

Simulation-based comparison of MMRM and dose-response MMRM for Ph2b dose-finding design in rheumatoid arthritis

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Introduction

- The primary analysis of a Ph2b dose-finding study is typically based on pairwise statistical tests of the study arms, for example using a mixed model for repeated measures (MMRM).
- Dose-response analysis
 - provides the potential to increase the precision in estimates, which would result in better informed Ph3 dose selection.
 - allows for optimization of other design aspects like sample size, doses to be explored and allocation ratios.
- A promising approach for analyzing Ph2b dose-finding trials is dose-response MMRM (DR-MMRM) [1].
- The DR-MMRM method makes limited assumptions about the shape of the longitudinal response while still borrowing information across doses.

Objectives

To compare the performance of DR-MMRM and MMRM for a Ph2b study design in rheumatoid arthritis (RA), with change from baseline (CFB) DAS28-CRP as endpoint, using clinical trial simulations.

Methods

- A simulation model for change from baseline DAS28-CRP was constructed (Figure 1, Table 1). The placebo model was informed by published data [2] and data from the TransCelerate database.
- An overview of the simulation/estimation framework for DAS28-CRP dose-response evaluation is illustrated in Figure 2.
- The MMRM and DR-MMRM model were estimated using the *nlme* package in R [4].

Figure 1: True dose-response for placebo-adjusted CFB DAS-28 CRP at Week 12

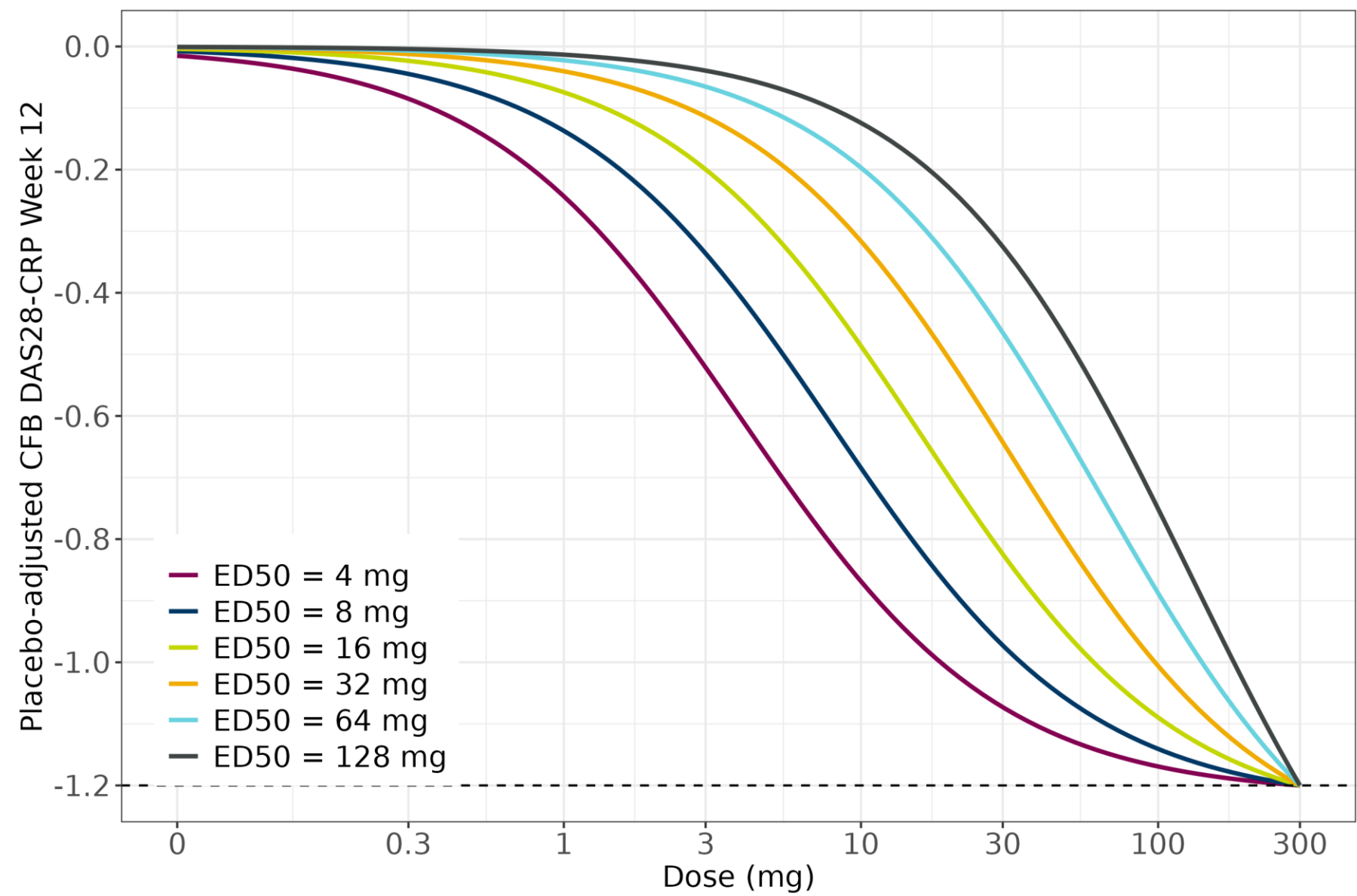
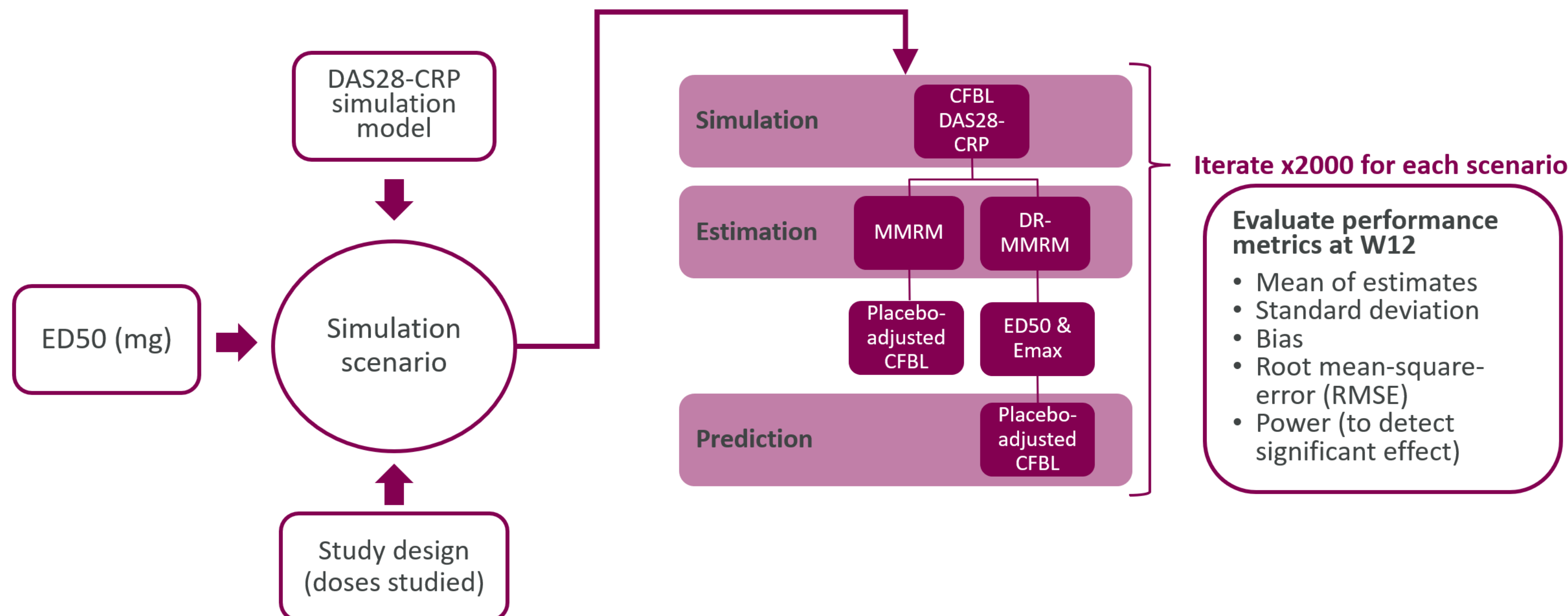


Figure 2: Overview of simulation/estimation framework for DAS28-CRP dose-response evaluation



Simulation model

$$CFB = E_p(t) + E_D(t, DOSE) + \eta, \quad \eta \sim N(0, \omega^2)$$
$$E_p(t) = P_{max} * \left(1 - e^{-\left(\frac{\log 2}{\tau_p}\right)t}\right)$$
$$E_D(t, DOSE) = E_{max}(t) * \frac{DOSE}{DOSE + ED_{50}} * \frac{300 + ED_{50}}{300}$$
$$E_{max}(t) = D_{max}(t) * \frac{t}{t + ET_{50}} * \frac{12 + ET_{50}}{12}$$
$$CFB_{obs} = CFB + \epsilon, \quad \epsilon \sim AR1(\rho, \sigma)$$

Table 1: Study designs and parameter values used for simulation scenarios

Design	Doses
Design 1	Placebo + 10, 30, 100, 300 mg
Design 2	Placebo + 3, 10, 30, 100, 300 mg
Design 3	Placebo + 10, 30, 100, 300, 1000 mg
Design 4	Placebo + 3, 10, 30, 100, 300, 1000 mg

Patients per arm: 26; Sampling points: Week 1, 2, 4, 6, 8, 12

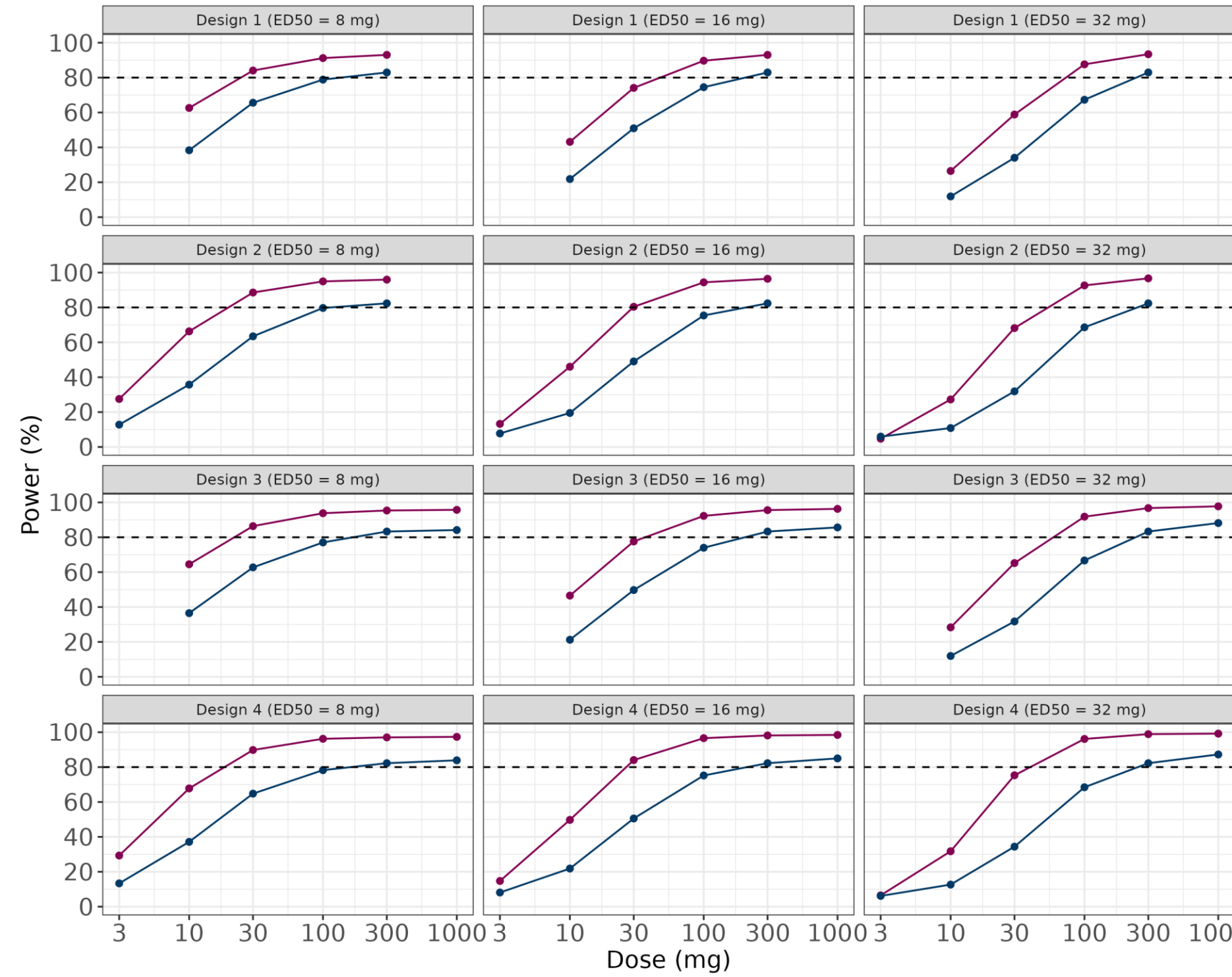
Parameter	Interpretation	Value
P_{max}	Maximal placebo effect on DAS28-CRP reduction	-1
τ_p	Half-life of placebo effect (weeks)	3.5
D_{max}	Drug effect W12, 300 mg [3]	-1.2
ET_{50}	Time to half-maximal drug effect (weeks)	2
ED_{50}	Dose giving half-maximal effect (mg)	4 to 128
σ	Within-subject variability	0.75
ρ	Correlation in AR(1)	0.46
ω	Between-subject variability	1.3

Results

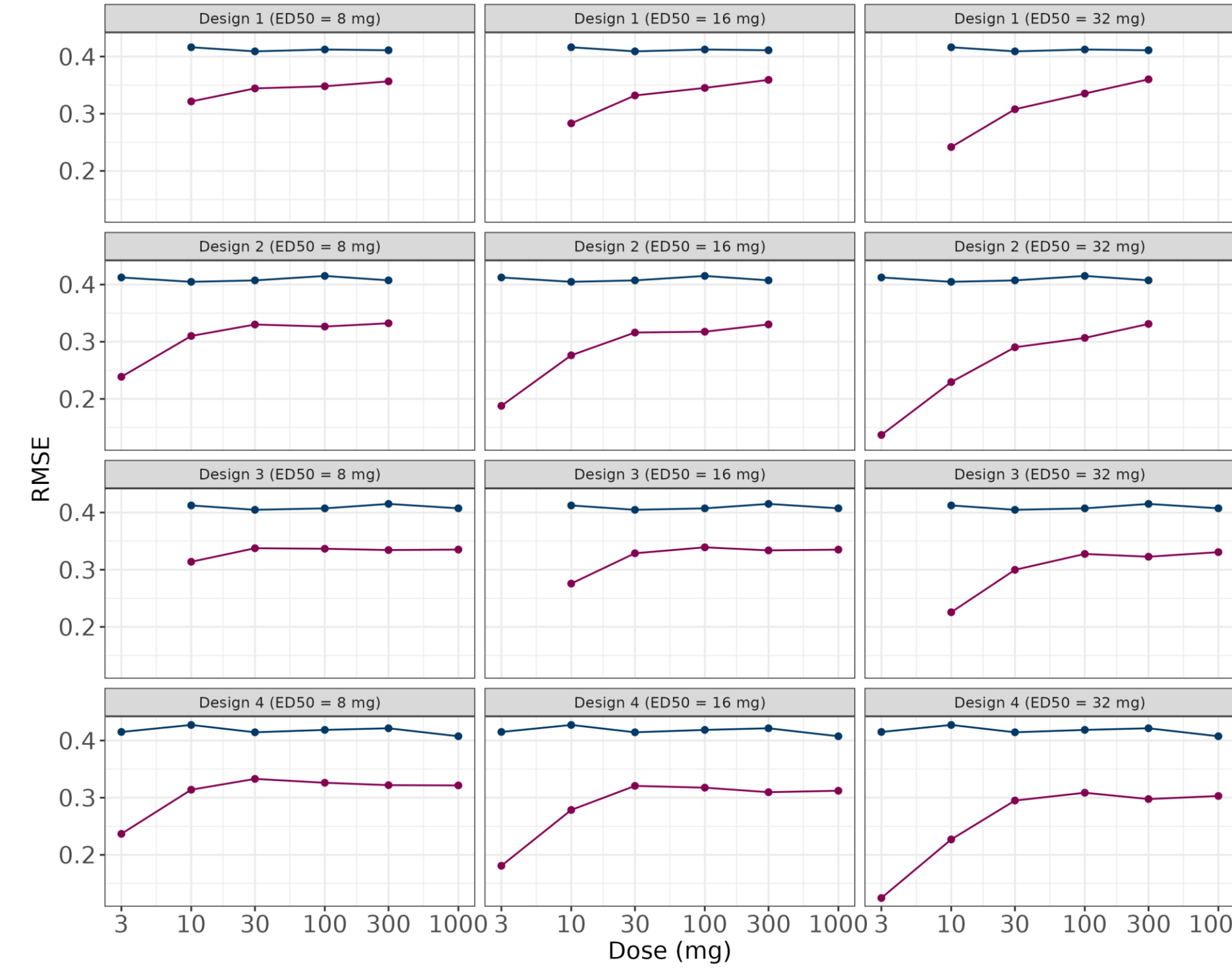
- DR-MMRM yielded higher precision of the effect estimate, with an improvement in RMSE compared to the MMRM approach across all simulation scenarios (Figure 3).
- For the 300 mg dose at Week 12, the statistical power increased from 83% using MMRM to 94-97% using the DR-MMRM approach (Figure 3).
- The bias introduced by DR-MMRM was in general low and dependent on ED50 and study design.
- The DR-MMRM estimation had a convergence rate ranging between 84-100%, with numerical problems emerging for the least informative study design.

Figure 3: Power (top) and RMSE (bottom) for DR-MMRM and MMRM for selected simulation scenarios (ED₅₀ 8/16/32 mg)

Power



RMSE



Conclusions

- MMRM and DR-MMRM have been evaluated across multiple simulation scenarios in a Ph2b setting with DAS28-CRP as endpoint.
- DR-MMRM results in more precise estimates and increases the statistical power compared to MMRM, while keeping the bias low
- The estimation convergence rate of the *nlme* estimation needs to be considered when planning DR-MMRM analyses in a Ph2b setting.

References

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