The Preclinical Research Unit: a hub to provide guidance in preclinical research towards robust evidence and clinical translation
External Advisor
Animal Welfare Officer

Use of animal models for the development and approval for medical devices and for education of surgeons

@Medizinisches Kompetenzzentrum
c/o HCx Consulting GmbH

Medizin im Grünen

Contact:
n.drude@medizin-im-gruennen.de

05.07.2022
Reproducibility crisis and the lack of translation – not field specific

Drug Delivery: Too Much Complexity, Not Enough Reproducibility?

Jean-Christophe Leroux*
Failure to connect two worlds, or rather multiple reasons for translational attrition?

- Complexity
- Someone else was there already: Low hanging fruits have been picked
- Lack of robustness and transparency of preclinical research results
- Lack of robustness and transparency of clinical study results
- Lack of resources (including time!)
- ...
Responsible PrecliniX

- builds a hub connecting researchers from different fields including core facilities
- provides counseling for research groups
- develops/ evaluates a robustness metric
- meta-analytically (self)assesses and accompany projects
Responsible preclinical research

Think unmet medical need and clinical translation

- Investigator's Brochure
- Investigational and Medicinal Product Dossier (IMPD)
- Regulatory submissions (marketing authorization)
- Common Technical Document

From: ICH Guideline M4 (R4)

Patient centric responsible preclinical research within the BIH/Charité ecosystem
Patient centric responsible preclinical research within the BIH/Charité ecosystem

Aligning communication and organizational objectives to support and improve research activities

- Responsible Translation
- Core Facilities
- Responsible Preclinix
- Feedback Loops
- Clinical Study Center (CSC)
- Experimental Medicine
- Biostatisticians
- Regulatory Affairs and Guidelines

- Reproducibility
- Training
- Reliability
- Internal Validity
Counseling process - towards behavioral change

Support and counsel researchers to improve reliability and validity to improve translational predictability
- Provide early support and guidance
- Generate predictive robust preclinical evidence
- Ensure data interoperability and transparency

Maintain high research standards with emphasis on quality, robustness, and reproducibility
- Provide education/training
- Core Facilities

⇒ Find meaningful, early markers of translational effectiveness
What are measures to estimate the likelihood of (clinical) translation?

Based on experimental/study design
Robustness metric = support measure

<table>
<thead>
<tr>
<th>Metric should assess:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal Validity</td>
</tr>
<tr>
<td>Reliability</td>
</tr>
<tr>
<td>External validity</td>
</tr>
<tr>
<td>Translational validity</td>
</tr>
<tr>
<td>Risk of bias</td>
</tr>
<tr>
<td>Consistency of measure</td>
</tr>
<tr>
<td>Generalizability</td>
</tr>
<tr>
<td>Model translatability to humans/clinic</td>
</tr>
</tbody>
</table>

Evaluation and refinement of question with **7 use-cases** at different stages of the preclinical research trajectory

**38 items** (9.5 ± 2.9 questions per category)
Blinding/ randomization - limitations and scoring

To avoid bias, the mouse was blinded when self-reporting outcomes. Image credit: Lorris Williams.

Social transfer of pain


Automation
Quality management
Preregistration

to reduce risk of bias
Scoring of all measures to reduce risk of bias

A priori (ideally preregistered) definition of:

**Primary outcome**

What is your most important measure? (The measure that you use to assess the effect of an intervention)

**Standard clinical care outcome measure(s)**

What did you base your sample size calculation on?

**Secondary outcomes** (see also external validity)

**Triangulation**

**Flanking experiments**
Scoring of all measures to reduce risk of bias

A priori (ideally preregistered) definition of:

**Inclusion/exclusion criteria** based on:
- Animal welfare (severity assessment and humane endpoint)
- Scientific outcome (outlier management)
- Characteristics of the model (genotype, phenotype, stage of disease)

**Outlier**
- technical (failure); extreme values (i.e., >3 SD), animal attrition

**Analysis plan**
Scoring of all measures to reduce risk of bias

Control groups:
• Positive and negative control groups?
• Baseline measures possible?

Is there an approved comparator drug/intervention in standard clinical care?

Effect size between naïve control versus e.g. standard clinical care
• Non-inferiority instead of superiority

Quality Control, Quality Assurance, Quality Management System, Standard operating procedures, ...

⇒ Involvement of core facilities
Reliability

Exploration, replication, confirmation?

What is the **sample size calculation** based on?

Have statistical analysis been pre-defined?

Analysis on the level of the **experimental unit**?

Relevant **confounding variables/ effect modifier** identified and addressed?
External validity – generalizability of results

**Replication experiments**
in-house or by external laboratories?

**Systematic heterogenization and the “standardization fallacy”**
Co-morbidities, different sexes, different strains

**TRIANGULATION**
Converging evidence
Discriminant evidence
Translational validity - similarity of the studied model system to human disease conditions

Is the target mechanism causal for the disease?

What is it I am measuring?

The Rodent Forced Swim Test Measures Stress-Coping Strategy, Not Depression-like Behavior

Kathryn G. Commons, Aram B. Cholanians, Jessica A. Babb, and Daniel G. Ehlinger

Department of Anesthesiology, Perioperative, and Pain Medicine, Boston Children's Hospital and Department of Anesthesia, Harvard Medical School, 300 Longwood Avenue, Boston, Massachusetts 02115, United States
Translational validity – (animal) model limitation
Translational validity

Clinical relevance of route of administration

- Bioavailability (pharmacokinetics)
- (Drug) dosing
- Might be irrelevant e.g., in case of mechanistical understanding

Are clinical biomarkers or companion diagnostics measured that reflect human conditions?

*→ Therapy companion diagnostics to *stratify patients* into subgroups with differential benefit/risk*
How to quantify the likelihood for clinical translation?

**No one-size-fits-all**

Transparency about limitations

Several experiments in each study – No Y/N scale

**Weighing of aspects in the metric**

![Graph showing metrics]

**Meta-analytical performance**

ALL results which are based on high quality studies are informative and relevant!!!
Outlook: reduce barrier for interaction

Two robustness metric

1. For **project assessment and evaluation by trained personnel** – detailed (internal, external, translational validity and reliability)

2. For **self-assessment** by the individual researcher and/or research group (max. 10 Questions)
   - Easy to access
   - Ideally immediate outcome
   - Easy to process
Outlook: reduce barrier for interaction

Two robustness metric

1. For **project assessment and evaluation by trained personnel** – detailed (internal, external, translational validity and reliability)

<table>
<thead>
<tr>
<th>Question</th>
<th>Explanation and elaboration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were critical control conditions included in the experimental design?</td>
<td>Critical control conditions refer to groups that allow the interpretation of the effect observed. Negative controls, where the only difference from the treatment group is the presence of the active intervention being tested, can be used to determine causality. Positive controls, where a known effect is expected, can be used to determine the appropriateness of the experimental procedures, tools and equipment or outcome assessment method. In cases where there is an approved intervention in the clinical setting, positive controls can be useful to establish comparability of the new intervention. Note, however, that which control groups are critical will vary among different experiments and different research questions.</td>
</tr>
</tbody>
</table>

Additional resources: [https://arriveguidelines.org/arrive-guidelines/study-design](https://arriveguidelines.org/arrive-guidelines/study-design), [https://www.youtube.com/watch?v=ESVv46J4pn0&list=PLkFbG8MLglksZn5suMsE37qMqBhRqBd&index=10](https://www.youtube.com/watch?v=ESVv46J4pn0&list=PLkFbG8MLglksZn5suMsE37qMqBhRqBd&index=10)
Outlook: reduce barrier for interaction

Two robustness metric

1. For **project assessment and evaluation by trained personnel** – detailed (internal, external, translational validity and reliability)

   - Were critical control conditions here refer to groups that allow the interpretation of the effect observed. Negative controls, where the only difference from the treatment group is the presence of the active intervention being tested.

<table>
<thead>
<tr>
<th>Question</th>
<th>Explanation and elaboration</th>
<th>result 1h</th>
<th>2h</th>
<th>3h</th>
<th>4h</th>
<th>5h</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Were critical control conditions here refer to groups that allow the interpretation of the effect observed. Negative controls, where the only difference from the treatment group is the presence of the active intervention being tested.</td>
<td></td>
<td>( \times )</td>
<td>( \times )</td>
<td>( \times )</td>
<td>( \times )</td>
<td>( \times )</td>
</tr>
</tbody>
</table>

Survey that allows us to send a tailored response

---

Clarissa F. D. Carneiro, MSc
Thank you!

Please do not hesitate to contact us!

Safe the Date
Kick-Off Event Responsible Preclinix at QUEST
4th October 2022

Responsible PrecliniX
natascha-ingrid.drude@bih-charite.de