

Use of interim analysis to improve efficiency of clinical trial simulations in treatment comparison trial design studies

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Introduction

- Clinical trial simulation using Monte Carlo (MC) technique has been increasingly used in pharmaceutical industry to make drug development more efficient, robust and informative.
- However, Monte Carlo simulation is time-consuming due to the large number of virtual individuals simulated.
- In the case where MC simulations are used to compare two treatment arms, we propose to use interim analysis (e.g., see [1, 2]) to avoid simulating unnecessary large number of subjects and hence improve the efficiency.

Objectives

- To demonstrate through a treatment comparison example that the interim analysis approach can be used to improve the efficiency of MC simulations.

Methods

A Treatment Comparison Example

- The example used to demonstrate this is based on the study conducted in [4], where MC simulation was used to confirm that the proposed dosing regimen and the approved one have equivalent clinical outcomes.
- This was done in [4] through comparing the steady-state time-concentration profiles between these two dosing regimens, where 100 replicates were simulated with each replicate consisting of 100 virtual individuals for each dosing regimen.

Proposed Approach

- Instead of visually comparing the steady-state time-concentration profiles of these two treatment arms, we used the FDA standard for the bioequivalence study (e.g., see [3]), 90% confidence interval of ratios of the area under the concentration time curve (AUC) of the two dosing regimens contained in the range of 80%-125% (same rule applies to the peak plasma concentration, Cmax), to ascertain whether they are equivalent.
- The repeated confidence interval approach [2] was used to determine whether these two treatment arms are equivalent and when to stop the simulation.
 - An innovative simulation engine using Pharsight modeling language (PML) was used to simulate one subject at a time.
 - The repeated confidence interval approach was used to ascertain whether the simulation can be stopped.

Simulation Engine Using Pharsight Modeling Language

- Compared to other languages for nonlinear-mixed effect models, PML was designed to be good for both model fitting and clinical trial simulations (see Figure 1 for PML simulation flow chart).

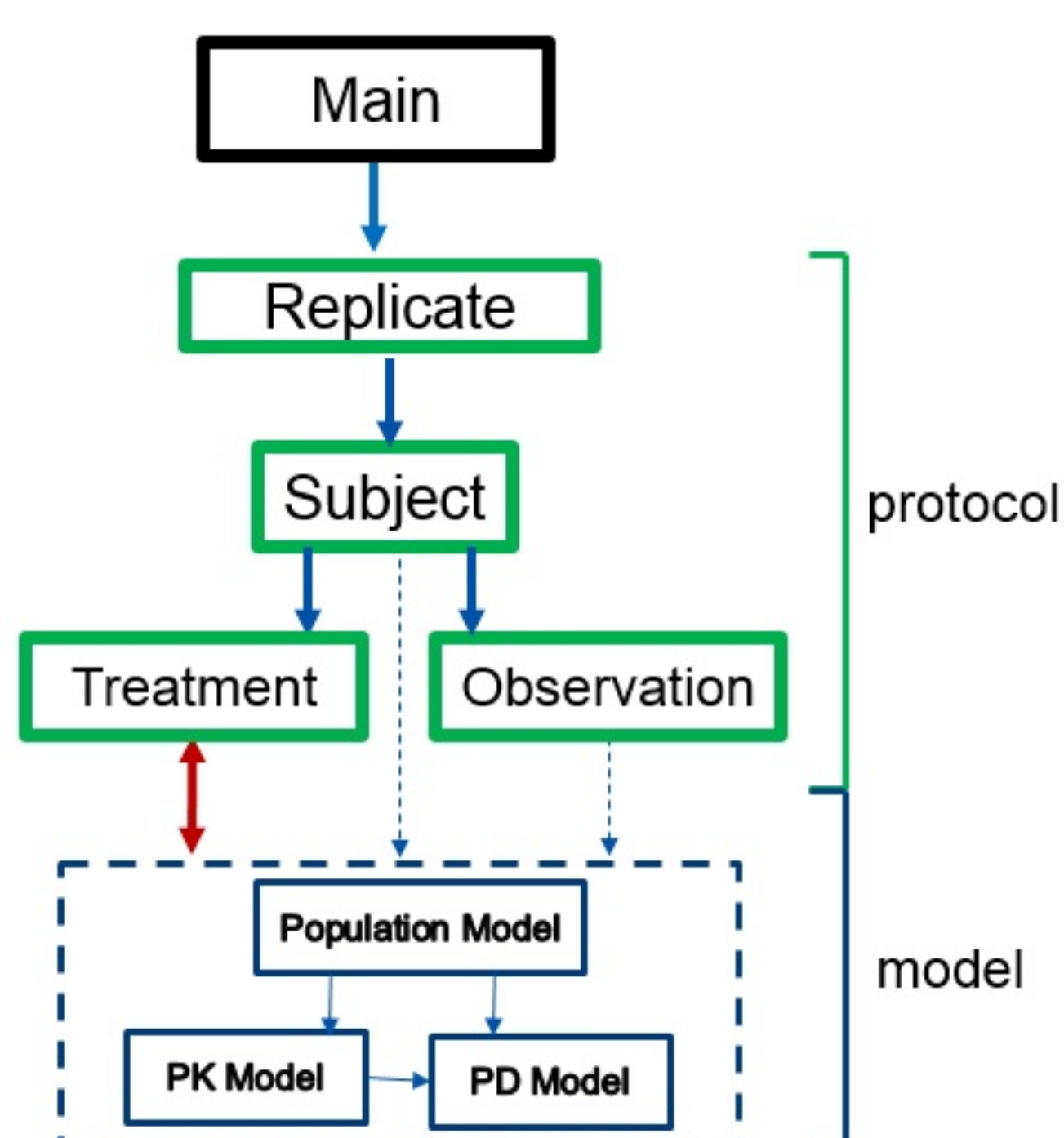


Figure 1: Pharsight modeling language simulation flow chart.

Algorithm

- 1 Specify type I error probability (or significance level) α , minimal effect size δ , number of interim analysis K and group size m , and set $k = 1$.
- 2 Calculate boundary or critical values $\{c_k\}_{k=1}^K$, which are chosen to control the type I error probability (e.g., Pocock's boundary, O'Brien and Fleming's boundary).
- 3 Calculate the confidence interval for the k th interim analysis

$$I_k = \left(\bar{\theta}_{n_k} - \frac{c_k \sigma_{n_k}}{\sqrt{n_k}}, \bar{\theta}_{n_k} + \frac{c_k \sigma_{n_k}}{\sqrt{n_k}} \right)$$

- $\bar{\theta}_{n_k}$ is the sample mean obtained using all n_k observations $\{\theta_i\}_{i=1}^{n_k}$ in the first k groups (that is, $\bar{\theta}_{n_k} = \frac{\sum_{i=1}^{n_k} \theta_i}{n_k}$), where $n_k = mk$, and θ_i denotes the difference between observations for the two-treatment groups at the i th observation point.
 - σ_{n_k} denotes the sample standard deviation obtained using all n_k observations $\{\theta_i\}_{i=1}^{n_k}$.
- 4 If $I_k \subset (-\delta, \delta)$, then one concludes that the two treatments are equivalent and stops simulation. Otherwise, if $k < K$, then set $k = k + 1$ and go to Step 3; and if $k = K$, then one stops simulation and concludes that the two treatments are not equivalent.

Results

- Numerical results show that after simulating 30 replicates, these two dosing regimens were found to be equivalent (see Figure 2).
- This eliminates the need for simulating another 70 replicates as done in [4] to obtain the same conclusion, and hence reduces the simulation time.

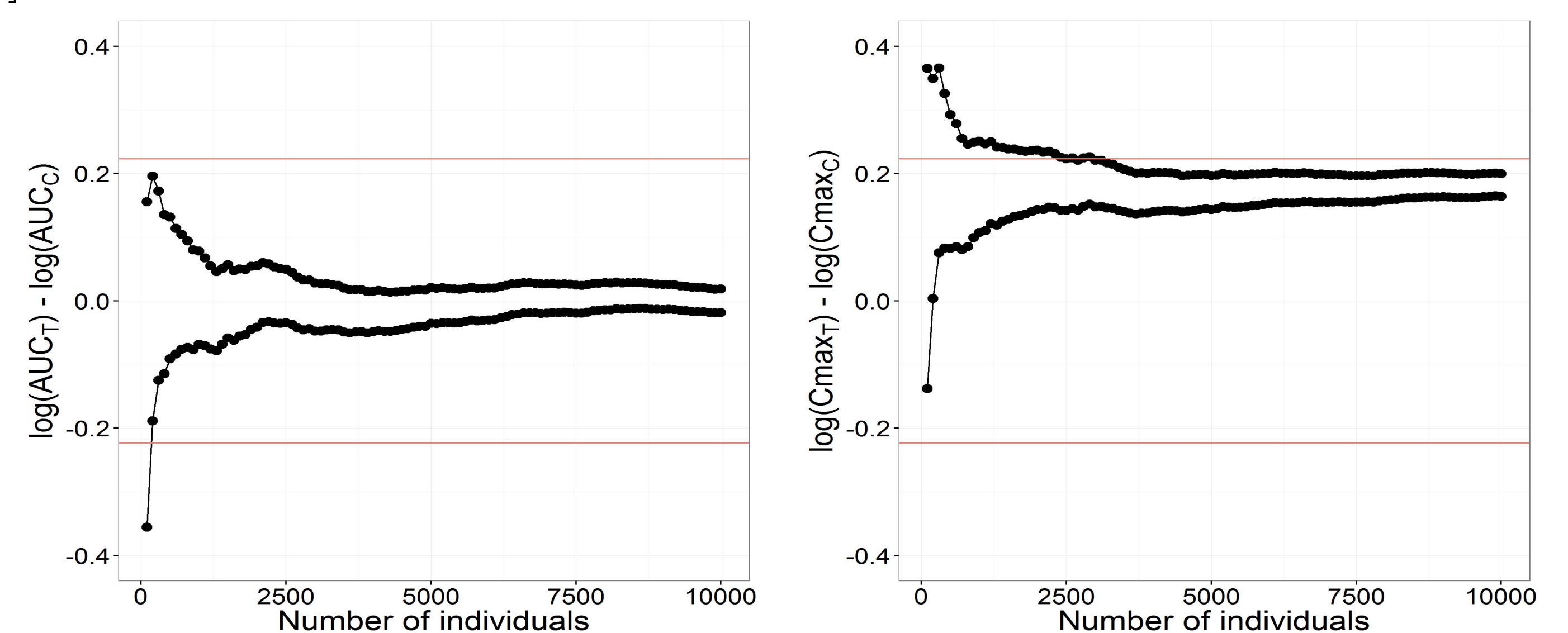


Figure 2: Results obtained for AUC (left panel) and Cmax (right panel) using Pocock's boundary with 100 interim analysis and group size being 100, where the interval between the two red lines denotes the minimal effect size interval.

Conclusions

- This example demonstrates that interim analysis combined with simulation engine using Pharsight modeling language can be used to improve the efficiency of clinical trial simulations in treatment comparison studies and create statistical results for decision-making.

References

- [1] C. Jennison and B.W. Turnbull, *Group sequential methods with applications to clinical trials*, Chapman and Hall/CRC, Boca Raton, FL, 1999.
- [2] C. Jennison and B.W. Turnbull, Interim analysis: the repeated confidence interval approach, *J. R. Statist. Soc. B*, 51 (1989), 305-361.
- [3] S. Rani and A. Pargal, Bioequivalence: an overview of statistical concepts, *Indian J. Pharmacol*, 36 (2004), 209-216.
- [4] Yim, et al., Population pharmacokinetic analysis and simulation of the time-concentration profile of etanercept in pediatric patients with juvenile rheumatoid arthritis, *J Clin Pharmacol.*, 45 (2005), 246-256.

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