

# Model-based adaptive optimal design for nonlinear mixed-effects models with model structure uncertainty.

## Application in a simulated dose-finding study

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### Introduction

Model-based adaptive optimal design (MBAOD) is a promising methodological tool for designing efficient dose-finding studies. MBAODs are allowed to adapt at prespecified interim evaluation steps, driven by study characteristics that optimize an optimal design criterion [1]. Simulation studies have shown that MBAODs are less susceptible to misspecification during the design phase, as compared to classical fixed optimal designs [2-4]. However, these findings were based on the assumption that the model structure is known a priori, which is typically not the case in most clinical development programs. Thus, we aimed to extend the MBAOD framework by introducing a Model Selection (MS) or a Model Averaging (MA) step at each interim step to account for model structure uncertainty

### Methods

- Clinical Trial Simulations for hypothetical dose-finding trials were performed.
- The “ground truth” simulation model was a simplified version of a population model describing the weight loss trajectories following daily s.c. administration of liraglutide 3.0 mg [5].

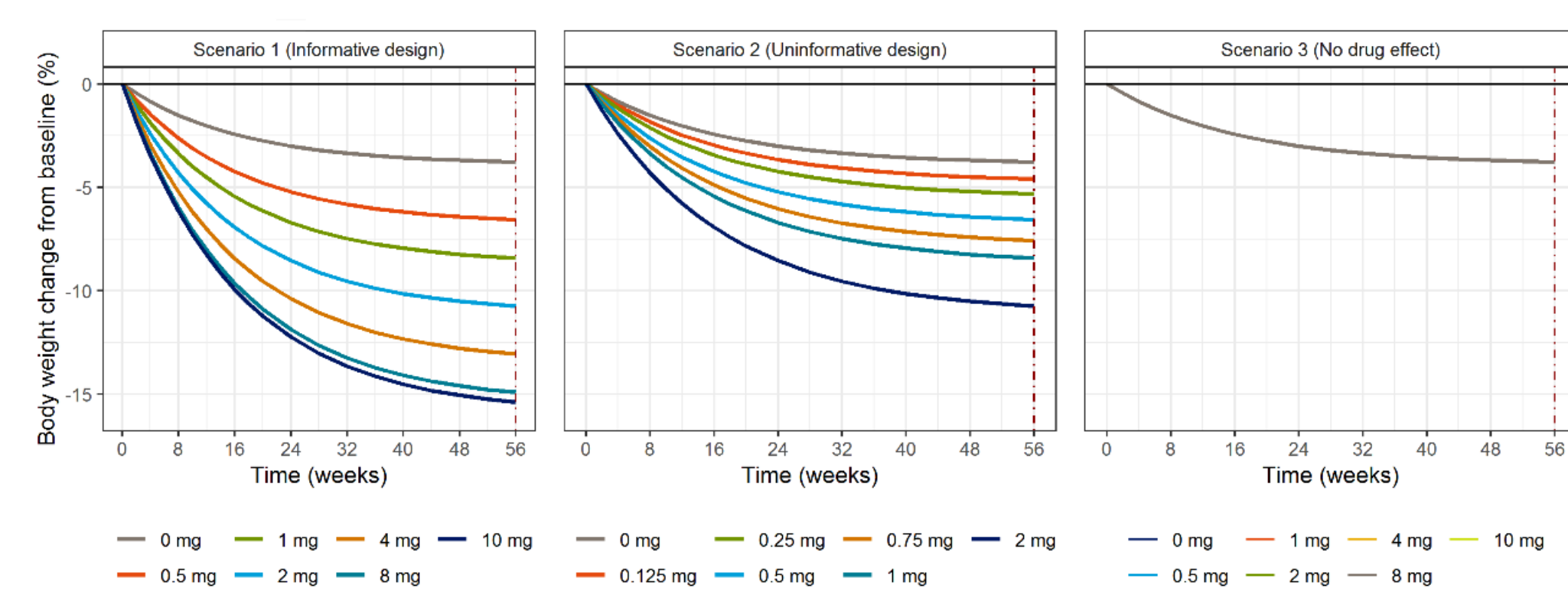


Figure 1: Body weight change trajectories for the true underlying dose-response relationships across the three explored scenarios.

- Response adaptive allocation probabilities were driven by the D-optimality criterion, computed
  - for the true simulation model (SM)
  - the best model in terms of AIC (MS)
  - by weighting models based on MA.
- Five, prespecified, candidate model structures were used to estimate the underlying Dose-Response (D-R) relationship (no drug effect, linear, log-linear, Emax and sigmoid Emax).
- Estimation and simulation of the time-course shared the same model structure (turnover model). Subjects were randomized 1:6 to placebo or one of six active treatment doses (adaptations were performed for the active groups only).

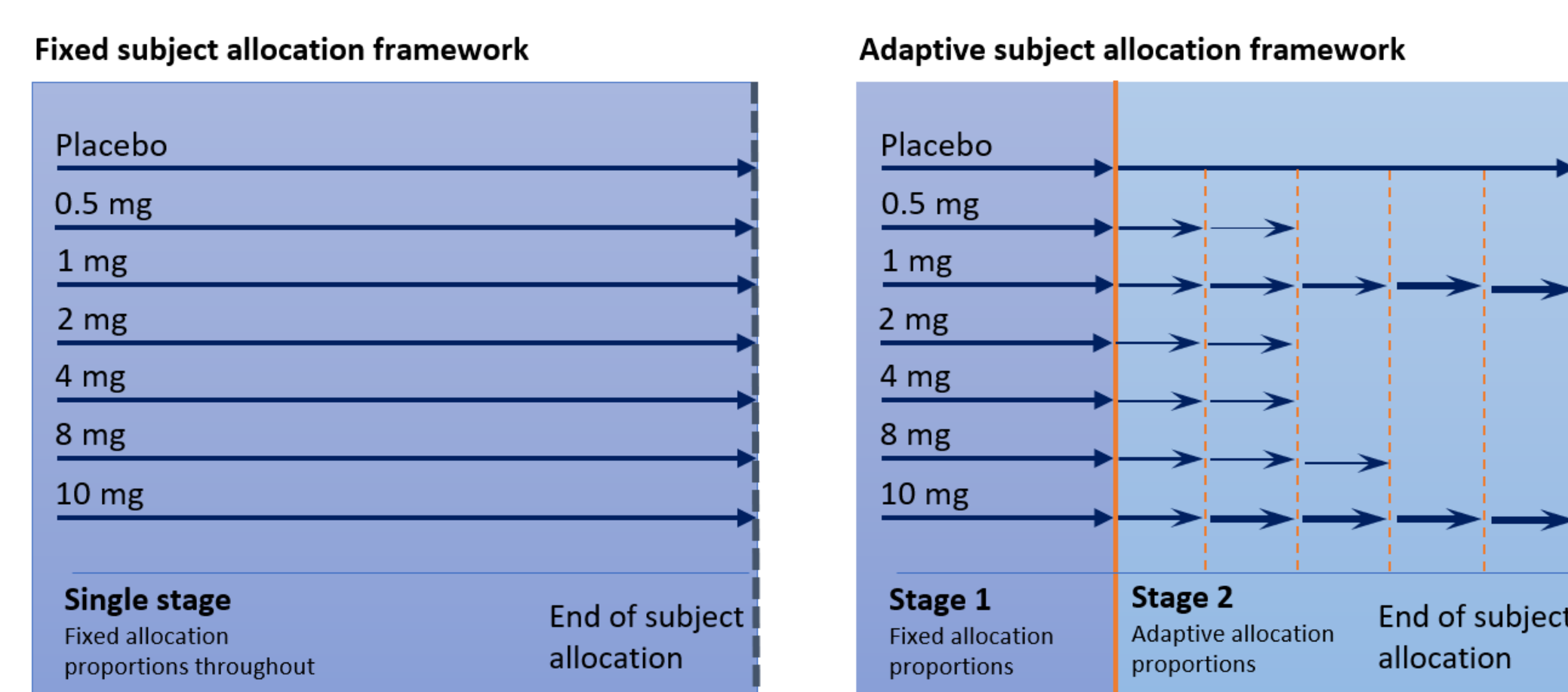


Figure 2: Schematic of the subjects allocation algorithm for (A) a typical study design, with fixed subject allocation and (B) a model-based adaptive optimal design with adaptive subject allocation. The arrow thickness represents the allocation probabilities in each dose level.

- The proposed methodology was tested under three scenarios (Figure 1):
  - Informative:** drug effect present and explored doses distributed around the hypothetical ED50
  - Uninformative:** drug effect present and explored doses below the hypothetical ED50
  - No drug effect
- The adaptive designs (Figure 2) consisted of 1) a fixed allocation period (learning phase) and 2) an adaptive allocation period (adaptive phase).
- During the learning phase, all subjects were randomized equally across arms. When 25% of the prespecified total study population completed 25% of the total trial duration, the adaptive phase was initiated.
- A stopping rule was included to stop the trials early for futility (lack of drug effect).
- 500 trials were simulated for each scenario and each modeling approach. Model based optimizations and MBAODs were performed using the R package PopED [6] and MBAOD [7], respectively. All simulations and estimations were performed in NONMEM version 7.3 [8] with PsN [9]

### Results

MBAODs lead to more accurate dose-finding as compared to fixed designs (Table 1 and Figure 4).

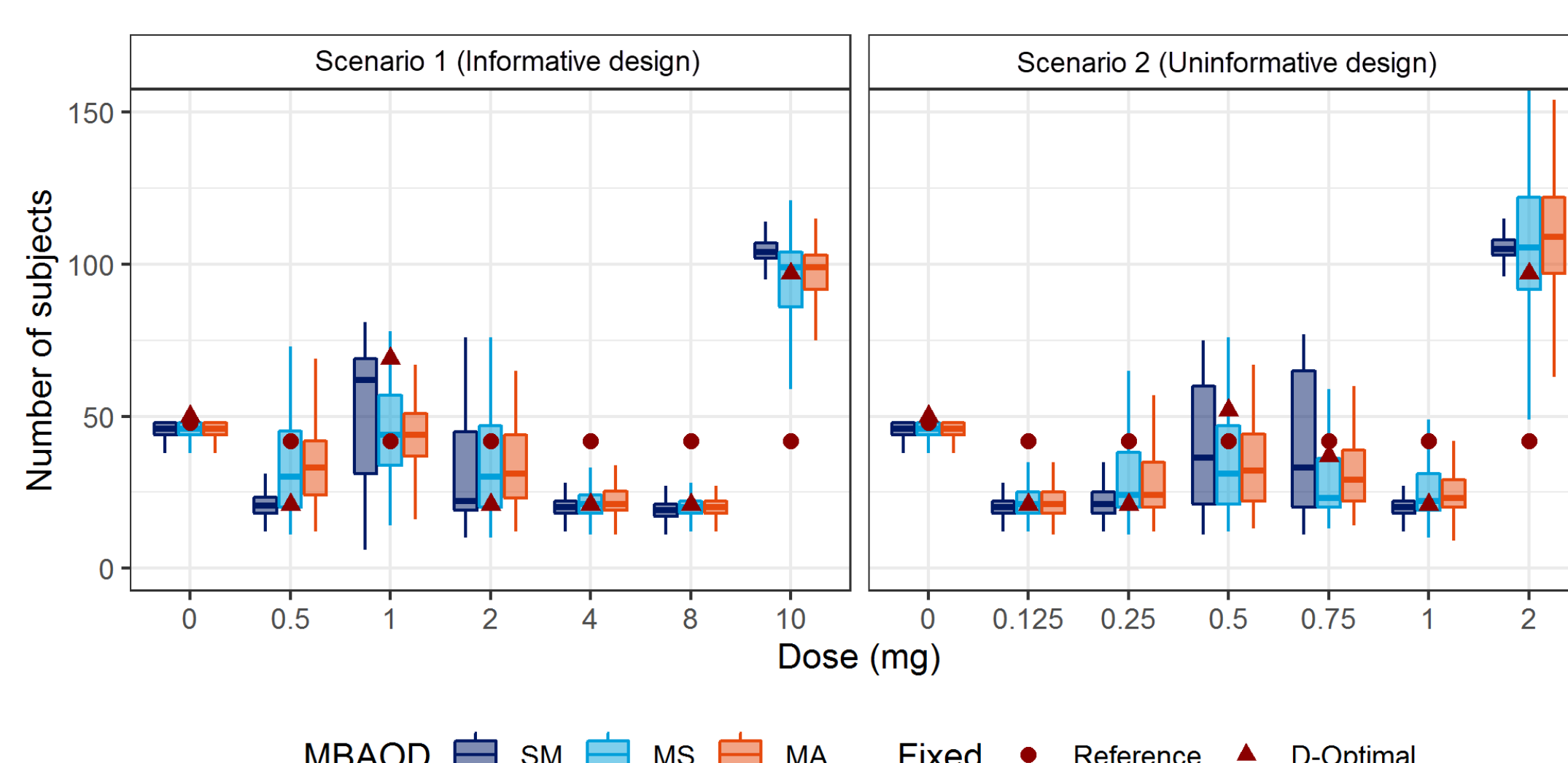


Figure 3: Distribution of the number of subjects allocated at each dose level under an adaptive optimal design setting based on the simulation model (SM; dark blue), model selection (MS; light blue) and model averaging (MA; light red), for the scenarios with an active drug present. The fixed allocation proportions for the reference (red circle) and the true D-optimal (red triangle) designs are shown.

When accounting for model uncertainty using MS or MA, the predictive performance was comparable to the one obtained under the true simulation model.

- Informative scenario: all methods led to accurate and precise prediction of the minimum effective dose.
- Uninformative scenario:
  - No design adaptations: MA led to better predictive performance as compared to MS.
  - With adaptations: improvements in both accuracy and precision of the minimum effective dose were observed across all evaluated methods.

The best performance improvement was seen for the MA approach when the true simulation model was not included in the estimation models set, followed by the MS approach.

No drug effect scenario: an early stop for futility was observed for SM and MS. The majority of trials did not to stop for futility with the MA approach.

Table 1. Relative bias and relative root mean squared error for the predicted minimum effective dose in trials indicating the presence of a clinically relevant effect.

| True MED<br>6 mg        | Bias (%)                           |           |       |                                      |           |       |
|-------------------------|------------------------------------|-----------|-------|--------------------------------------|-----------|-------|
|                         | Scenario 1<br>(Informative design) |           |       | Scenario 2<br>(Uninformative design) |           |       |
|                         | Reference                          | D-Optimal | MBAOD | Reference                            | D-Optimal | MBAOD |
| MA                      | 0.6                                | 3.3       | 1.8   | -23.4                                | -20       | -17.7 |
| MS                      | -0.2                               | -0.2      | 3.2   | -28.3                                | -24       | -17.4 |
| MA w/o simulation model | 2.6                                | -6.6      | 0.7   | -12.7                                | -24       | -16.8 |
| MS w/o simulation model | 3.2                                | 5.6       | 0.3   | -27.8                                | -25       | -20.4 |
| Simulation model        | -0.9                               | 0.2       | -0.8  | -16.1                                | -11.5     | -11.1 |

|                         | RMSE (%)                           |           |       |                                      |           |       |
|-------------------------|------------------------------------|-----------|-------|--------------------------------------|-----------|-------|
|                         | Scenario 1<br>(Informative Design) |           |       | Scenario 2<br>(Uninformative design) |           |       |
|                         | Reference                          | D-Optimal | MBAOD | Reference                            | D-Optimal | MBAOD |
| MA                      | 6.4                                | 7.7       | 9.7   | 12.5                                 | 10.5      | 10.6  |
| MS                      | 6.7                                | 7.3       | 10    | 15.5                                 | 10.5      | 11    |
| MA w/o simulation model | 7.9                                | 9.8       | 8.6   | 9.3                                  | 8.4       | 11.2  |
| MS w/o simulation model | 6.7                                | 9.2       | 8.2   | 14.5                                 | 12.5      | 10.9  |
| Simulation model        | 6.7                                | 8         | 7.9   | 11.4                                 | 9.8       | 10.4  |

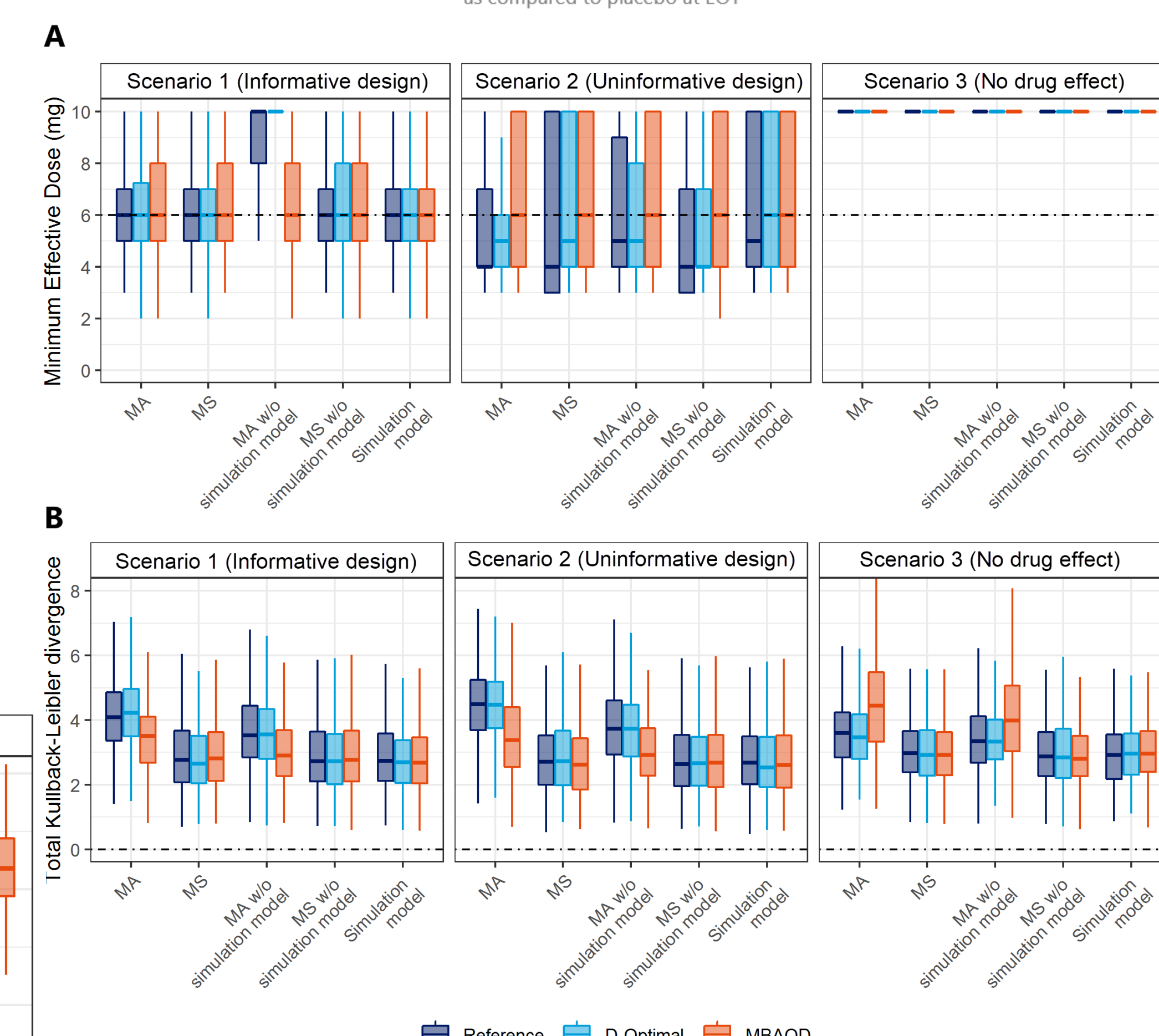


Figure 4: (A) Distribution of (A) the predicted minimum effective doses and (B) the total Kullback–Leibler divergence for each model-based adaptation method and fixed designs across the three studied scenarios. The dashed line represents the true MED based on the true model parameters and model structure (6 mg).

### Conclusions

- Model structure uncertainty can be taken into account when performing MBAOD with minimal to no impact to model-based decision-making at the end of a dose-finding study as compared to the “best-case” situation where the ground truth is known a priori.
- The best results were seen when MBAOD methods were paired with a model-selection step at the interim evaluations.
- MBAOD with MA: Similar MED identification performance – challenged when no drug effect was present.
- The proposed methods can help to relax the assumptions regarding the model structure, and potentially increase the applicability of MBAOD in dose-finding trials.

### Acknowledgments

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