

Increasing robustness of preclinical research towards successful translation:

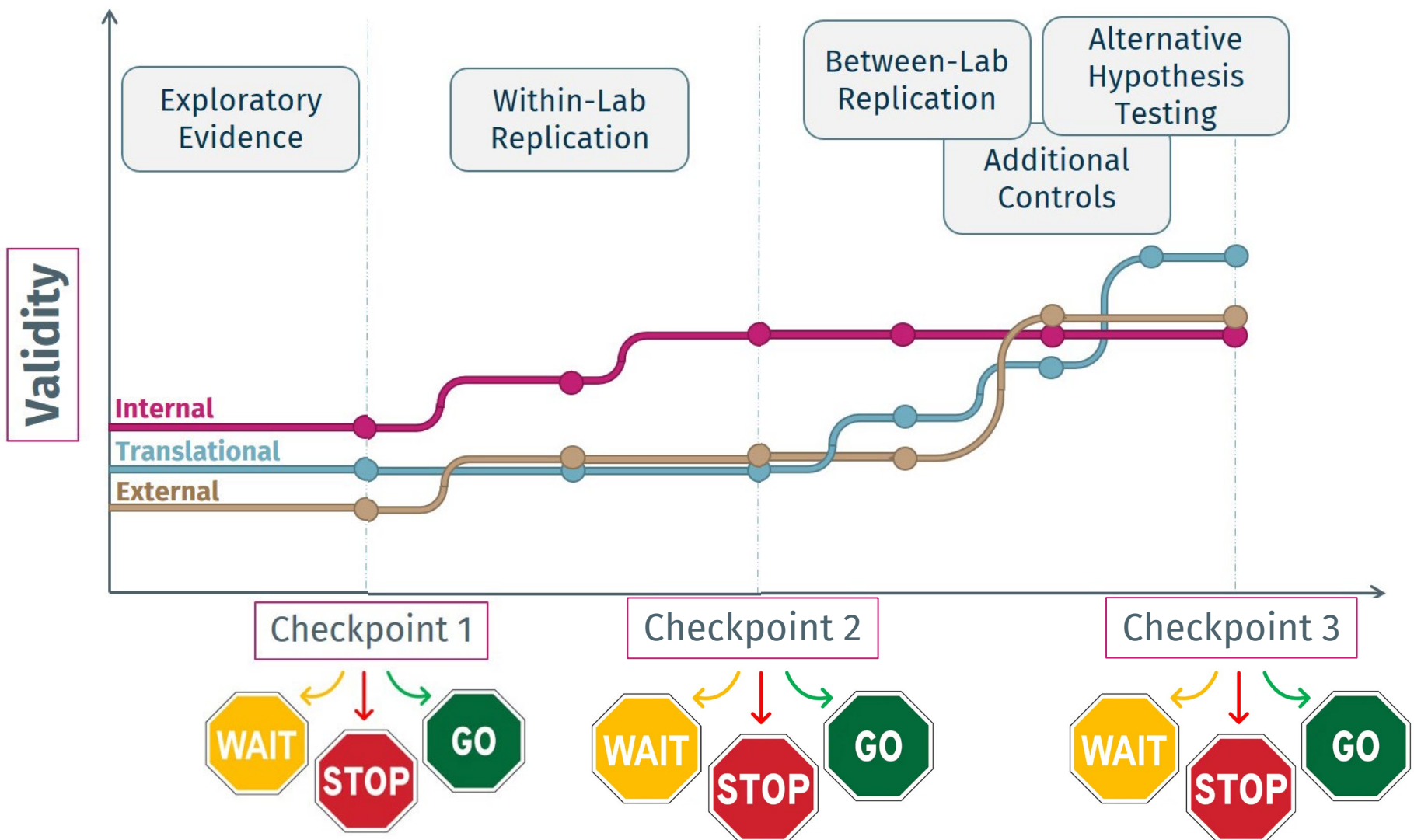
An assessment of the evolution of protocols from exploration to confirmation

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The preclinical pathway



How can we be confident about these decisions?

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

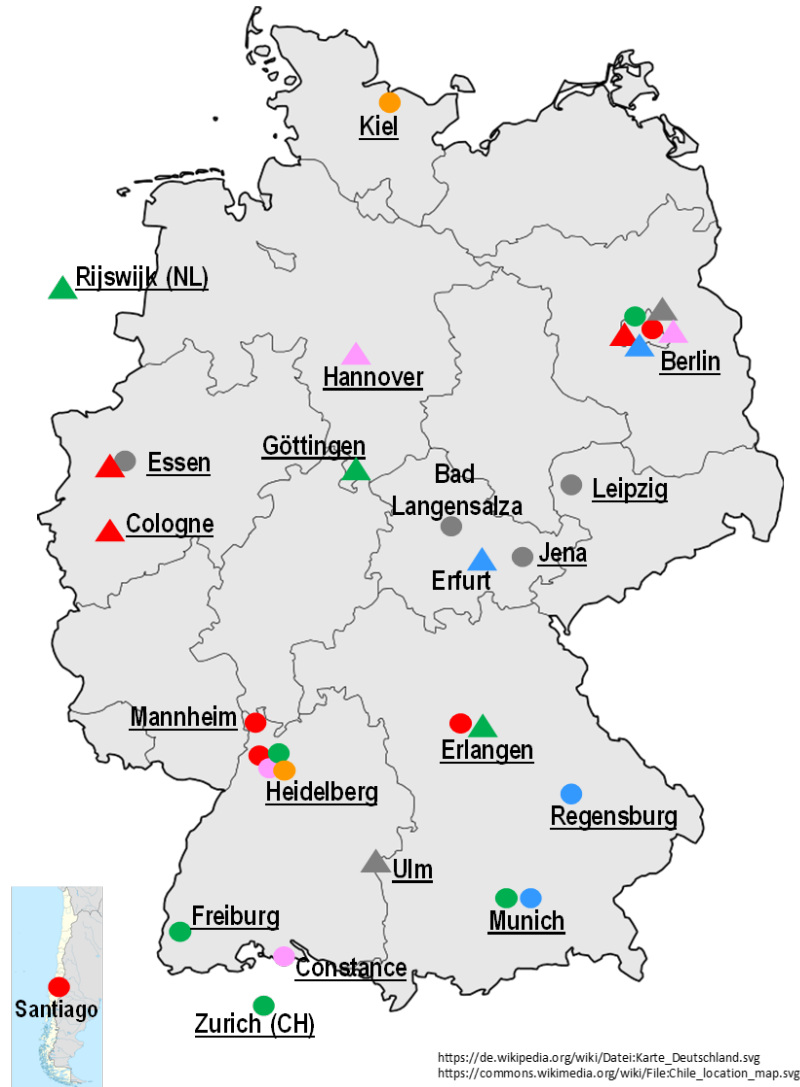
The accompanying project for the funding call:
Confirmatory Preclinical Studies and Systematic Reviews

Research practices relevant for study design
validity and reliability

DECIDE team
@ QUEST

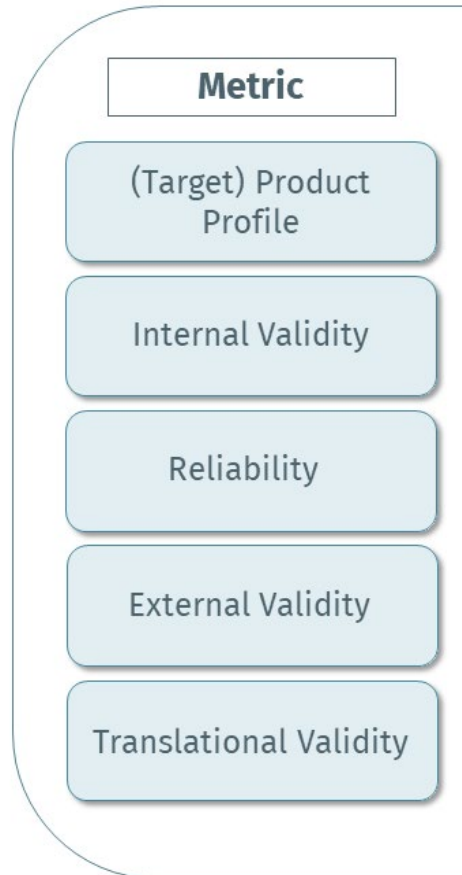
Multi-lab
consortia

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



Robustness framework

Responsible Preclinix



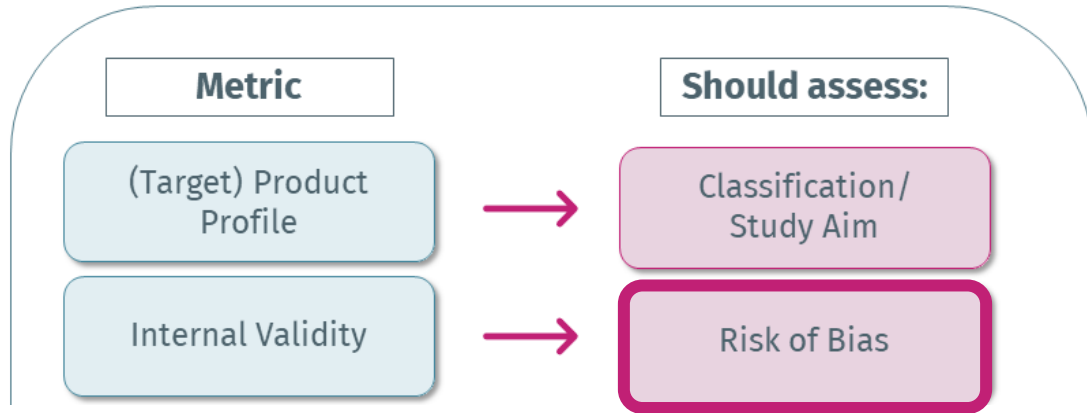
47 items based on

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

**Constantly refined based on interaction
with research groups**

Robustness framework

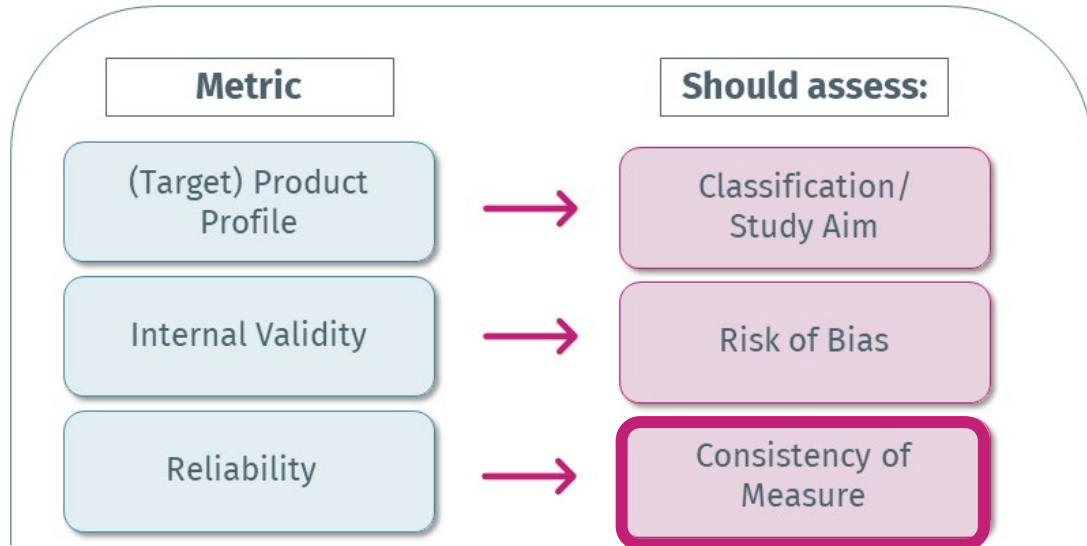
Responsible Preclinix



- Blinding
 - Randomization
 - Inclusion/exclusion criteria
 - Control conditions
 - Primary outcome
 - Experience: training/protocols/DMP
 - Data availability/ analysis pipeline
- } Pre-registration

Robustness framework

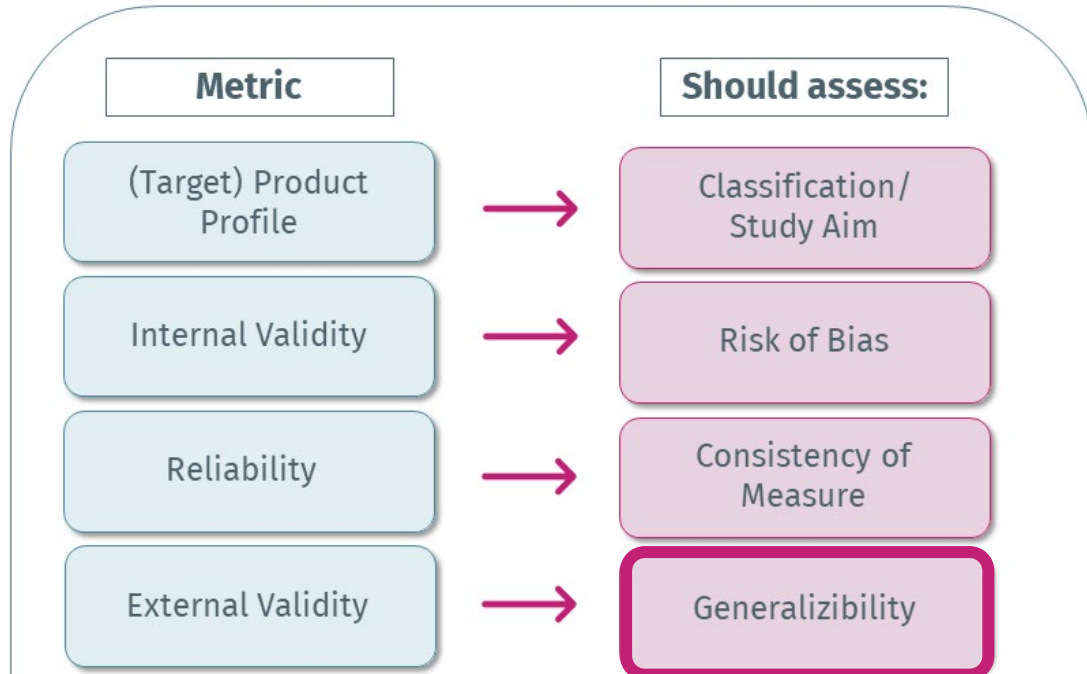
Responsible PreclinIX



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

Robustness framework

Responsible Preclinix

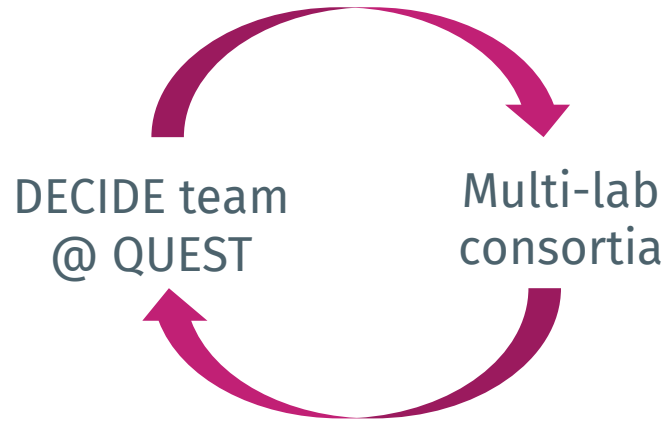


- Replication in-house
- Different batches
- Replication across laboratories
- **Systematic heterogenization** (both sexes, comorbidities, strains, ...)
- **Triangulation**
- Converging evidence
- Discriminant evidence
- Consideration of alternative hypothesis

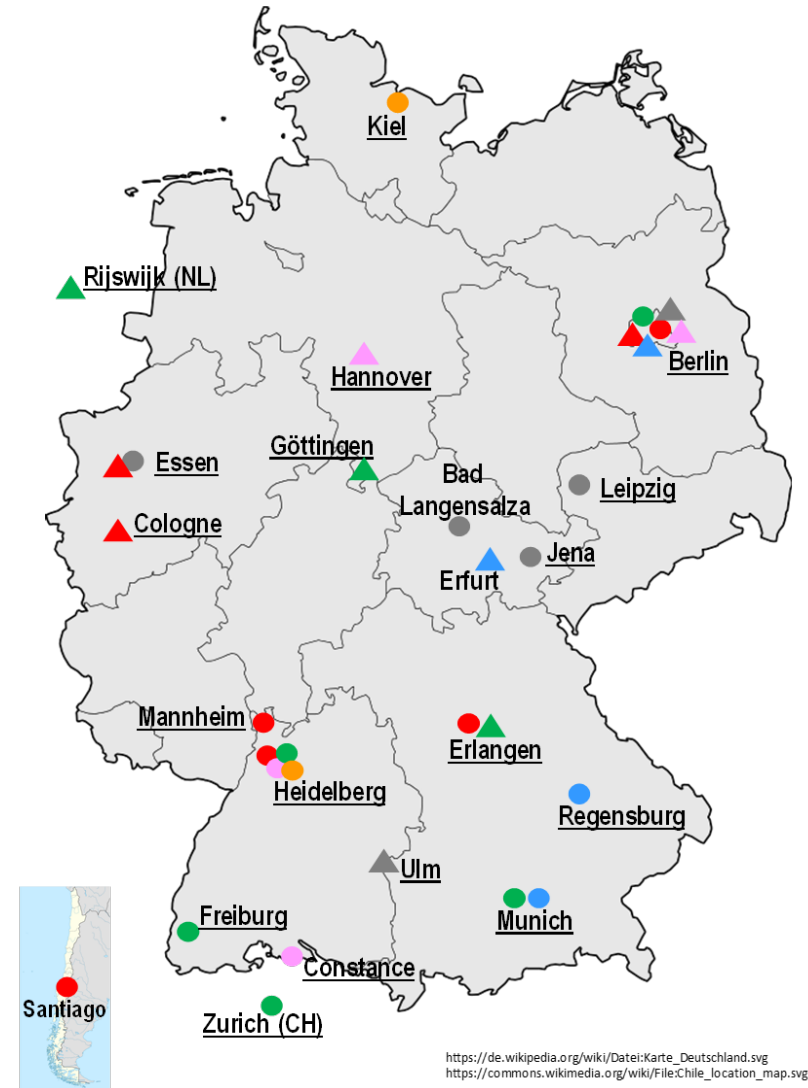
DECIDE - Decision-Enabling Confirmation of Innovative Discoveries and Exploratory Evidence

The accompanying project for the funding call:
Confirmatory Preclinical Studies and Systematic Reviews

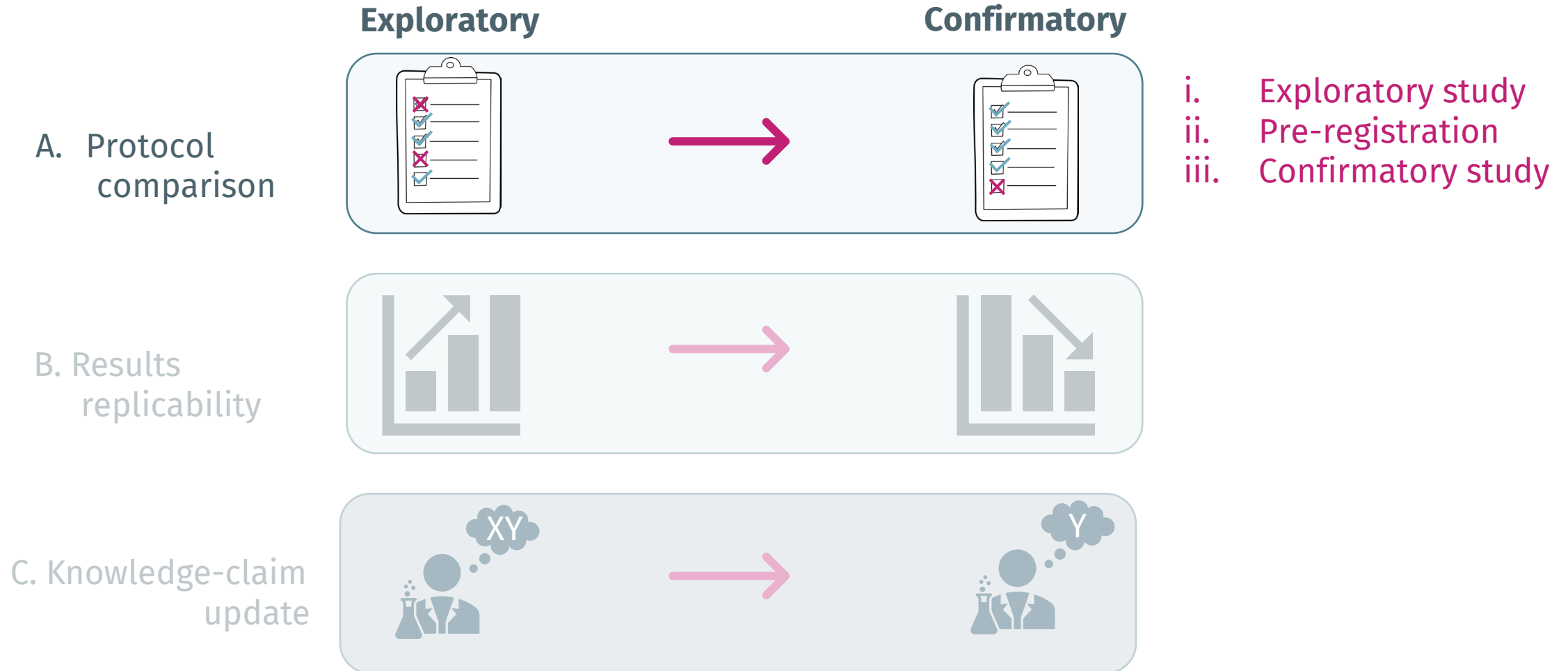
Research practices relevant for study design
validity and reliability



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



Meta-research: Exploratory vs. Confirmatory studies



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

Population characteristics		Were critical controls used?		Statistics	
Species *	Positive *	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Not applic	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Not applicable/unclear	Which center?	Please specify the primary outcome, include units: <input type="text"/> E.g., distance travelled in cm.
Strain(s) *	Negative *	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Not applic	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Not applicable/unclear	Was the primary outcome defined a-priori (i.e., before data acquisition) *	Wert zurücksetzen
Age(s) *		<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Not applic	<input type="checkbox"/> No <input type="checkbox"/> Yes, from project member <input type="checkbox"/> Yes, from a statistician within the project <input type="checkbox"/> Yes, from a statistician within my institution <input type="checkbox"/> Yes, from other <input type="checkbox"/> Not applicable/Unclear	Did the experiment receive statistical advice? *	Select all that apply.
Sex *	Drug comparator or commercial competitor *	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Not applic	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Not applicable/unclear	Was a power calculation performed for this experiment? *	Wert zurücksetzen
	Did the project use *				

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

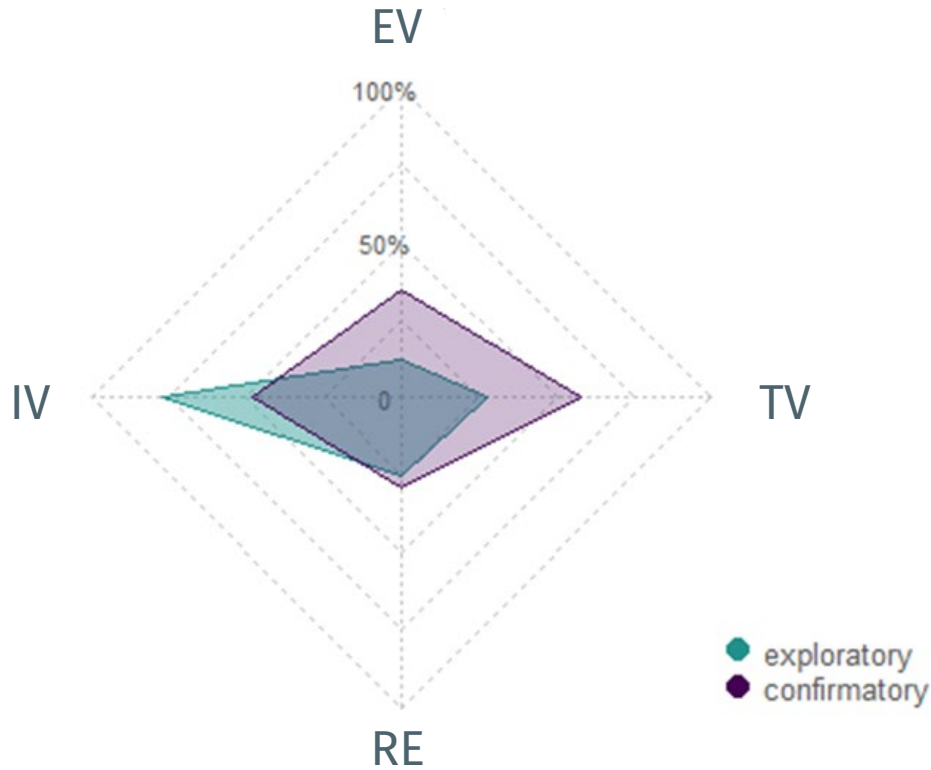
Outcome: Classification of plaque formation in the hippocampus (low, high)

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

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**

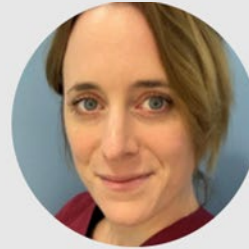
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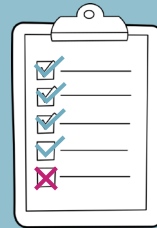


Sophia Rotter, MSc

Thank you!

Exploratory

Confirmatory



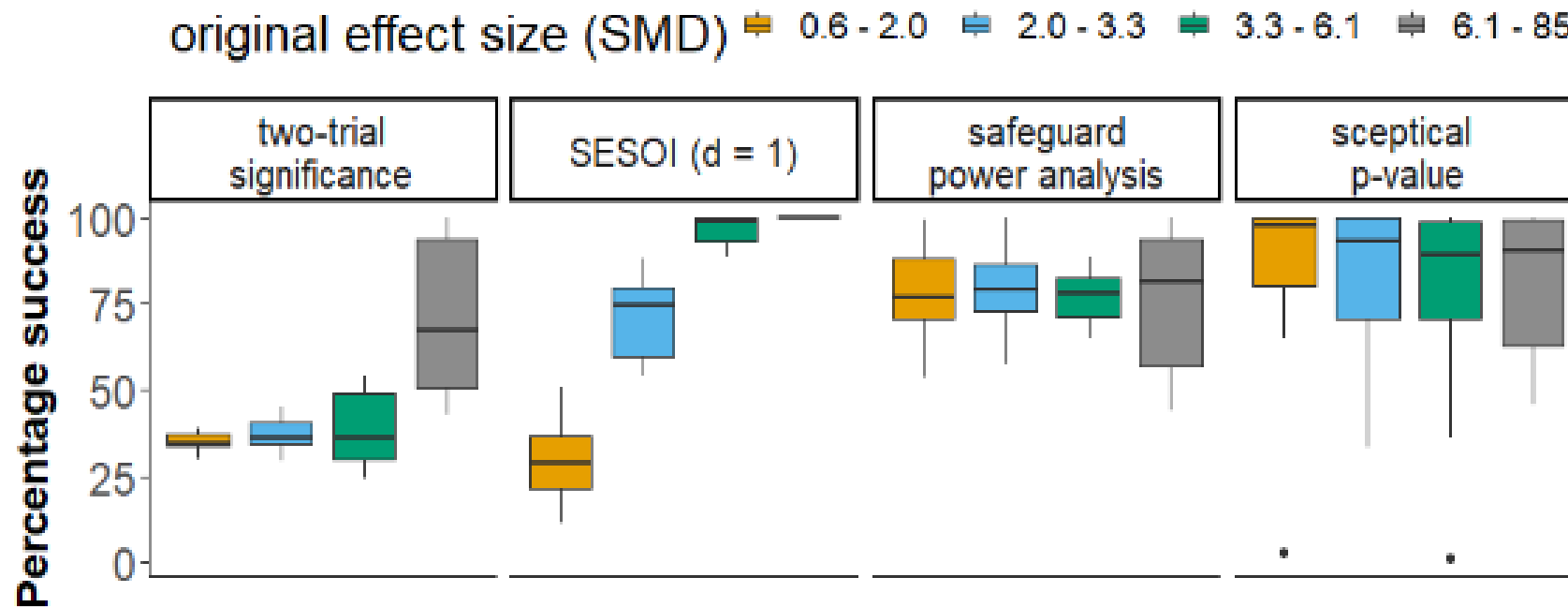
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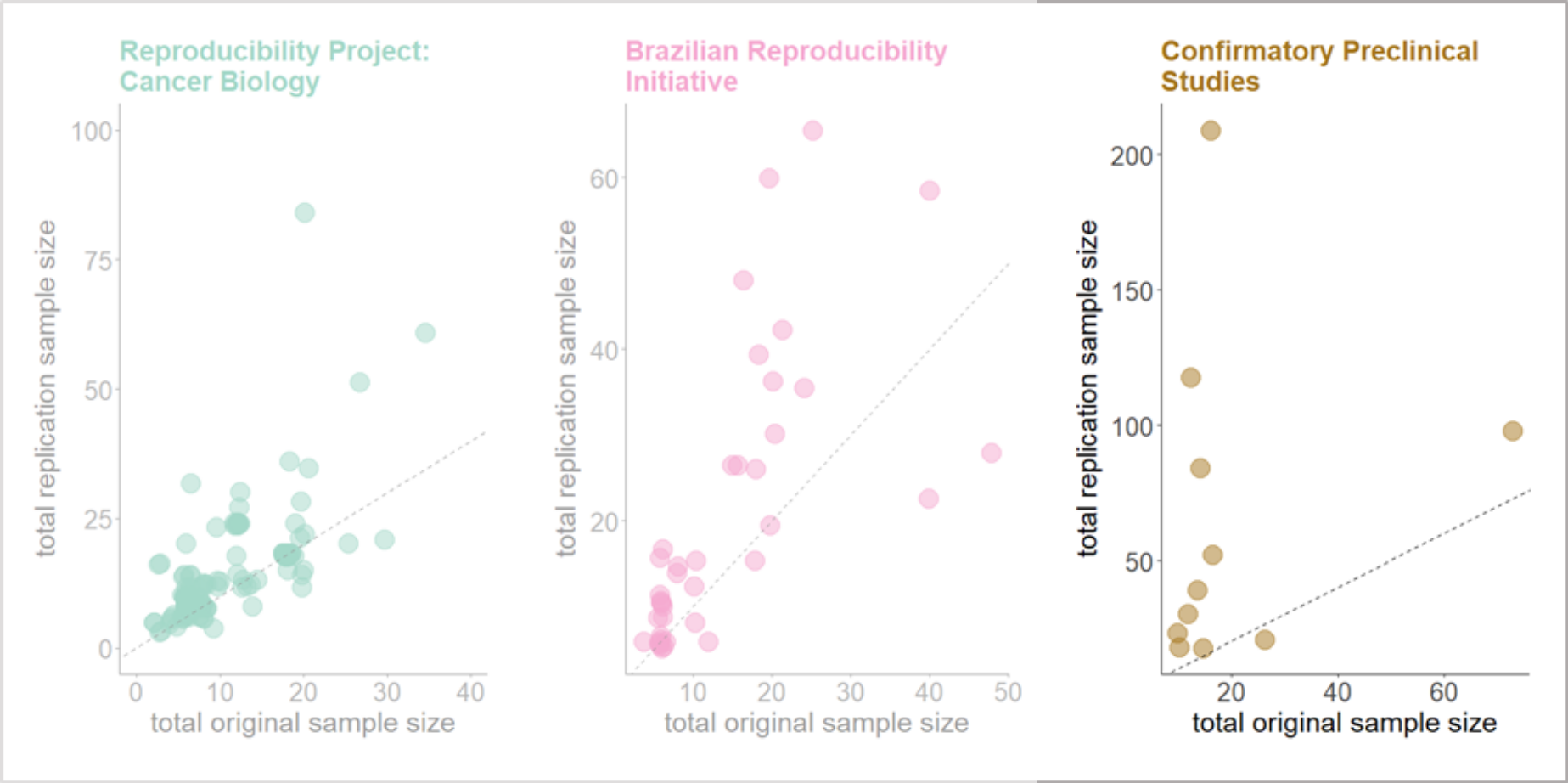
<https://rr-in-action2025.org>

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



Collazo et al, in preparation

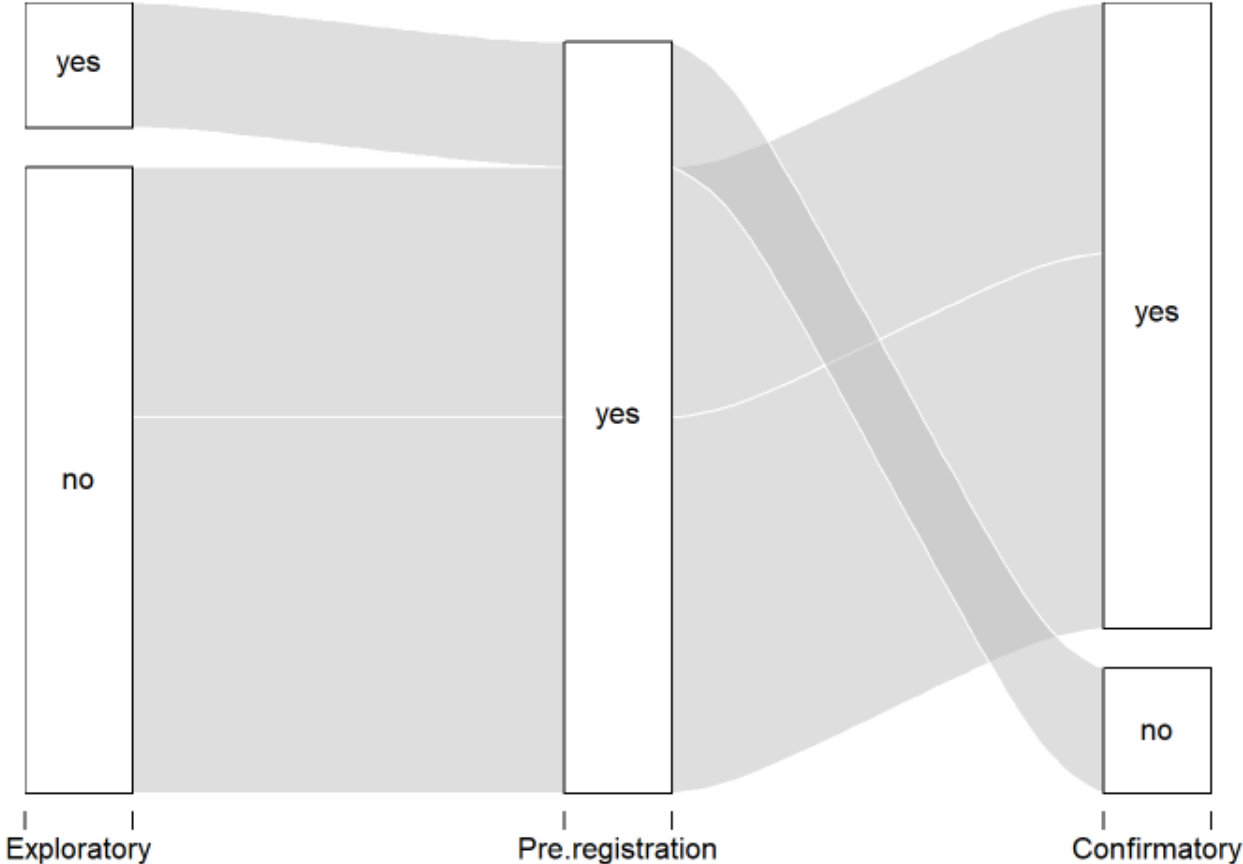
Sample sizes used in the different groups



Collazo et al, in preparation

Transition of protocols from exploratory to confirmatory

Blinded outcome assessment



**not real data*

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>

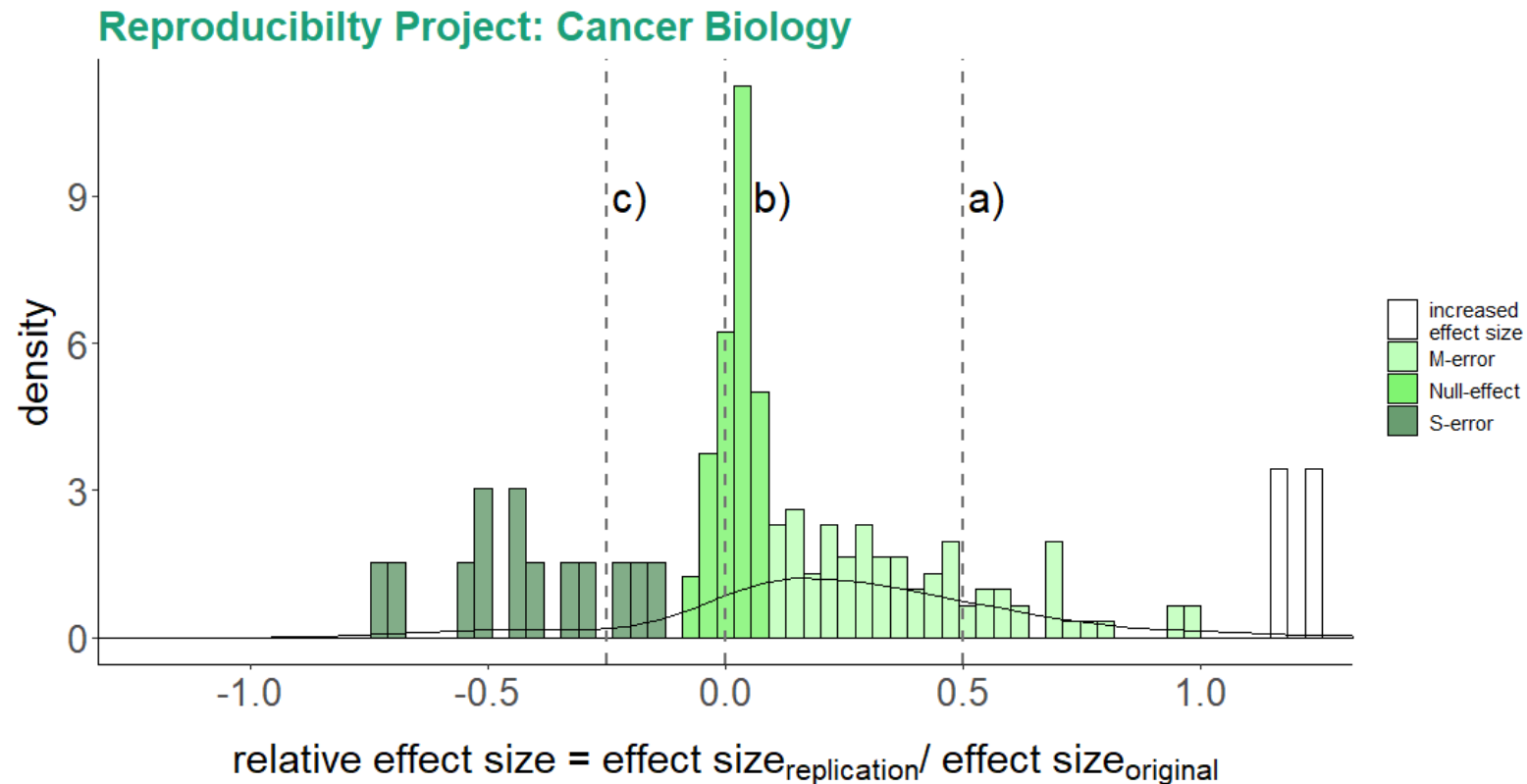
Statistical planning and analyses:

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