

Development of a template for clinical trial simulations in COPD

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Introduction

Clinical Trial Simulation (CTS) is an essential tool to test assumptions, generate hypothesis and optimise overall protocol design. The principle of CTS [1] usually comprises:

- (i) creation of virtual study population;
- (ii) randomisation of subjects into a study protocol;
- (iii) evaluation of different scenarios, including different drug-disease models and possible protocol deviations;
- (iv) evaluation of the impact of different statistical methods.

Despite the mounting evidence regarding the relevance of model-based drug development, CTS remains underutilised due to the lack of integrated software packages, in which all CTS components are available and easily adapted to accommodate user requirements.

The objective of this exercise is to define a general, modular template for CTS in which scenarios with different design factors can be used in a semi-automated manner. Simulations using a previously defined model are performed with graphical and statistical summaries as standard output.

Methods

The template was implemented in R, and conceived in a modular manner using different scripts, each one with a specific functionality. All scripts are managed through a control file in which the user can define trial design factors, model specification and define the number of simulations. Thanks to the modular structure, the template can be used in conjunction with different software packages, including WinBUGS, NONMEM and R. In the current example, an automated call to NONMEM VI is used to generate FEV1 responses in a COPD trial.

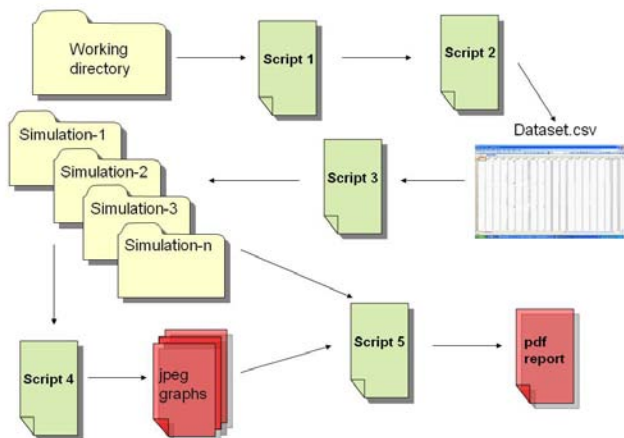


Figure 1. Structure of the CTS template

Virtual patients are created using MSToolkit, an R library for clinical trial simulation [2]. The user can select design factors such as sampling schedule and dosing regimens. Covariates may be specified by defining their distribution or by sampling from a pre-existing pool of patients.

For each simulation a new dataset is created, which complies to NONMEM format requirements. The trial output is managed by a predefined folder structure and includes standard plots and summary statistics. An overall summary is also available in LaTeX, which creates an updated report with plots and tables.

Results

The CTS template was used to simulate 100 clinical trials in which trough FEV1 was used as primary endpoint. Response was assessed in three treatment groups according to a parallel, placebo-controlled design with 150 patients/arm. The impact of treatment on disease progression was evaluated at week 24 and 52. Plots of the change from baseline are reported.

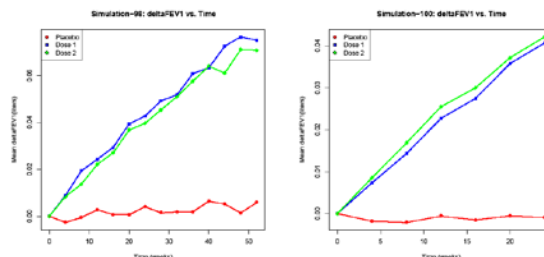


Figure 2. Example of plots of individual simulations of a 52 and 24 weeks trials (respectively left and right) representing mean Δ FEV1 vs. time.

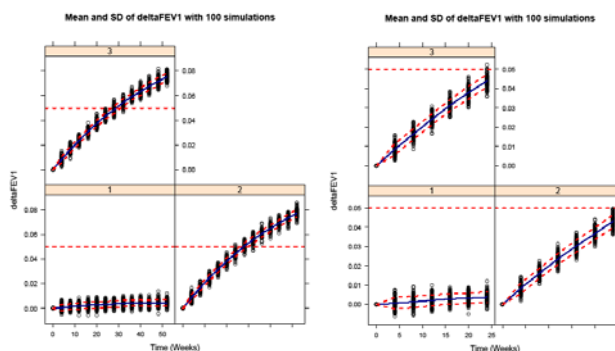


Figure 3. Example summary plots of the 100 simulations of a 52 (left) and 24 (right) weeks trials representing mean \pm SD for Δ FEV1 vs. time. The horizontal red line represent clinically relevant threshold for the response.

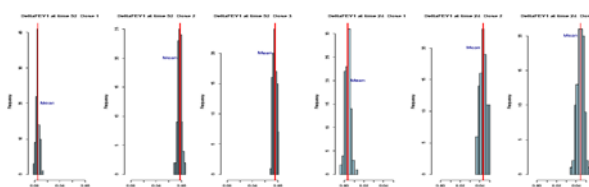


Figure 4. Δ FEV1 distribution at last time-point of 100 simulations of a 52 (left) and 24 (right) weeks trials (vertical red line represent the mean value).

The simulations show that at least a 30-week trial is necessary to reach statistically significant changes from the baseline for the active treatment arms.

Conclusion

The combination of MSToolkit with modular R scripts has provided key components for the creation of design scenarios and enabled the execution, analysis and reporting of clinical trial simulation results, making it very easy to adapt CTS design factors.

As this is part of an ongoing effort, future functionality will also focus on the exchangeability between NONMEM and other simulation software packages.

References

- [1] Chabaud et al. (2002) Clinical Trial Simulation Using Therapeutic Effect Modelling: Application to Ivabradine Efficacy in Patients with Angina Pectoris. *J. Pharmacokinetic and Pharmacodynamics*. 29 (4)
- [2] Smith M. et al. (2009) MSToolkit – An R library for simulating and evaluating clinical trial designs and scenarios. *Poster at PAGE Meeting 2009*.

