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Evaluating two strategies for the design of pediatric pharmacokinetic studies

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Background

1. *Pediatric pharmacokinetic (PK) studies* are difficult to design, due to:

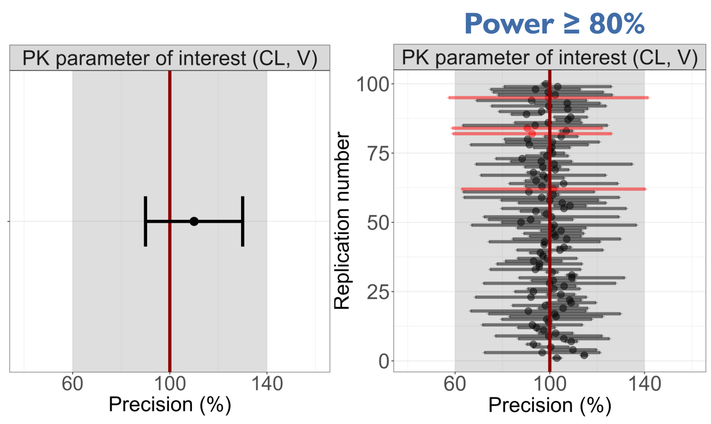
- Complex developmental changes
- Need to limit sampling to a minimum for ethical and practical reasons

AIM to compare ADS approach with PP approach including estimated power and sensitivity to different variables, using model-based simulation and re-estimation.

2. *Evaluation of pediatric PK study designs*

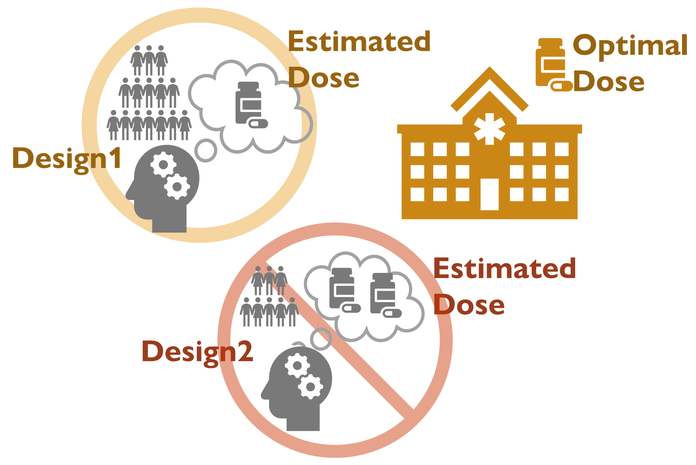
Common evaluation[1] (PP)

Parameter-precision focused



Proposed novel evaluation[2] (ADS)

Accurate-dose-selection focused



Methods

1. *Simulation components*

Drug: pretomanid, for treatment of tuberculosis.

Adult PK model: scaled by allometry and maturation function.

Study to design: single-dose PK study in children with the objective to inform doses for a subsequent long-term study.

2. *Calculation of power*

General workflow of two approaches is shown below.

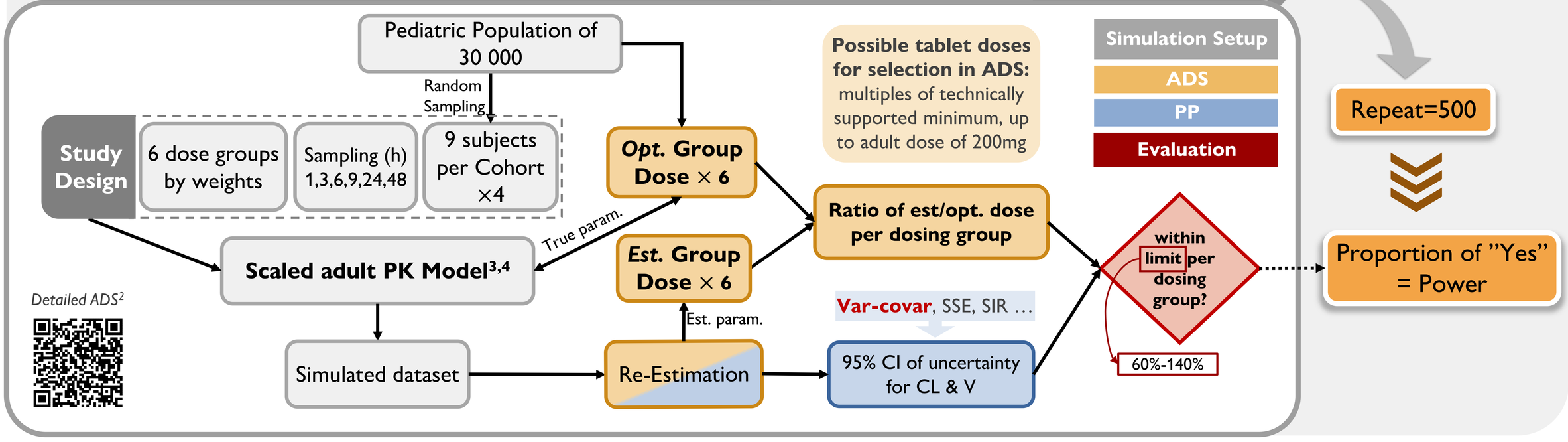
The PP approach was implemented per original publication.[1]

Detailed algorithm of ADS was described in previous work.[2]

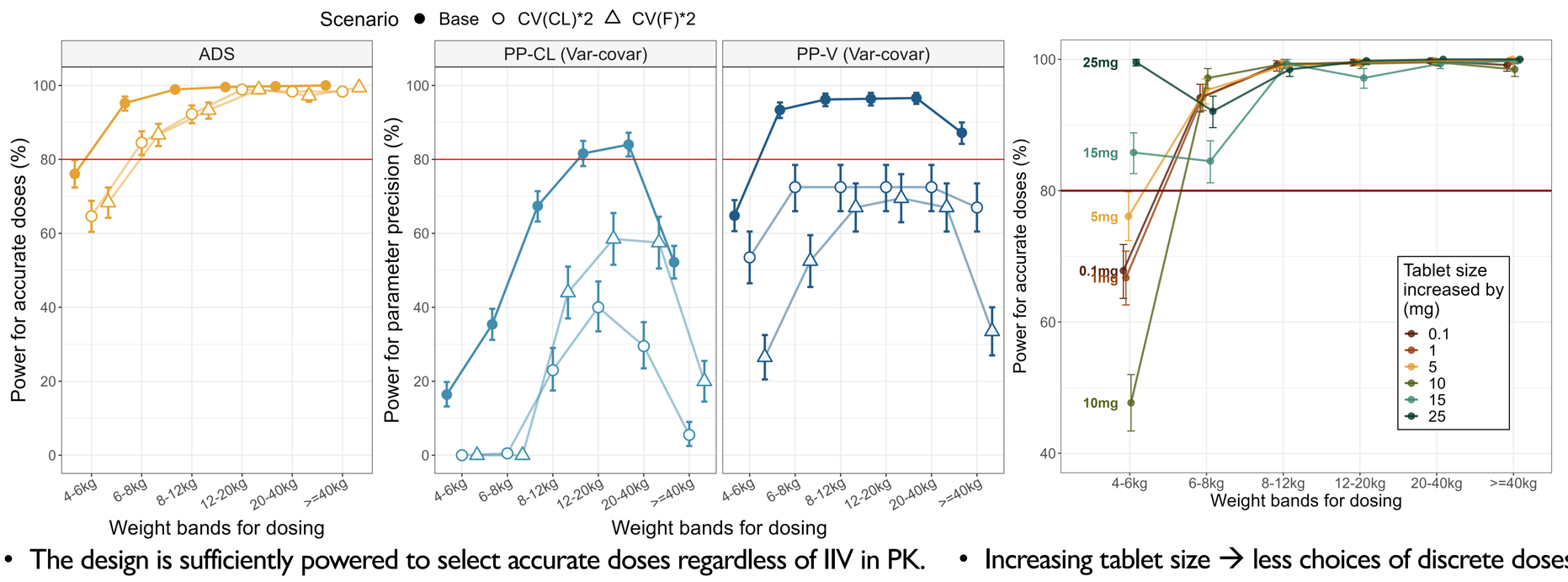
3. *Sensitivity analysis*

- **High variation of PK for ADS&PP:** Doubled CV% of IIV in CL and F.
- **Possible doses of selection for ADS:** Technically supported minimum 0.1~25mg.

Algorithm Flowchart



Results



- The design is sufficiently powered to select accurate doses regardless of IIV in PK.
- The design is poorly powered for CL precision, more so with increasing IIV in PK.
- Increasing tablet size → less choices of discrete doses
- Non-monotonic pattern in the change of power.

Conclusion

The ADS approach could be a good alternative for study power evaluation, allowing lower sample size when the study is focused on determining doses using discrete tablet sizes.

References

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2. Zou Y, et.al. In: *Population Approach Group Europe (PAGE)*. ; 2021:I-72.
3. Salinger DH, et.al. Antimicrob Agents Chemother. 2019;63(10).
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Abbreviations: CL, clearance; V, Volume; F, bioavailability; CV, coefficient variation; IIV, interindividual variability; CI, confidence interval; Var-covar, variance-covariance matrix; SSE, stochastic simulation estimation; SIR, sampling importance resampling

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