A novel approach to evaluate the design of pediatric PK studies focused on accurate dose selection

UPPSALA UNIVERSITET

Yuanxi Zou[1], Jerry Nedelman[3], Mats O Karlsson[1] and Elin M Svensson[1,2]

[1] Department of Pharmacy, Uppsala University, Sweden; [2] Department of Pharmacy, Radboud Institute of Health Sciences, Radboud University Medical Center, The Netherlands;
[3] TB Alliance, New York, USA

BACKGROUND

A commonly used criterion to justify the design of a pediatric PK study is that the study must be powered to target a 95% confidence interval within a specified limit of the geometric mean estimates of the important PK parameters with at least 80% power [1]. However, that criterion does not directly investigate the clinically relevant target, such as dose selection. This work proposes an alternative evaluation method based on the accuracy of dose selection.

Pretomanid, a newly developed nitroimidazole for treatment of tuberculosis (TB), is used to demonstrate this approach. Currently, pretomanid is being investigated for use in children. A population pharmacokinetic (PK) model was previously built based on adult data, suggesting that maximum concentrations are reached around 6 h after dose, and that the half-life is about 15 h. This model was used to help design the first-in-pediatric single-dose clinical trial of pretomanid, an objective of which is to select doses for a subsequent safety and efficacy study.

METHODS

- Population simulation. A pediatric population with TB with age uniformly distributed between 0 and 18 years old was simulated [2]. 30 000 children with weight above 4 kg were selected. Patients were assigned to six dosing groups by weight to enable different doses for different weight bands: 4 – <6, 6 – <8, 8 – <12, 12 – <20, 20 – <40, ≥40 kg.
- Optimal dose calculation. The adult population PK model for pretomanid was scaled to children by accounting for clearance maturation and allometric scaling. This model was used to generate the true PK parameters for each virtual patient (i) given weight and age. Based on all individuals within a weight band, an optimal group dose (GD^*) was selected to provide AUC_{inf} closest to that in adults at the clinical dose, AUC_{target}, by minimizing the RMSE defined below. Doses were selected only among multiples of 5 mg from 5 mg to 200 mg, because for pretomanid, 5 mg is the technically supported minimum while 200 mg is the approved dose for adults.

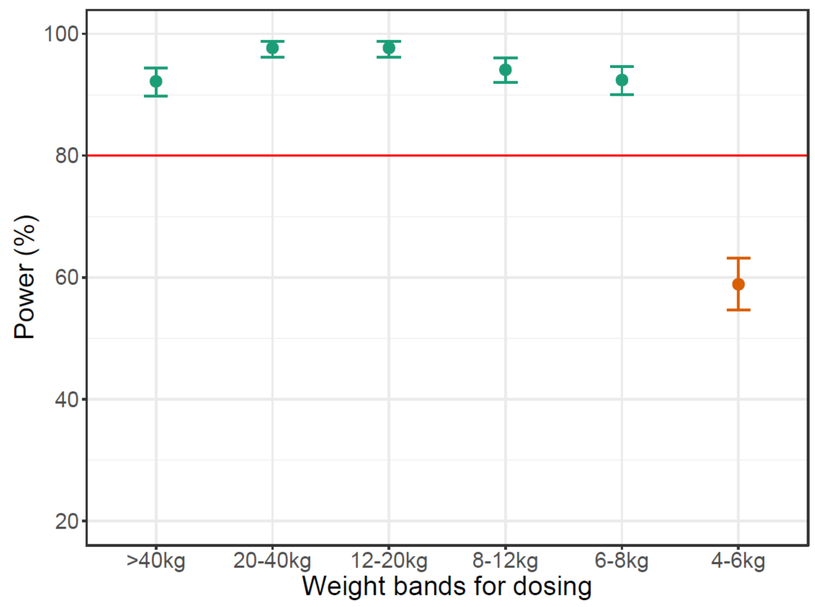
$$RMSE = \sqrt{\frac{\sum_{i=1}^{n=Ngrp_m} [\log(AUC_{dose,i}) - \log(AUC_{target})]^2}{n}}$$

$Ngrp_m$: Number of subjects in the m^{th} dosing group
$AUC_{dose,i}$: The AUC of i^{th} subject at a given dose
AUC_{target} : 50.9 μg.hr/mL

- Data simulation. A proposed PK sampling schedule was tested with a sample size of 36 (9 per cohort). Patients were randomly sampled from the simulated population; PK observations were simulated according to the sampling schedule and corresponding GD^* that patients received.
- Re-estimation. The model was re-fitted to the simulated data and the PK parameters were re-estimated, including allometric scaling factors, but maturation-related parameters were fixed (assuming that the maturity was well defined based on knowledge of the metabolic pathway). Based on the re-estimated parameter set, six estimated *GD* ($\widehat{GD}$) were selected. The ratio of the $\widehat{GD}$ to the GD^* was calculated for each group.
- The previous two steps were repeated 500 times to create 500 replicates of the study.
- Power calculation. The power of the study design for each dosing group was summarized as the percentage of the 500 ratios within a specified limit of 80%-125%.

RESULT

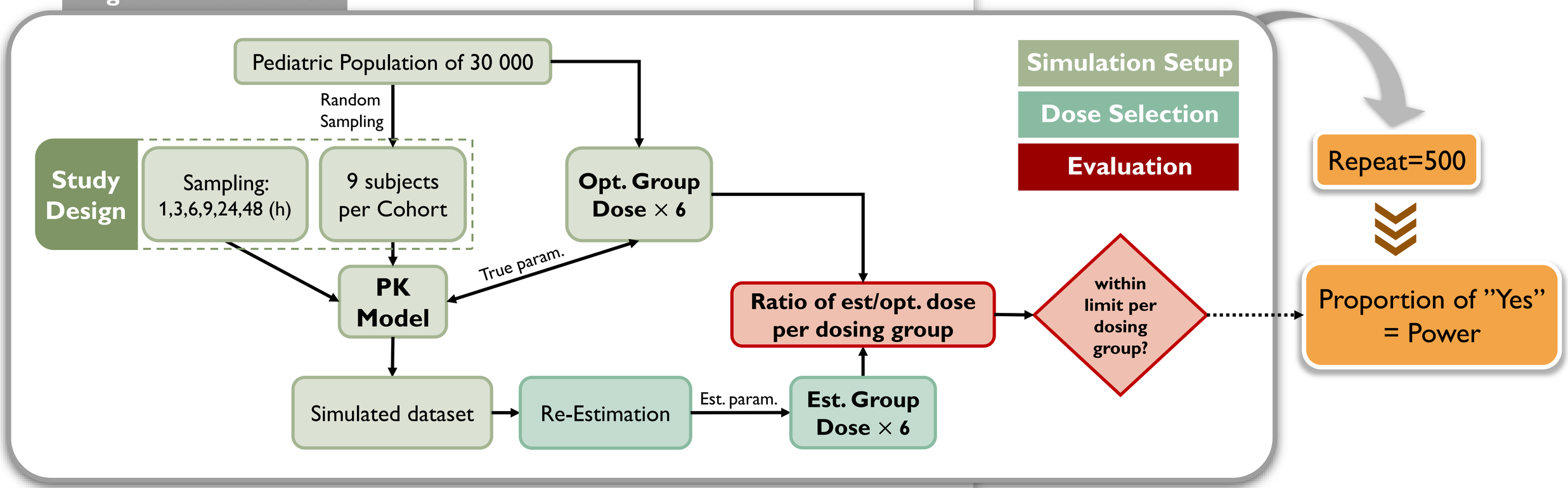
The precision of the dose selection was estimated with above 80% power for all dosing groups except the group <6 kg. The power for the group <6 kg was reduced to less than 60%, due to the greater impact of a 5 mg difference at lower doses.



CONCLUSION

The proposed approach practically evaluates the precision in dose selection given the study design and enables interesting comparisons of power between different dosing groups, especially when those groups are limited by available dosage strengths. It provides a more relevant decision criterion for designing pediatric trials when the aim is dose selection than purely evaluating power based on parameter precision.

Algorithm Flowchart



References

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