Multivariate patient simulation for clinical trial optimisation in COPD

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Introduction

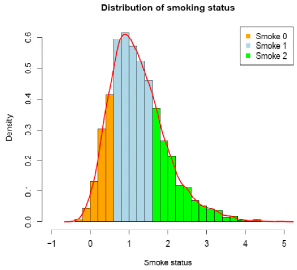
Clinical Trial Simulation (CTS) can be a valuable tool for decision-making in drug development [1]. It consists of three main components: a drug model, a disease-placebo model and a trial design model. The latter component is often overlooked, but has major implications for trial outcome. Here we show how a covariate distribution model can be used to incorporate patient-specific factors that account for inter-individual differences in pharmacokinetics and pharmacodynamics. This is particularly important when collinearity exists and covariate effects are sufficiently large to affect the outcome of a trial. Useful covariates typically include demographics, concomitant drug use and disease risk or heath status biomarkers.

The objective of this exercise is to evaluate the performance of different methods to simulate demographic covariates of patients for a Chronic Obstructive Pulmonary Disease (COPD) trial.

Methods

Virtual patients with varying demographic characteristics were simulated by re-sampling with replacement, sampling from a univariate distribution and sampling from a multivariate distribution.
Covariates have been simulated from an empirical distribution represented by four COPD trials from the TI Pharma database.
Simulations of continuous and categorical covariates using a multivariate distribution were performed in R according to the method described by Tannenbaum et al. [2]. Based on this approach, categorical and continuous covariates from the empirical distribution are log-transformed and used to define the multivariate distribution from which covariates are sampled. The simulated values for the categorical covariates have been subsequently converted in categories according to critical values or cut-off calculated from the empirical distribution.

Protocol Design	
Treatment duration	60 weeks
Dose levels	0 and 250 µg
No. of patients per arm	3498
Endpoints	Trough FEV1
Patients covariates	COPD Severity, Smoking status, Gender, Weight, Height, Age



Simulation steps

Definition of the R function

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Validation to reproduce covariate correlation (*Figure 2*)

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Validation to reproduce a trial (with drug response) (*Figure 3A*)

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Validation to simulate trials with new populations (*Figure 3B*)

Figure 1. *Representation of the calculation of discrete values for smoking status from a continuous distribution.*

In order to evaluate the ability of different methods to replicate the covariate effect and the results of a clinical trial, a model was used to simulate the response obtained from the empirical distribution as well as from the virtual populations.
A KPD model was used to generate FEV1 (Forced Expiratory Volume in 1 second) responses in the COPD trials using NONMEM. Patient demographics were generated by the different methods and treatment effect compared at the end of the trial. A CTS template has been used to simulate 100 clinical trials, each one with a different simulated population. The global covariates simulation procedure has been implemented in an R function and included in the template.

Results

Simulations based on multivariate distribution allows covariate correlations to be characterised using an empirical distribution. Covariate correlations simulated from a multivariate distribution were representative of the real patient population. The CTS scenarios performed with these virtual patients were comparable to the results obtained in the original trial and by re-sampling of the trial population.

Real data (3498 subj) Simulated data (3500 subj)

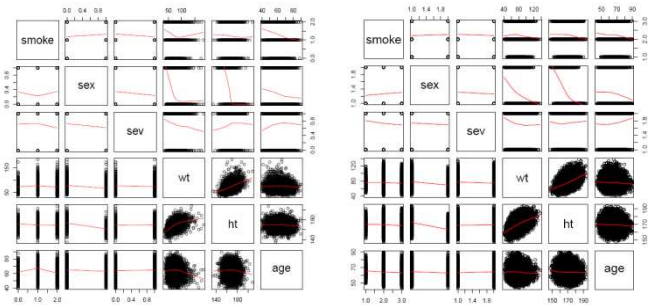
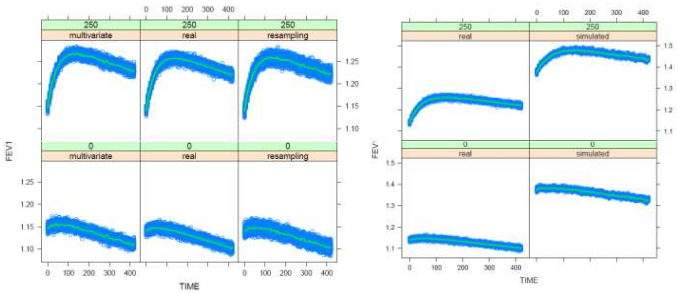


Figure 2. *Real and simulated covariate distributions obtained with a multivariate normal distribution.*



A *B*

Figure 3 (A). *Clinical Trial Simulation (100 trials) for placebo (lower panel) and active arm (upper panel) for the real population and simulated populations (resampling and multivariate distribution) and* ***(B)*** *impact of different stratification rules, as defined by the proportion of severe patients in a trial (from 1:2 to 2:1 for mild and moderate severity).*

Conclusion

1) Multivariate distribution methods may be applied to continuous and categorical covariates.
2) This procedure accounts for collinearity between covariates, allowing comprehensive evaluation of the effects of covariates beyond the range of values imposed by inclusion and exclusion criteria.
3)This feature overcomes one of the main limitations of re-sampling methods.
4) Thanks to its implementation in R, the method can be easily integrated into complex CTS exercises.

References

[1] Girard P. (2005) Clinical Trial Simulation: A Tool for Understanding Study Failures and Preventing Them. Basic & Clinical Pharmacology & Toxicology. 96:228–234.
[2] Tannenbaum et al. (2006) Simulation of Correlated Continuous and Categorical Variables using a Single Multivariate Distribution. Journal of Pharmacokinetics and Pharmacodynamics. 33(6):773-794

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TI PHARMA

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