

# Dose recommendations across related indications

EMA Methodology Working Party

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# Dose selection in similar indications

## Questions of interest:

- How to best leverage the knowledge available to optimize dose selection for a specific indication, given the evidence collected in a similar disease/same drug and/or same indication/different drug?
- More specifically: how to best integrate dose-exposure-response analysis in the trial design/ decision making?
- How to assess “similarity” btw. the two disease types? What type of data/analyses and metrics are required?

## Challenges:

Understanding the heterogeneity of disease and dose-exposure-response relationships on both efficacy and safety

- How to define “similar”?
- How to provide robust dose-exposure-response assessment, esp. when the data is sparse?
- What are the criteria for “robustness” of such an extrapolation, esp. in rare disease indications?
- Pooling data: confounding study vs. indication effect?

# Further methodological developments needed

- How to improve robustness of exposure-response modelling for assessing treatment effects and causality?
  - Accounting for uncertainty in models to improve extrapolation capability
  - Model-based Estimands
- How to increase use and acceptance of in-silico trials (model-based virtual patients' generation methods) fit to different data sources (incl. RWD) to cope with missing or low-quality knowledge?
- How to create a consolidated framework to be used and accepted by all stakeholders (modelers, statisticians, regulatory, HTA bodies, etc.)?

# INVENTS Horizon EU: Innovative designs, extrapolation, simulation methods and evidence-tools for **rare diseases** addressing regulatory needs

- **Funding:** Horizon Europe (N 101136365)
- **Budget:** €6M
- **Coordinator:** INSERM
- **Duration:** 5 years (Jan 2024 - Dec 2029)
- **Overall objective:** To provide clinical trial stakeholders, trialists and regulators with a generalizable framework encompassing methods, workflows and evidence-tools to improve the level of evidence in regulatory decision making in rare diseases.
- **Framework** to be used to make the most of sparse evidence, to synthesize (seemingly) disparate data, and to robustly bridge between more or less well-understood indications



# References

- [1] Musuamba FT, Skottheim Rusten I, Lesage R, et al. Scientific and regulatory evaluation of mechanistic in silico drug and disease models in drug development: Building model credibility. CPT Pharmacometrics Syst Pharmacol. 2021;10:804–825. 10.1002/psp4.12669
- [2] ICD 10. “International Statistical Classification of Diseases and Related Health Problems 10th Revision”. 2019.
- [3] ICH E11A. “ICH guideline E11A on pediatric extrapolation - Scientific guideline”. 2022.
- [4] ISO/DTS 9491-1. “Biotechnology — Recommendations and requirements for predictive computational models in personalized medicine research — Part 1: Guidelines for constructing, verifying and validating models”. 2023. <https://www.iso.org/standard/83516.html>
- [4] INVENTS project <https://ecrin.org/projects/invents>