Using mixture priors for robust inference: application in Bayesian dose escalation trials

Astrid Jullion, Beat Neuenschwander, Daniel Lorand

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Agenda

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  - EWOC criterion
- Meta-Analyic-Predictive Priors
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  - Between-strata heterogeneity
  - Mixture prior
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  - Change of formulation within the dose-escalation phase
- Simulations
- Conclusions

Dose escalation in oncology phase I trial

Bayesian logistic regression model

- Data
  - For each tested dose d:
    - Number of evaluable patients : n_d
    - Number of dose-limiting toxicities (DLT) observed in the first cycle of treatment : r_d
- Bayesian logistic regression model (BLRM)

$$r_d|n_d \sim Binomial(\pi_d, n_d)$$

$$logit(\pi_d) = \log(\alpha) + \beta \log\left(\frac{d}{d^*}\right)$$

$$(\log(\alpha), \log(\beta)) \sim MVN_2(\mu, \Psi)$$

  - With
    - π_d: DLT rate at a given dose, d
    - α, $\beta > 0$
    - d^* : scaling dose
    - μ: prior means (μ_a , μ_b)
    - Ψ: prior covariance matrix (composed of σ_a, σ_b and ρ)

Dose escalation in oncology phase I trial

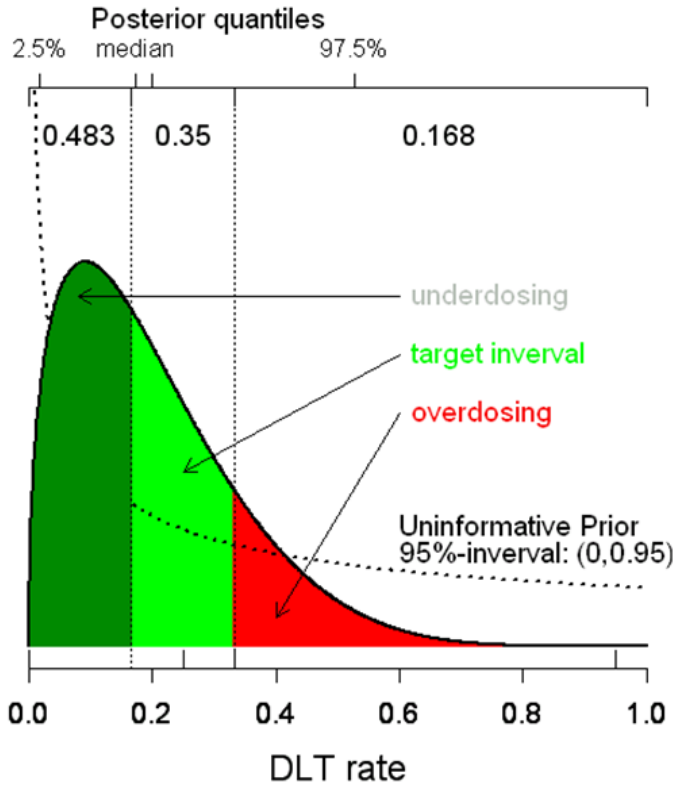
EWOC criterion

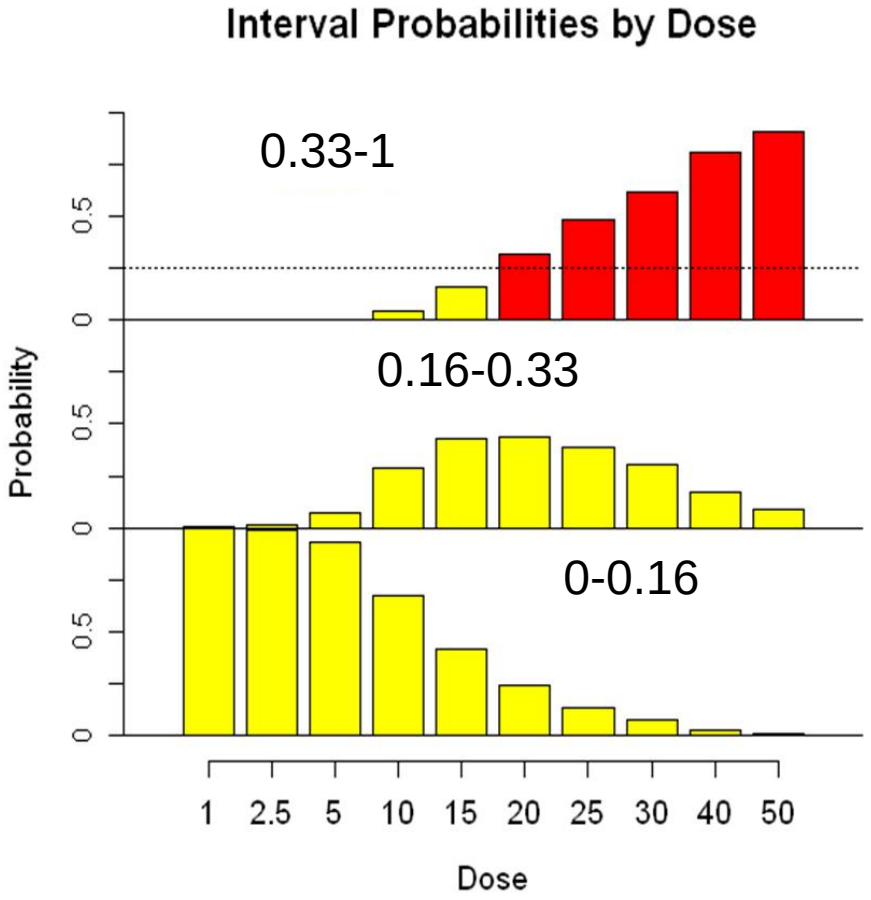
- Bayesian modeling provides the posterior probability of DLT rate at each dose
- Toxicity intervals
  - <16% : underdosing
  - 16%-33% : target toxicity rate
  - >33% : excessive toxicity
- Escalate with overdose control (EWOC) *Babb et al, 1998*
  - P(excessive toxicity) < 0.25
- Dose recommendation
  - Dose must satisfy the EWOC criterion
  - Dose with highest probability of DLT rate being in the target interval

Dose escalation in oncology phase I trial

EWOC criterion

Posterior distribution of the DLT rate at one given dose





Meta-Analytic-Predictive Priors

Introduction

- In dose escalation studies, the use of complementary data may be justified.
  - For a study performed in a different population (Western -> Japanese)
  - For combination trials (information from single agent studies)
  - When different groups of patients with potentially different safety profiles need to be studied
  - Within a trial
    - Change in schedule
    - Change in formulation
- These complementary data are incorporated via Meta-Analytic-Predictive Priors.

Meta-Analytic-Predictive Priors

Hierarchical model

- MAP prior for the parameter θ^* in a new trial is the conditional distribution of the parameter given the external data from S strata:

$$\theta^* | Y_1, \ldots, Y_S$$

- MAP priors are based on hierarchical model where the difference between strata is taken into account

- Let $\boldsymbol{r_{d,s}}$ and $\boldsymbol{n_{d,s}}$ be the number of patients with a DLT and total number of patients at dose $\boldsymbol{d}$ in stratum $\boldsymbol{s}$:

$$r_{d,s} | n_{d,s} \sim Binomial(\pi_{d,s}, n_{d,s})$$

$$logit(\pi_{d,s}) = \log(\alpha_s) + \beta_s \log\left(\frac{d}{d^*}\right)$$

- What is the prior for $\theta^* = (\log(\alpha^*), \log(\beta^*))$ in the new trial ?

Meta-Analytic-Predictive Priors

Hierarchical model

Under the exchangeability assumption, we have:

$$(\log(\alpha_s), \log(\beta_s)) \sim MVN_2(\mu, \Psi), \qquad s = 1, \ldots, S$$

$$(\log(\alpha^*), \log(\beta^*)) \sim MVN_2(\mu, \Psi)$$

where $\mu = (\mu_a, \mu_b)$ and Ψ is the between-strata covariance matrix with standard deviation τ_a, τ_b and correlation ρ.

The hyperpriors are:

$$\mu_a \sim N(\mu_{0a}, \sigma_a); \quad \mu_b \sim N(\mu_{0b}, \sigma_b)$$

$$\tau_a \sim logN(\tau_{0a}, log(2)/1.96); \quad \tau_b \sim logN(\tau_{0b}, log(2)/1.96)$$

$$\rho \sim U[-1,1]$$

Meta-Analytic-Predictive Priors

Between-strata heterogeneity

- The parameters τ_a, τ_b quantify the degree of between strata heterogeneity

- Different degrees: small, moderate, substantial, large and very large

- Differential discounting for different strata is allowed.
  - Quality or relevance of external data may differ

Meta-Analytic-Predictive Priors

Mixture prior

- The choice of the between-strata heterogeneity shoud be justified
- Scenarios are performed to check the dose recommendation with the chosen level of heterogeneity
- In case conflict between prior information and trial data is deemed possible, using mixture prior with a weakly informative component add robustness to the statisical inference
  - First component: MAP prior (output from the hierarchical modeling of historical data)
  - Second component: weakly informative prior
- Robust Mixture Prior: w x MAP-Prior + (1-w) x Weakly-Informative-Prior
  - w=0.8 for instance

Motivating example

Presentation of the case

- First dose escalation study in patients
- Change from **capsule** to powder in bottle (**PIB**)
- Small between formulation variability is a reasonable assumption
  - Same powder for capsule and PIB
  - Formulation study in dogs shows similar PK
- Starting dose in PIB: highest tested dose in capsules that satisfies the EWOC criterion, after having taken into account the between formulation variability
- Maximum increase of one step in the provisional dose levels:

120mg	240mg	480mg	960mg	1800mg	3600mg	7200mg	10000mg	15000mg

Motivating example

- Available capsule data at the time of the formulation change

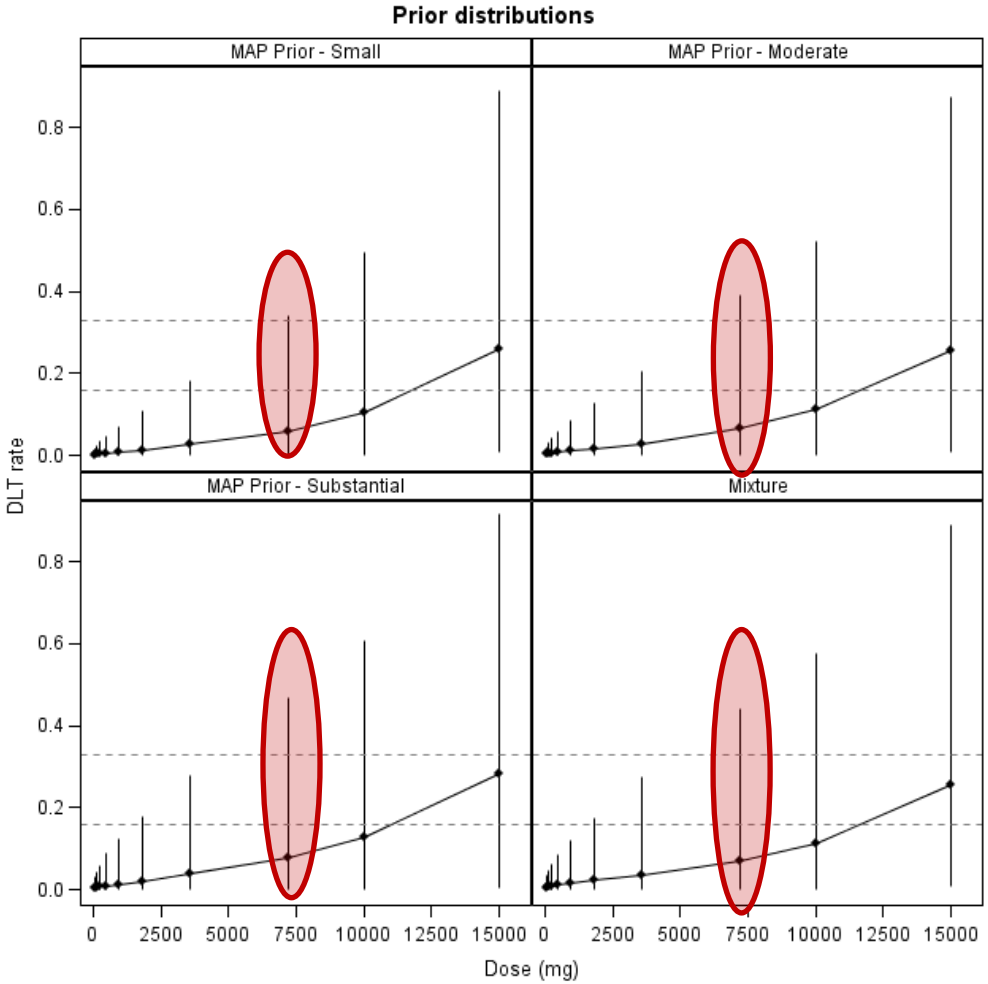
Total dose/cycle:	120mg	240mg	480mg	960mg	1800mg	3600mg	7200mg
Number of patients	1	1	3	4	3	3	7
Number of DLTs	0	0	0	0	0	0	0

- Scenarios for the upcoming PIB cohorts will be performed considering:
  - Small, moderate, substantial between formulation variability
  - Mixture prior
    - Small between formulation heterogeneity: 0.8
    - Weakly informative prior : 0.2

Motivating example

Prior

- Prior with small, moderate ad substantial between formulation variability
- Mixture: weakly informative + MAP (small between formulation variability)



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Motivating example

Results

- Hypothetical PIB data using prior from Capsule with different heterogeneity assumptions for MAP.

			Recommended dose			
	Dose (mg)	r/n	Small heterogeneity	Moderate heterogeneity	Substantial heterogeneity	Mixture
Starting dose			7200	7200	7200	7200
Scenario 1	7200	0 / 3	10000	10000	10000	10000
Scenario 2	7200	1 / 3	10000	10000	7200	7200
Scenario 3	7200	2 / 3	3600	3600	3600	3600
Scenario 4	7200 7200	1 / 3 0 / 3			10000	10000
Scenario 5	7200 7200 10000	1 / 3 0 / 3 0 / 3			10000	15000

Motivating example

Results

- Perform hypothetical scenarios to check the dose recommendations
- Using a mixture prior may allow to get more appropriate dose recommendations
- Discussion on these scenarios with the clinical team

Simulations

Set-up

- Cohort of 3 patients
- Maximum of 10 cohorts
- MTD definition: highest dose such that
  - P(DLT)<0.33
  - EWOC criterion is satisfied : P (excessive toxicity < 0.25)
- Trial stops when
  1. At least 6 patients are treated at the recommended MTD, $\tilde{d}$
  2. One of the following conditions is met:
     1. The probability of targeted toxicity at $\tilde{d}$ exceeds 0.5
     2. Or a minimum of 18 patients have already been treated

Simulations

Set-up

- Available historical data

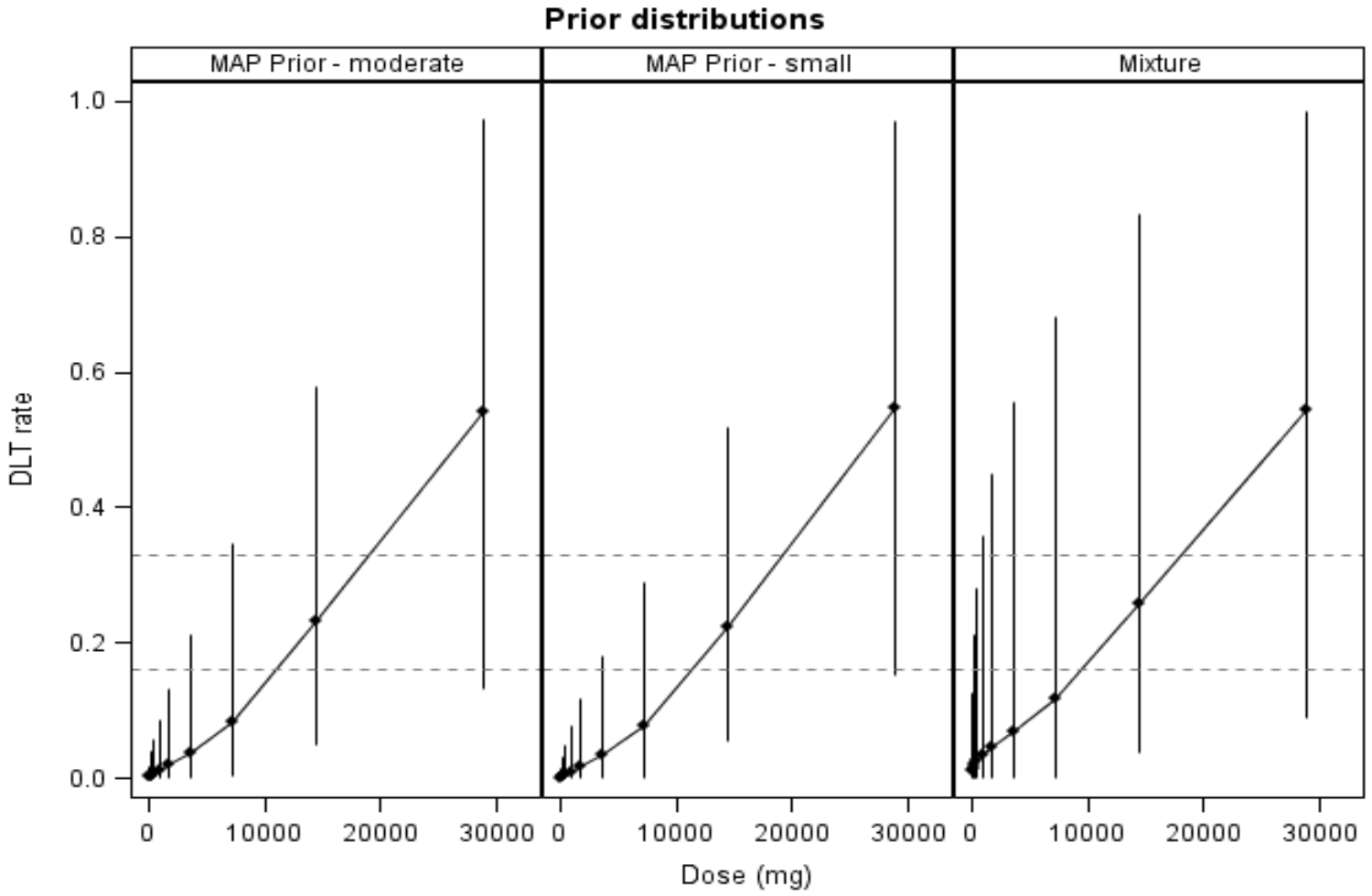
Dose(mg)	60	120	240	480	960	1800	3600	7200	14400	28800
Number of patients	1	1	1	3	3	3	3	3	6	3
Number of DLTs	0	0	0	0	0	0	0	0	1	2

MTD

- MAP prior with
  - Small between-trial heterogeneity
  - Moderate between-trial heterogeneity
  - Mixture prior:
    - Small between-trial heterogeneity (80%)
    - Weakly informative prior (20%)

Simulations

Prior distributions



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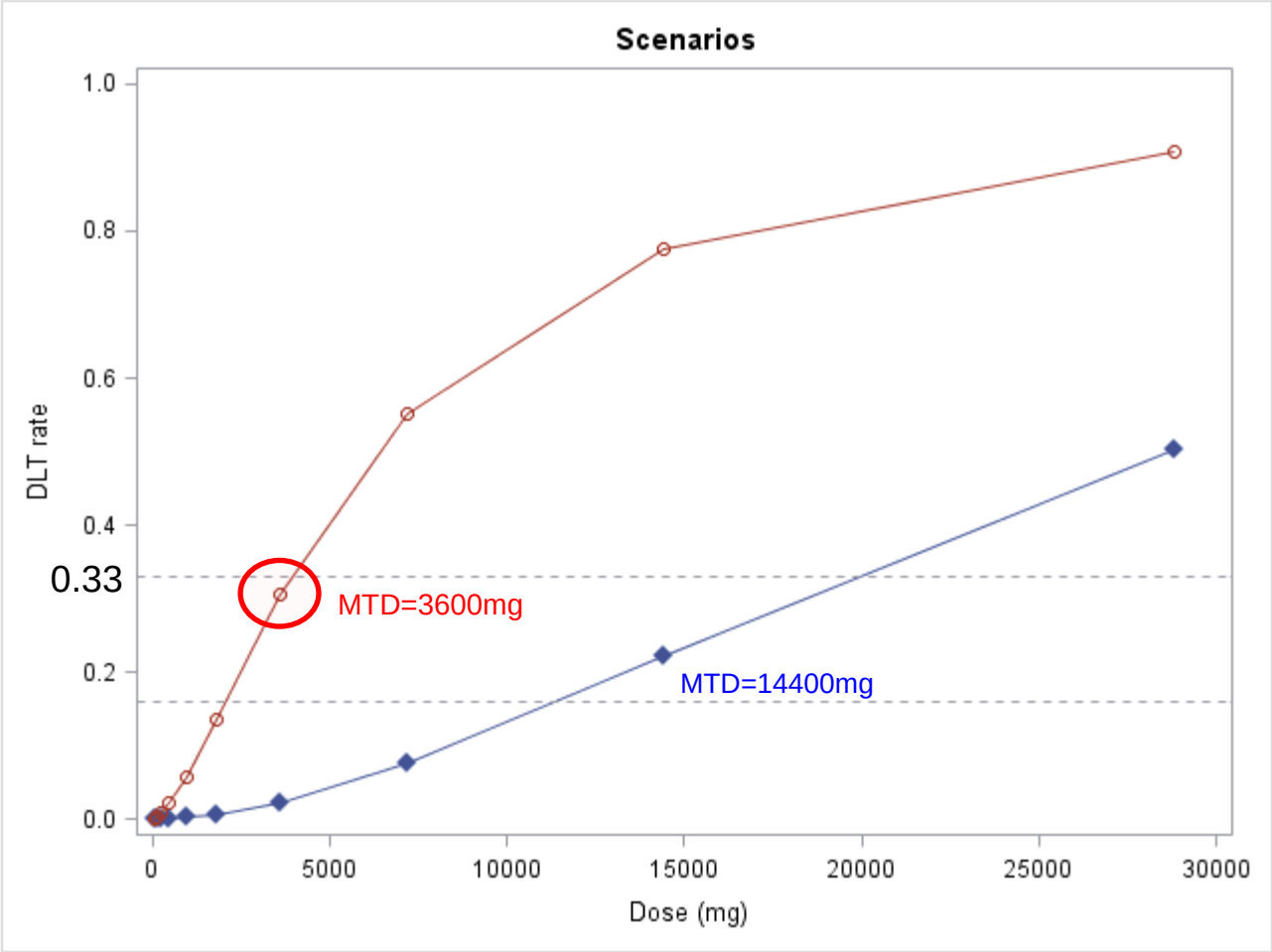
Simulations

Two true dose-toxicity scenarios

- Scenario 1: similar to the historical ones
- Scenario 2: highly dissimilar to the historical ones



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Simulations

Results

- Percentage of MTD declaration at end of trial:
  - Under: at the declared MTD, DLT rate < 0.16
  - Correct: at the declared MTD, DLT rate in 0.16-0.33 (correct declaration)
  - Over: at the declared MTD, DLT rate > 0.33

MTD estimation

Scenario	MTD estimation	Mixture: MAP and weakly informative	MAP - Moderate	MAP - Small
1	Under	31%	30%	26%
	Correct	69%	70%	74%
	Over	0%	0%	0%
2	Under	25%	4%	2%
	Correct	54%	57%	54%
	Over	21%	38%	44%

- Other metrics are available:
  - Probability to recommend a dose with true P(DLT)>33% as the MTD
  - Probability to recommend a dose with true P(DLT)<16% as the MTD
  - Average proportion of patients receiving a target dose on study
  - Average proportion of patients receiving a dose with P(DLT)>33% on study
  - Average number of patients per study
  - Average number of DLT per study

Conclusions

- MAP prior assume similarity (exchangeability) of historical and current parameters
- Using mixutre prior with a weakly informative component:
  - Safeguarding against unwarranted used of historical data
  - Allow for more robust inferences in case of prior-data conflict
  - Should be used whenever conflict between the prior information and the trial data is deemed possible
- Recommendations:
  - Perform scenarios : on-study dose recommendations are appropriate – Individual ethics
  - Perform simulations: long-run operating characteristics are satisfactory – Group ethics
  - Discuss these results with the clinical team

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