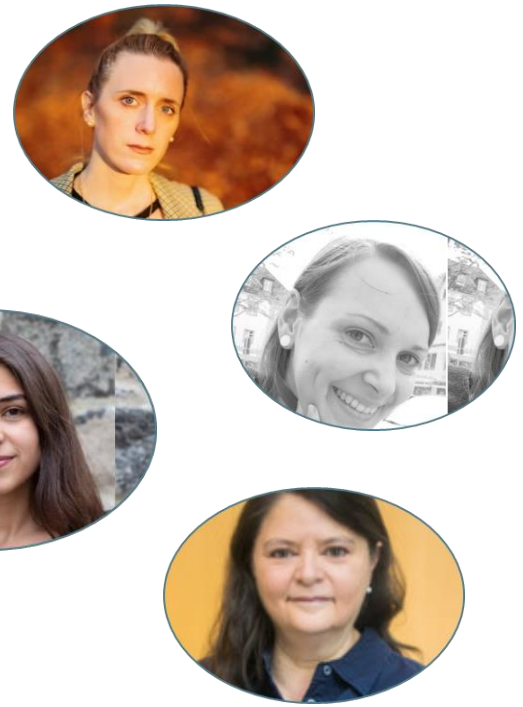
Previous activities: Consultation and counseling

- **How to improve the experimental design**
  - Internal validity: blinding, randomization, …
  - Reliability: sample size calculation, control groups…
  - External validity: systematic heterogenization, using both sexes…
  - Translational validity: animal models, outcome selection…

- Responsible PreCliniX:

https://www.bihealth.org/en/quest/service/service/responsible-preclinix

Full references



The role of replications:

Drude et al 2021, eLife

https://doi.org/10.7554/eLife.62101

Practical considerations for planning and execution:

Drude et al 2022, Translational Medicine Communications

https://doi.org/10.1186/s41231-022-00130-8

Strategies to improve external validity:

Carneiro et al 2023, Expert Opinion on Drug Discovery

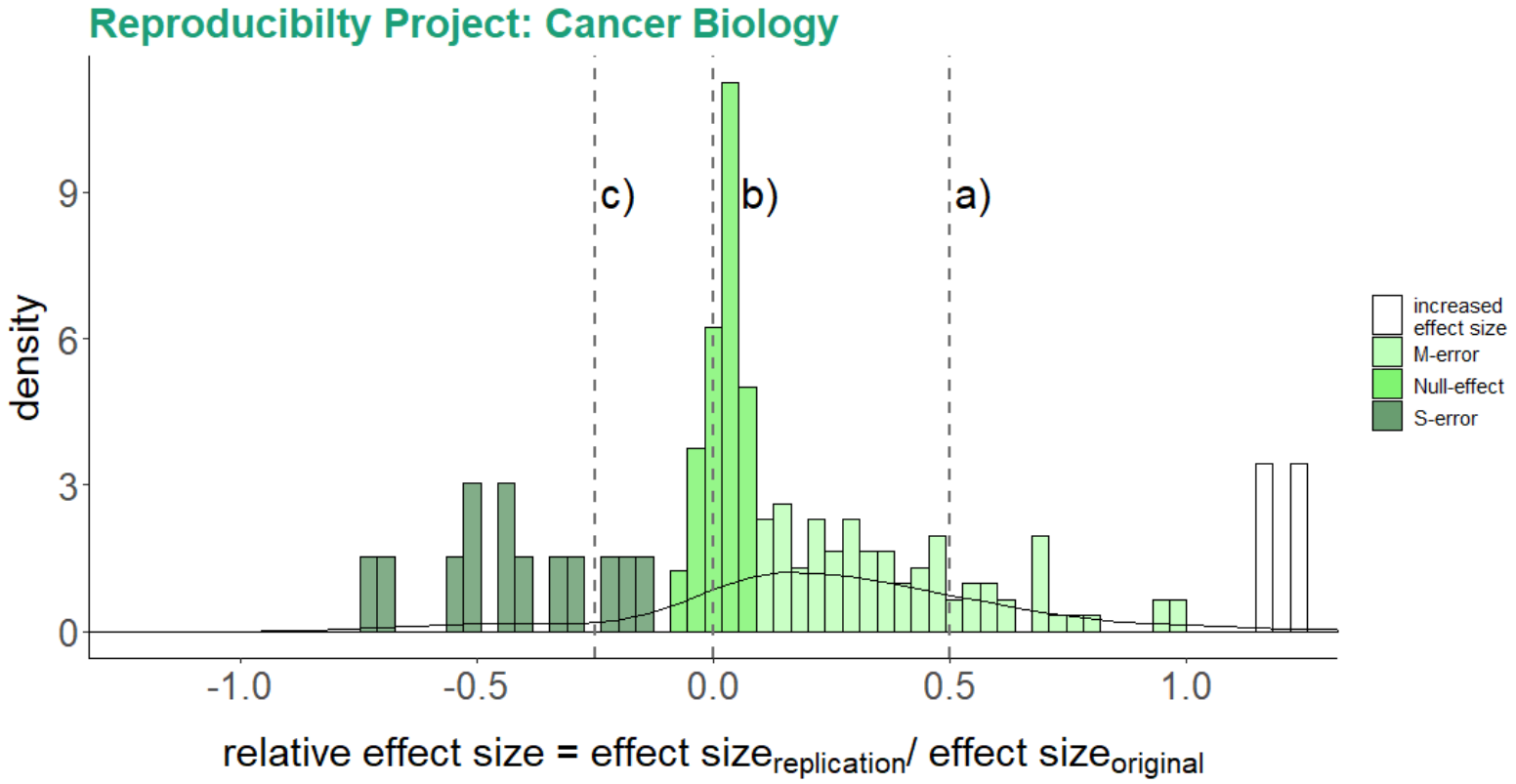
https://doi.org/10.1080/17460441.2023.2251886

Statistical planning and analyses:

Danziger et al 2022, bioRxiv https://doi.org/10.1101/2022.01.17.476585,

Carneiro et al *(in preparation)*, Arroyo-Araujo et al *(in preparation)*

Meta-research: Sample size calculation in replication experiments



Collazo et al, in preparation

BIH QUEST Center for Responsible Research