# Bayesian Model Averaging for POCRM – Update

Week of 13th December 2021

## Case Study

This case study aims to illustrate a specific instance where the partial ordering continual reassessment method (POCRM) performs unintuitively (2a in publication plan). We consider a setting with 6 dose levels and 3 partial orderings which can be expressed as:

$$m = 1 : 1 \rightarrow 2 \rightarrow 3 \rightarrow 4 \rightarrow 5 \rightarrow 6$$
$$m = 2 : 1 \rightarrow 3 \rightarrow 2 \rightarrow 4 \rightarrow 6 \rightarrow 5$$
$$m = 3 : 1 \rightarrow 4 \rightarrow 3 \rightarrow 2 \rightarrow 6 \rightarrow 5$$

where $m$ is the ordering, and the position of each dose level in the toxicity ordering is represented by the its placement, where the leftmost dose level is the least toxic and the rightmost dose level is the most toxic. Dose selection for a target toxiticity rate (TTR) of 0.40, using POCRM, is run assuming the following trial results:

$$n = (0, 2, 1, 0, 0, 0)$$
$$y = (0, 1, 1, 0, 0, 0)$$

where $n$ is the number of patients assigned each dose level and $y$ is the number of patients that suffered a dose limiting toxicity (DLT) at each dose level. The $i$-th element in each vector corresponds to the $i$-th dose level. For example, dose level 2 has been assigned to 2 patients and 1 patient has suffered a DLT under this level.

Given these results, the POCRM approach recommends dose level 1 as the next dose based on the following ordering probabilities and dose toxicity estimates:

**POCRM Run 1:**

$$p(m = 1) = 0.38$$
$$p(m = 2) = 0.28$$
$$p(m = 3) = 0.34$$

$$\textit{POCRM estimated probability of toxicity for each dose} = (0.38, 0.53, 0.67, \mathbf{0.77}, 0.85, 0.90)$$

where the estimated probability of the $m$-th toxicity ordering is $p(m)$, and the estimated probability of toxicity corresponding to the $i$-th dose is the $i$-th element in the given vector. No DLT is observed at the selected dose level of 1 which gives the trial results expressed below.

$$n = (1, 2, 1, 0, 0, 0)$$
$$y = (0, 1, 1, 0, 0, 0)$$

Moreover, running POCRM on the new data gives the next recommended dose level as level 4 based on the following model probabilities and dose toxicity estimates:

**POCRM Run 2:**

$$p(m = 1) = 0.36$$
$$p(m = 2) = 0.26$$
$$p(m = 3) = 0.37$$

$$\textit{POCRM estimated probability of toxicity for each dose} = (0.19, 0.64, 0.50, \mathbf{0.34}, 0.83, 0.75)$$

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From the probabilities given in runs 1 and 2, it is clear that the POCRM approach has some unintuitive behaviour. After testing at dose level 1, the selected ordering changes from ordering 1 to ordering 3, which is unexpected since dose level 1 has the lowest assumed toxicity in all 3 candidate orderings. Thus, it is unjustified for new data on dose level 1 to lead to a change in the selected ordering. The similarity in the probability corresponding to dose orderings 1 and 3 at run 1 is likely the cause of the sudden change in preference since a small change in the data has led to a change in the selected dose ordering for dose allocation.

A consequence of the change in preferred orderings, is an frantic change in the probability of toxicity estimated for dose level 4. The estimate corresponding to this dose level goes from being 0.77 at run 1, almost twice as high as the TTR, to 0.34 at run 2, which is below the TTR. This can be attributed to a change in the selected ordering from ordering 1 to ordering 3 where the placement of dose level 4 goes from being considered to be more toxic than dose levels 2 and 3 to less toxic. This sudden change in the probability of toxicity estimate is dangerous as it can be harmful to patients if the initial estimate of the probability of toxicity for dose level 4 were correct.

## Case Study – Revisited

We return to examine the previous case study, now applying the BMA approach instead of the POCRM. Assuming that we begin with the same trial results as for the POCRM, BMA recommends dose level 1 as the next dose based on the following ordering probabilities and probability of toxicity estimates:

**BMA Run 1:**

$$p(m = 1) = 0.38$$
$$p(m = 2) = 0.28$$
$$p(m = 3) = 0.34$$

*BMA estimated probability of toxicity for each dose* = (0.34, 0.64, 0.49, **0.75**, 0.89, 0.84)

Assuming that once again no DLT is observed under dose level 1, the BMA approach recommends dose level 3 based on the following ordering probabilities and probability of toxicity estimates:

**BMA Run 2:**

$$p(m = 1) = 0.36$$
$$p(m = 2) = 0.27$$
$$p(m = 3) = 0.37$$

*BMA estimated probability of toxicity for each dose* = (0.27, 0.54, 0.50, **0.56**, 0.81, 0.79)

Since the ordering probabilities are computed in the same way for both methods, we have the same values for both. However, the ordering probabilities affect the estimates given by the BMA approach far less. Dose level 4 saw the greatest change in probability of toxicity estimate under both approaches, due to the change in ordering with highest probability. The change in the estimated probability of toxicity for dose level 4 under BMA was (0.56 – 0.75)/0.75 = -25.33% while for the POCRM appraoch it was (0.34 – 0.77)/0.77 = -55.84% which is almost twice as high relative to the BMA. Moreover, the estimate for the POCRM approach went from being greater than the TTR to being lower than it, whereas the estimate for the BMA approach did not see this kind of change.