Joint model for dropout in longitudinal trials in COPD patients

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Introduction

Background: Long-term longitudinal clinical trials often have large dropout rates. The dropout is termed informative if it is related to or dependent on the values of the primary variable used for the assessment of efficacy. The objective of this investigation was to assess the joint modelling of longitudinal measurements and time to dropout data based on Forced exhaled volume in one second (FEV1) [1].

Methods

Data from 1356 COPD patients (28% female) from a 52-week study treated with placebo were evaluated. Mean age was 64.4 (SD=8.9) years.

The FEV1 over time is modelling by two-level mix model using *lme()* function of the *nlme* package in R [2].

$$fev1_{ij} = \beta_0 + \beta_1 t_{ij} + u_{0i} + u_{1i} t_{ij} + \varepsilon_{ij} \quad (1)$$

Subject *i* at time *j*

The hazard of dropping out of the trial is modelled by Cox proportional hazard model with initial FEV1 (fev_{0i}) as covariate.

$$\lambda_i(t) = \lambda_0(t) \exp(\beta_2 fev_{0i}) \quad (2)$$

The basal hazard $\lambda_0(t)$ and β_2 were estimated using the R

package *survival()* function.

For the joint model simulations the random parts of the two-level mix model for FEV1 (equation 1) indicating individual differences were included in the computation of hazard over time.

$$\lambda_i(t) = \lambda_0(t) \exp(\beta_2 \beta_0 + \gamma_1 u_{0i} + \gamma_2 u_{1i} t_{ij} + \gamma_3)) \quad (3)$$

Results

The two-level mix model (eq. 1) predictions for FEV1 is shown in Figure 1.

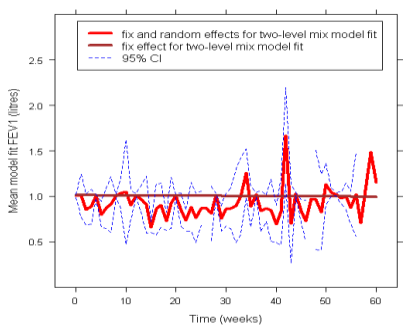


Fig. 1: Two-level mix model predictions (mean) for FEV1.

The Kaplan-Meier plot representing proportions remaining in trial is shown in Figure 2. The base hazard computed from the Cox regression (proportional hazard model) is shown in Figure 3 with addition of linear regression line.

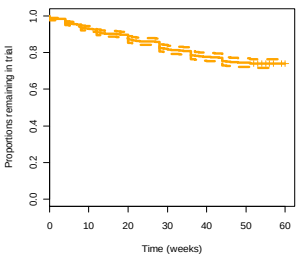


Fig. 2: Kaplan-Meier curve.

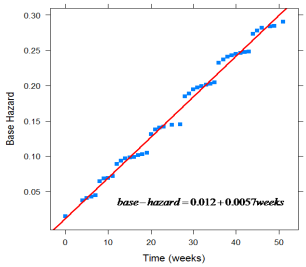


Fig. 3: Cox regression base hazard.

The risk of dropping out was computed as the accumulation (integration) of hazard with the survival being the exponentiated risk. The joint model simulation (equation 3) with γ's set to zero and to (0.5,0.5,-0.3) are shown in Figures 4 and 5.

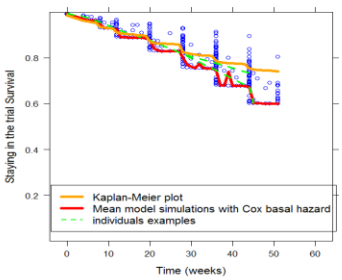


Fig. 4: Joint model simulation with γ 's set to zero (eq. 3).

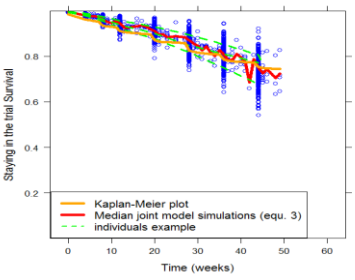
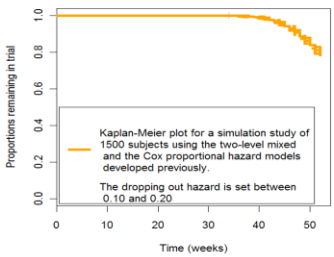


Fig. 5: Joint model simulation with γ 's set to 0.5, 0.5 and -0.3 (eq. 3).

A hypothetical simulation study with 1500 subjects.

Model parameters were from the two-level mix model and the Cox regression. In this simulation it was assumed a subject would dropped out of the study once the first occurrence of hazard was between 0.10-0.20 with γ's as in figure 5.



Conclusions

The Cox proportional hazard model with the addition of random effects to account for between-subject variability provides the basis for the simulation of survival in placebo treated COPD patients. Our simulations suggest that not only differences in baseline, but also changes in FEV1 over time contribute to the hazard or survival during the trial.

References:

[1] Henderson et al, Biostatistics (2000) 1,4, pp 465-480

[2] http://cran.r-project.org

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