

Effect on bias in EC_{50} when using interval censoring or exact dropout times in the presence of informative dropout

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Background and Objectives:

Informative dropout can cause bias in parameter estimates. The use of a dropout model can lower this bias. The objective of this simulation study was to compare bias in EC_{50} estimates when using interval censored dropout and data where the exact time of dropout is known, in the case of informative dropout.

Methods:

- An efficacy variable was simulated using an inhibitory E_{max} drug effect model combined with an exponential placebo effect model (Fig. 1).

- Simultaneously, dropout was simulated using a hazard function in which the hazard was exponentially related to the individual predicted efficacy variable, adapted from Björnsson and Simonsson [1] (Fig 1).

- Dropout was either recorded at the actual time of dropout, or interval censored, i.e. dropout occurred somewhere between two pre-defined assessment times.

- The impact of interval between pre-defined assessment times, and hence the number of assessments, as well as the impact of extent of dropout was evaluated.

- The simulated efficacy and dropout data were simultaneously analysed using non-linear mixed effects modelling. NONMEM 7 and PsN [2] were used for the stochastic simulations and estimations.

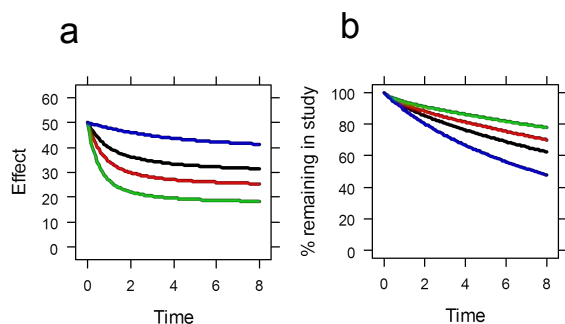


Figure 1: a) Efficacy Score, and b) Probability of remaining in the study vs. time, for a typical individual on Placebo (blue), Low Dose (black), Medium Dose (red) and High Dose (green) in the Base Scenario.

Results:

In all simulations bias in EC_{50} was low, less than 10%. When simulations were performed using interval censoring, bias in EC_{50} was higher than when the exact time of dropout was recorded. This was especially evident when there were few measurements of the effect variable (Fig 2). Bias in EC_{50} also increased with increasing dropout rate, regardless of whether exact times or interval censoring is used (Fig 3).

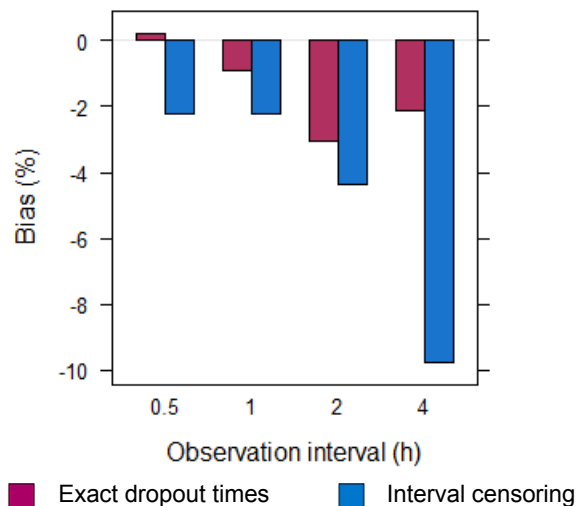


Figure 2: Bias in EC_{50} with increasing interval between observation (and hence fewer observations per patient).

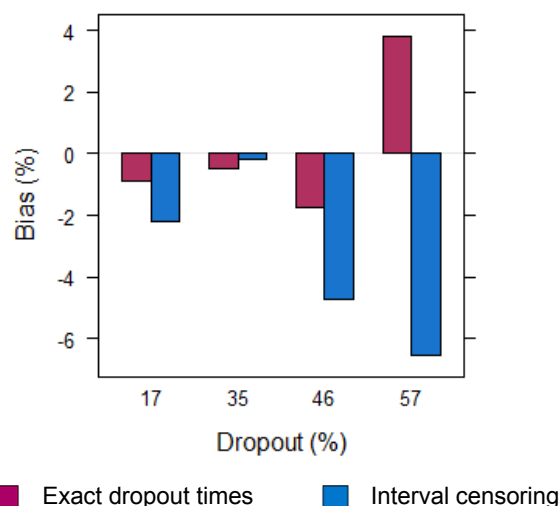


Figure 3: Bias in EC_{50} with increasing dropout rate

Conclusions:

Although bias may be low, using the exact dropout times when modeling informative dropout gives a lower bias in EC_{50} than when interval censoring is used, especially if the interval between observations is long or the extent of dropout is large.

References:

- [1] Björnsson MA, Simonsson USH. Br J Clin Pharmacol 2011; 71:899-906
- [2] Lindbom L, Pihlgren P, Jonsson EN. Comput Methods Programs Biomed 2005; 79:241-257