Performance of non-linear mixed effects models with and without taking informative dropout into account

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Objectives:

The objective of this simulation study was to investigate the performance of non-linear mixed effects models with and without taking informative dropout into account.

Methods:

- Simulations were performed using an inhibitory E_{max} drug effect model combined with an exponential placebo effect model and a dropout model in which the hazard was exponentially related to the individual predicted efficacy score, adapted from Björnsson and Simonsson [1] (Fig 1).
- Base Scenario consisted of a placebo group and three active treatment groups with a 1:2:4 relationship in the dose, 45 subjects in each group, and 9 observations per subject.
- Analysis of the simulated data was performed using non-linear mixed effects modeling with or without including the dropout model.
- Impact of number of subjects per group, number of observations per subject, dropout rate, and size of the placebo effect were investigated with respect to bias in the parameter estimates.
- The Laplacian estimation method in NONMEM 7 [2] and PsN [3] were used for the stochastic simulations and estimations. 1000 replicates simulated for each scenario.

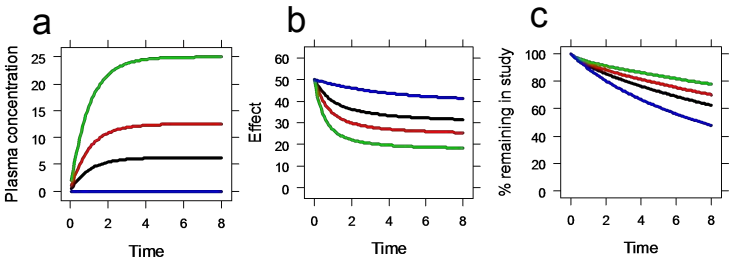

Figure 1: **a)** Plasma concentrations, **b)** Efficacy Score, and **c)** Probability of remaining in the study *vs*. time, for a typical individual on Placebo (blue), Low Dose (black), Medium Dose (red) and High Dose (green) in the Base Scenario.

Results:

In the base scenario, bias was less than 3% in all fixed effects parameters when the same model, including dropout, was used for simulation and estimation. Bias was larger in EC_{50} when dropout was not included in the estimation model, although the bias was still low for the base scenario (Fig. 2). The bias in EC_{50} increased with increasing dropout rate, increasing placebo effect and decreasing number of observations per subject (Fig 2). The increase in bias was larger when dropout was ignored. The bias did not lead to any major differences in the efficacy score for the Base Scenario (Fig. 3).

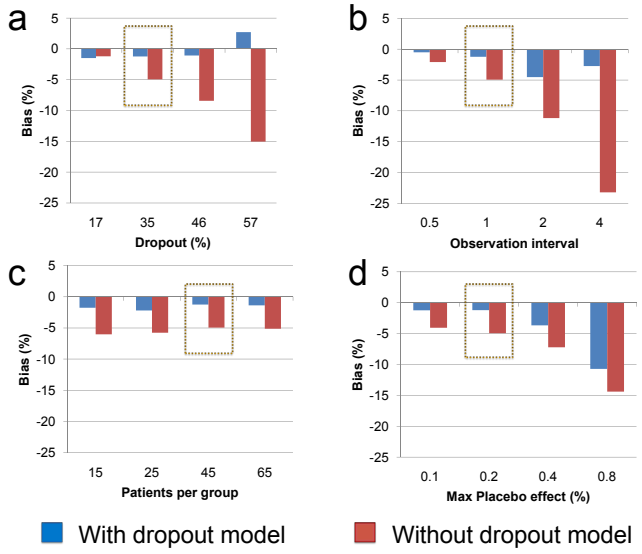

Figure 2: The effect of **a)** magnitude of dropout, **b)** observation interval, **c)** number of patients, **d)** size of placebo effect, on bias in EC_{50} when data is analyzed with (blue) or without (red) a dropout model. Base Scenario is marked with yellow lines.

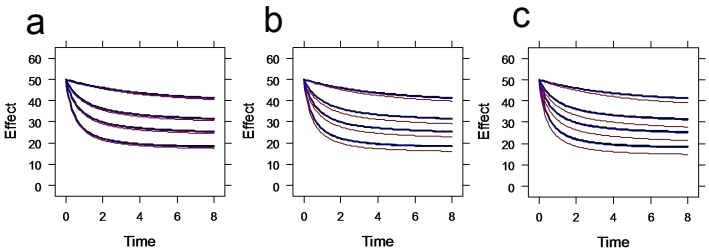

Figure 3: Efficacy score for a typical individual on Placebo, Low Dose, Medium Dose and High Dose in **a)** the Base Scenario, **b)** a scenario with 57% dropout, **c)** a scenario with 3 observations per patient. Simulations based on true parameters (black), parameters estimated with dropout model (blue), parameters estimated without dropout model (red).

Conclusions:

- Ignoring informative dropout can lead to biased parameter estimates, although the bias in many cases was found to be relatively low.
- The bias was dependent on dropout rate, magnitude of placebo effect and number of observations per patient, but independent on number of subjects.

References:

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[3] Lindbom L, Pihlgren P, Jonsson EN. Comput Methods Programs Biomed 2005; 79:241-257

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