

Comparison of longitudinal data analysis to end of treatment data analysis when evaluating precision in dose-exposure-response in neuropathic pain studies

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Objectives:

In neuropathic pain, the primary endpoint for detecting the presence of dose-response has typically been the end of treatment (EOT) response in the Numeric Rating Scale (NRS) ¹.

The objective of this simulation study was to evaluate the precision in the dose-exposure-response relationship when using change from baseline at end of treatment as compared to when longitudinal data, i.e. all individual data from all time points are used. In addition the impact of introducing an effect delay in the longitudinal model was evaluated.

Methods:

For the longitudinal data analysis a simulation model was developed based on placebo-response (NRS) data from a phase IIa study in patients with Painful Diabetic Neuralgia.

For both the longitudinal and EOT model an assumed dose-exposure-response relationship was applied with a sigmoid E_{max} model driving the response. In the estimation step a sigmoid E-max model was over parameterized in most cases. The model used in the estimation step was selected based on a likelihood ratio test after fitting a no effect model, a linear model, an E_{max} and a sigmoid E_{max} model to data.

Different study-designs with varying number of dose arms and number of patients were evaluated. For the longitudinal analysis, a direct response model was compared to a link-model with the response reaching 95% of maximum effect half-way through the study.

The precision in dose-exposure-response was evaluated by estimating the percentage of studies with an estimated delta NRS within 0.7-1.3 given a true effect (simulated effect) of delta NRS equal to 1.

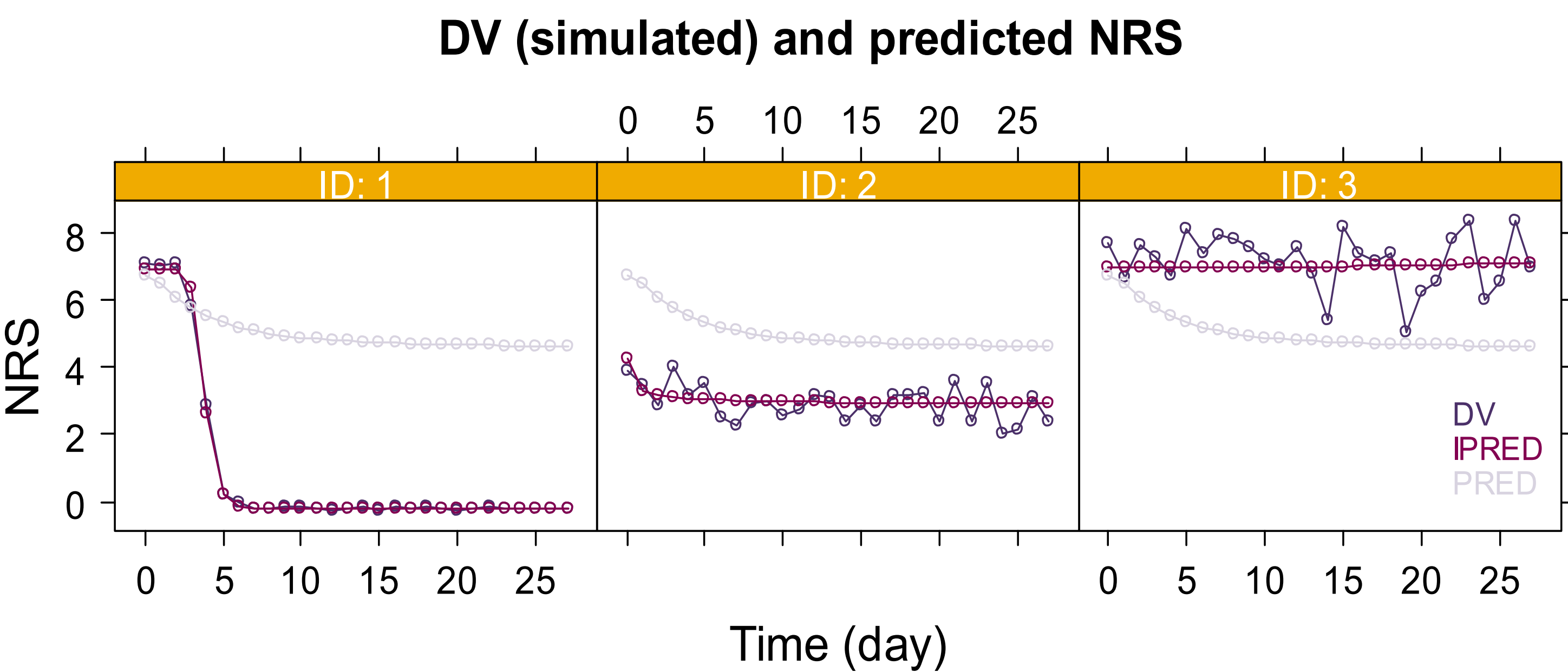


Figure 1: Simulated observations and model predictions for 3 individuals. The study duration was 28 days and there was one NRS observation each day.

Results:

In a simulated study with 4 dose arms and 54 patients in each dose arm the precision in dose-exposure-response was increased from 33% to 97% when using longitudinal data as compared to EOT. Introducing a time-delay in the efficacy reduced the precision from 97% to 83%. Reducing the number of patients from 54 to 20 in each dose arm reduced the precision from 97% to 81%.

Model	Data	On target
1. Direct effect (n=54/arm)	EOT	33%
2. Direct effect (n=54/arm)	Long.	97%
3. Link model (n=54/arm)	Long.	83%
4. Direct effect (n=20/arm)	Long.	81%
5. Link model (n=20/arm)	Long.	51%

Table 1: The percentage of studies with estimated effect between 0.7 and 1.3 for a true (simulated) effect of delta NRS=1

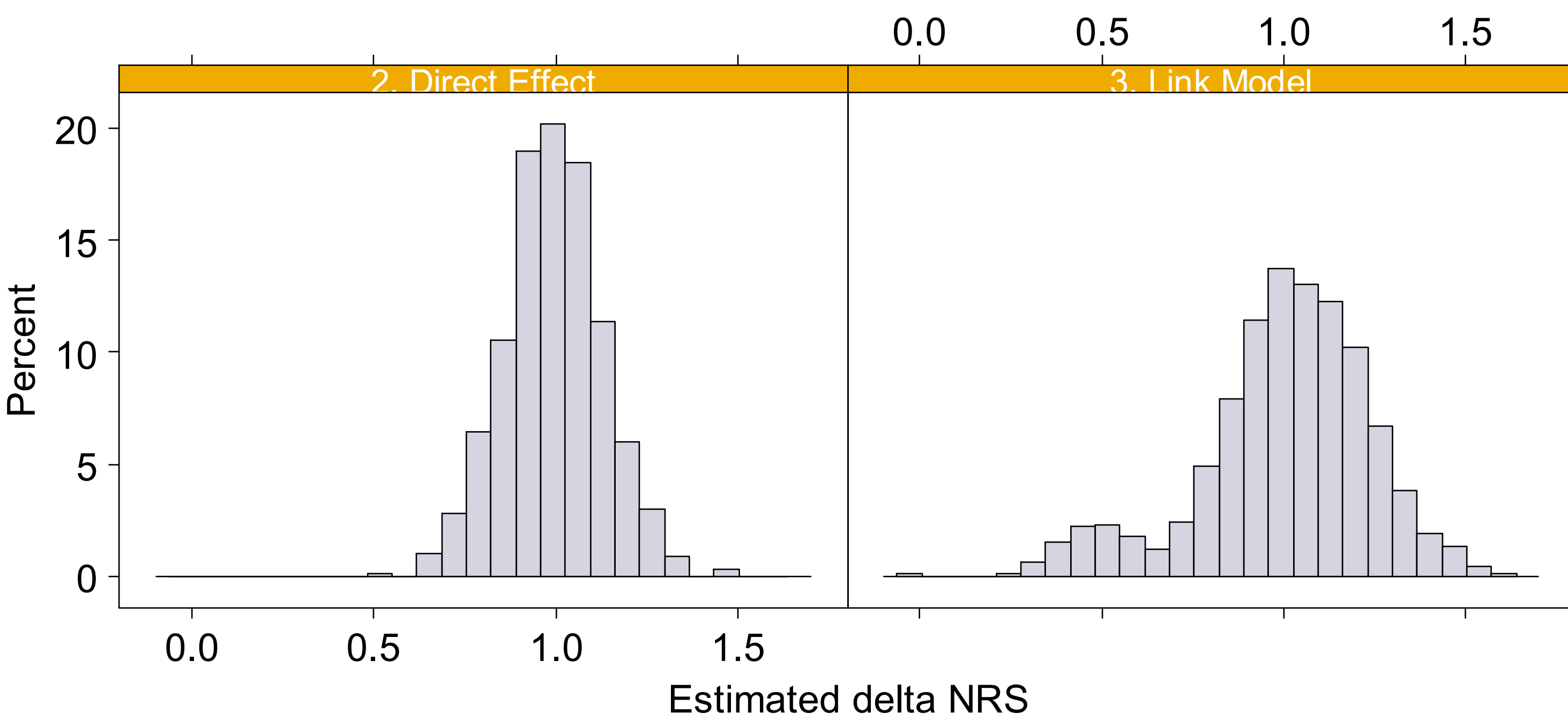


Figure 2: Distribution of the estimated delta NRS given a true effect (simulated) of 1.

Conclusion:

Including all time point of efficacy assessments increased the precision in dose-exposure-response to a large extent.

When performing a simulation based evaluation of a longitudinal analysis it is important to account for potential time-delays (or other complexities) in order to avoid being overly optimistic about the precision.

References:

Bornkamp B. et al. Innovative approaches for designing and analyzing adaptive dose-ranging trials. Journal of Biopharmaceutical Statistics. 17: 965–995, 2007.