# Supplementary Data

## Appendix A: Details of the Trial Designs

### A1. 3+3 design

There are many different versions of the 3+3 design. We chose a commonly used version for our simulation study, described as follows:

1. Treat the first cohort of 3 patients at the first dose level.
2. Given that 3 patients have been treated at the current dose level,
    a. If there is zero DLT, escalate to the next higher dose level.
    b. If there is one DLT, stay at the current dose level.
    c. If there is more than one DLT, de-escalate to the next lower dose level. If there are 6 patients treated at the next lower dose level, claim it as the MTD; otherwise treat 3 more patients at the next lower dose level.
3. Given that 6 patients have been treated at the current dose level,
    a. If there is zero or one DLT, check the number of patients treated at the next higher dose level. If it is zero, escalate to the next higher dose level; otherwise, claim the current dose level as the MTD.
    b. If there is more than one DLT, de-escalate to the next lower dose level. If there are 6 patients treated at the next lower dose level, claim it as the MTD; otherwise treat 3 more patients at the next lower dose level.

### A2. One-parameter CRM model

In the CRM, we used the one-parameter power model, given by

$$p_j = a_j^{\exp(\alpha)}, \text{ for } j = 1, \ldots, J,$$

where $\alpha$ is the unknown parameter, $p_j$ is the DLT rate at dose $j$, and $0 < a_1 < \cdots < a_J < 1$ are prior guesses for the DLT probability at each dose, which are often called the "skeleton" of CRM. In our simulation, given the target DLT probability of 0.25, we set the skeleton $(a_1 \ldots a_6)$ = (0.062, 0.140, 0.25, 0.376, 0.502, 0.615), obtained by the getprior() function in the "dfcrm" R package, with the dose level 3 as the prior MTD and the half-width of the indifference interval equal to 0.06 (Lee and Cheung, 2009). For target DLT probability of 0.2 and 0.3, we used the skeletons $(a_1 \ldots a_6)$ = (0.032, 0.095, 0.2, 0.332, 0.470, 0.596) and (0.095, 0.186, 0.3, 0.422, 0.540, 0.643), respectively. We used normal prior $\alpha \sim N(0, 2)$.

The CRM starts the trial by treating the first cohort of patients at the lowest dose $d_1$. After each patient cohort is treated, the CRM updates the estimate of the dose-toxicity curve based on the accumulating DLT data across all dose levels, and assigns the next cohort of patients to the "optimal" dose, defined as the dose whose posterior mean estimate of the DLT probability is closest to the target $\phi$. In our simulation, we forbidden dose skipping and restricted the dose escalation/de-escalation one level at a time. Thus, if the estimated optimal dose is higher than the current dose, we escalate the dose for one level; of the estimated optimal dose is lower than the current dose, we de-escalate the dose for one level.

In the CRM, we imposed the following safety stopping rule: stop the trial if the posterior probability that the DLT probability of the lowest dose is greater than the target $\phi$ exceeds 0.95. That is, the trial will be terminated if

$$\Pr(p_1 > \phi | data) > 0.95.$$

The CRM-DS is the same as the CRM except that it allows dose skipping and always assigns the next cohort of patients to the dose whose estimated toxicity probability is closest to the target, as proposed by the original CRM.

**A3. Dose escalation with overdose control (EWOC)**
The EWOC utilizes a two-parameter logistic model:

$$logit(p_j) = \beta_0 + \beta_1 d_j, \quad \beta_1 > 0, j = 1, \dots, J,$$

where $\beta_0, \beta_1$ are the unknown intercept and slope parameters, $p_j$ is the DLT rate at dose level $j$ and $d_j$ is the raw dosage at dose level $j$. In our simulation, the dosages of six doses are (12.5, 25, 50, 100, 150, 200) mg. To facilitate the interpretation, the EWOC reparameterizes the two-parameter logistic model using the MTD $\gamma$ and the DLT probability at the first dose (i.e., $p_1$), as follows:

$$\gamma = \frac{1}{\beta_1}(\log(\phi) - \log(1-\phi) - \beta_0),$$
$$p_1 = \frac{\exp(\beta_0 + \beta_1 d_1)}{1 + \exp(\beta_0 + \beta_1 d_1)},$$

where $\phi$ is the target DLT probability at the MTD $\gamma$. Following Babb *et al.* 1998, we used the non-informative priors for $\gamma$ and $p_1$ as $\gamma \sim Unif(d_1, 2d_J - d_{J-1})$, $p_1 \sim Unif(0, \phi)$.

The EWOC starts by treating the first cohort of patients at the lowest dose $d_1$. After each patient cohort is treated, the EWOC updates the estimate of the dose-toxicity curve based on the accumulating DLT data across all dose levels, and assigns the next cohort of patients to the "optimal" dose, defined as the highest dose whose posterior probability of greater than the MTD $\gamma$ is equal to or less than $\alpha$, i.e.,

$$\Pr(d_j > \gamma | data) \leq \alpha.$$

In our simulation, we used $\alpha$ =0.25, as recommendation by Babb *et al.* 1998. In the EWOC, dose skipping is not allowed. Thus, if the estimated optimal dose is higher than the current dose, we escalate the dose for one level; of the estimated optimal dose is lower than the current dose, we de-escalate the dose for one level. In our simulation, we used the same safety stopping rule as the CRM for the EWOC, i.e., the trial will be terminated if

$$\Pr(p_1 > \phi | data) > 0.95.$$

**A4. Two-parameter Bayesian logistic regression model (BLRM)**
The BLRM utilizes a two-parameter logistic model:

$$logit(p_j) = \log\alpha + \beta \log\left(\frac{d_j}{d^*}\right), \quad \alpha, \beta > 0, j = 1, \dots, J,$$

where $\alpha, \beta$ are the unknown parameters, $p_j$ is the DLT rate at dose level $j$, $d_j$ is the raw dosage at dose level $j$, and $d^*$ is the reference dose. In our simulation, the dosages of six doses are (12.5,

25, 50, 100, 150, 200) mg, and the reference dose $d^*$ = 200mg. Following Neuenschwander *et al.* 2008, we used the vague bivariate normal distribution for the prior of $(\log\alpha, \log\beta)$, such that

$$(\log\alpha, \log\beta) \sim N\left(\begin{pmatrix}-0.847\\0.381\end{pmatrix}, \begin{pmatrix}2.015^2 & 0\\0 & 1.027^2\end{pmatrix}\right).$$

The BLRM requires defining the proper dosing interval $(\delta_1, \delta_2)$, defined as the range of DLT probabilities regarded as acceptable. In our simulation, we set $(\delta_1, \delta_2) = (\phi - 0.05, \phi + 0.05)$, same as the mTPI and keyboard designs. For example, for target DLT probability $\phi$=0.25, the proper dosing interval $(\delta_1, \delta_2)$ = (0.2, 0.3); and for target DLT probability $\phi$=0.2, the proper dosing interval $(\delta_1, \delta_2)$ = (0.15, 0.25). The BLRM imposes an overdose control rule as follows: if the observed data suggest that there is ≥ 25% posterior probability that the DLT rate of a dose is greater than $\delta_2$, i.e., $\Pr(p_j > \delta_2 | data) \geq 0.25$, that dose is an overdose and cannot be used to treat patients.

The BLRM starts the trial by treating the first cohort of patients at the lowest dose $d_1$. After each patient cohort is treated, the BLRM updates the estimate of the dose-toxicity curve based on the accumulating DLT data across all dose levels, and assigns the next cohort of patients to the "optimal" dose. Under the above overdose control rule, the "optimal" dose is defined as the dose *j* that satisfies the overdose control condition $\Pr(p_j > \delta_2 | data) \geq 0.25$ and meanwhile maximize the posterior probability of the proper dosing interval $(\delta_1, \delta_2)$, i.e., $\Pr(p_j \in (\delta_1, \delta_2) | data)$. In BLRM, dose skipping is not allowed. Thus, if the estimated optimal dose is higher than the current dose, we escalate the dose for one level; of the estimated optimal dose is lower than the current dose, we de-escalate the dose for one level. The above overdose control rule leads to the following safety stopping rule: stop the trial if the lowest dose is an overdose. That is, the trial will be terminated if $\Pr(p_1 > \delta_2 | data) \geq 0.25$.

The BLRM-NOC is the same as the BLRM, but without applying the overdose control rule. Thus, for the BLRM-NOC, the "optimal" dose is defined as the dose that maximizes the posterior probability of the proper dosing interval $(\delta_1, \delta_2)$, i.e., $\Pr(p_j \in (\delta_1, \delta_2) | data)$. For the BLRM-NOC, the safety stopping rule described above cannot be used because it does not use the overdose control rule. Thus, in BLRM-NOC, we used the same safety stopping rule as the CRM, i.e., the trial will be terminated if

$$\Pr(p_1 > \phi | data) > 0.95.$$

**A5. Summary of the design parameters used in the simulation.**

**Table S1.** Summary of design parameters.

| | CRM | CRM-DS | EWOC | BLRM | BLRM-NOC | mTPI | Keyboard | BOIN |
|---|---|---|---|---|---|---|---|---|
| Model | $p_j = a_j^{\exp(\alpha)}$ | | $logit(p_j) = \beta_0 + \beta_1 d_j$ | $logit(p_j) = \log\alpha + \beta\log(d_j/d^*)$ | | $y_j \mid n_j \sim Binomial(p_j)$ | | |
| Prior | $\alpha \sim N(0, 2)$, $(a_1 \dots a_6)$[§] | | $\gamma \sim Unif(d_1, 2d_J - d_{J-1})$ $p_1 \sim Unif(0, \phi)$[‡] | $(\log\alpha, \log\beta) \sim N\left(\begin{pmatrix}-0.847\\0.381\end{pmatrix}, \begin{pmatrix}2.015^2 & 0\\0 & 1.027^2\end{pmatrix}\right)$ | | $p_j \sim Beta(1,1)$* | | |
| Proper dosing interval | N/A | | N/A | $(\delta_1, \delta_2) = (\phi - 0.05, \phi + 0.05)$ | | $(\phi - 0.05, \phi + 0.05)$ | | N/A |
| Dose skipping | No | Yes | No | No | No | No | No | No |
| Starting dose | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Overdose control rule | N/A | N/A | $\Pr(d_j > \gamma \mid data) \le 0.25$ | $\Pr(p_j > \delta_2 \mid data) \le 0.25$ | N/A | $\Pr(p_j > \phi \mid data) \le 0.95$ | | |
| Stopping rule | $\Pr(p_1 > \phi \mid data) > 0.95$ | | | $\Pr(p_1 > \delta_2 \mid data) > 0.25$ | $\Pr(p_1 > \phi \mid data) > 0.95$ | $\Pr(p_1 > \phi \mid data) > 0.95$ | | |

Notation: $\phi$ denotes the target DLT probability; $p_j$ denotes the true DLT probability of dose level $j$; $d_j$ is the dosage of dose level $j$; $y_j$ denotes the number patients experienced DLTs at dose level $j$; $n_j$ denotes the number of patients treated at dose level $j$; for $j = 1, \dots, J$, and $d^*$ is the reference dose.

[§] In our simulation, we used skeletons $(a_1 \dots a_6)$ = (0.032, 0.095, 0.2, 0.332, 0.470, 0.596), (0.062, 0.140, 0.25, 0.376, 0.502, 0.615), (0.095, 0.186, 0.3, 0.422, 0.540, 0.643) for target DLT probabilities 0.2, 0.25, 0.3, respectively, obtained using the method of Lee and Cheung (2009) from R package "dfcrm".

[‡] $\gamma = \frac{1}{\beta_1}(\log(\phi) - \log(1-\phi) - \beta_0)$ and $p_1 = \frac{\exp(\beta_0 + \beta_1 d_1)}{1 + \exp(\beta_0 + \beta_1 d_1)}$.

* BOIN uses this prior only for overdose control, and its dose escalation/de-escalation rule does not require specifying a prior for $p_j$. mTPI and keyboard require this prior to determine dose escalation and de-escalation, and also for overdose control.

## Appendix B: Algorithm to Generate 1000 Random Dose-Toxicity Scenarios

We generated true dose-toxicity scenarios using the pseudo-uniform scenario algorithm (Clertant and O'Quigley, 2017). Given a target toxicity rate $\phi$ and $J$ dose levels, we generated scenarios as follows:

a. Select one of the $J$ dose levels as the MTD with equal probabilities.
b. Sample $M \sim Beta(\max\{J-j, 0.5\}, 1)$, where $j$ denotes the selected dose level, and set an upper bound $B = \phi + (1-\phi) \times M$ for the toxicity probabilities.
c. Repeatedly sample $J$ toxicity probabilities uniformly on [0, $B$] until these correspond to a scenario in which dose level $j$ is the MTD.

One advantage of this algorithm is that it generates scenarios that all doses are overly toxic, as it may happen in practice. In our simulation, if the DLT probability of the lowest dose > target DLT probability + 0.1, all doses are deemed as overly toxic. For example, when the target DLT probability $\phi$ = 0.25, if the DLT probability of the lowest dose > 0.35, all doses are deemed overly toxic. In these scenarios, the trial should be terminated early and no dose should be selected as the MTD.

Figure S1 shows the shows 25 randomly selected scenarios and distribution of the DLT probabilities by dose level from the 1000 scenarios. We can see that the simulated dose-toxicity curves cover various shapes and a wide range of toxicity probabilities. The algorithm above guarantees that the generated dose-toxicity curves are monotonically increasing, i.e., higher doses have higher toxicity.

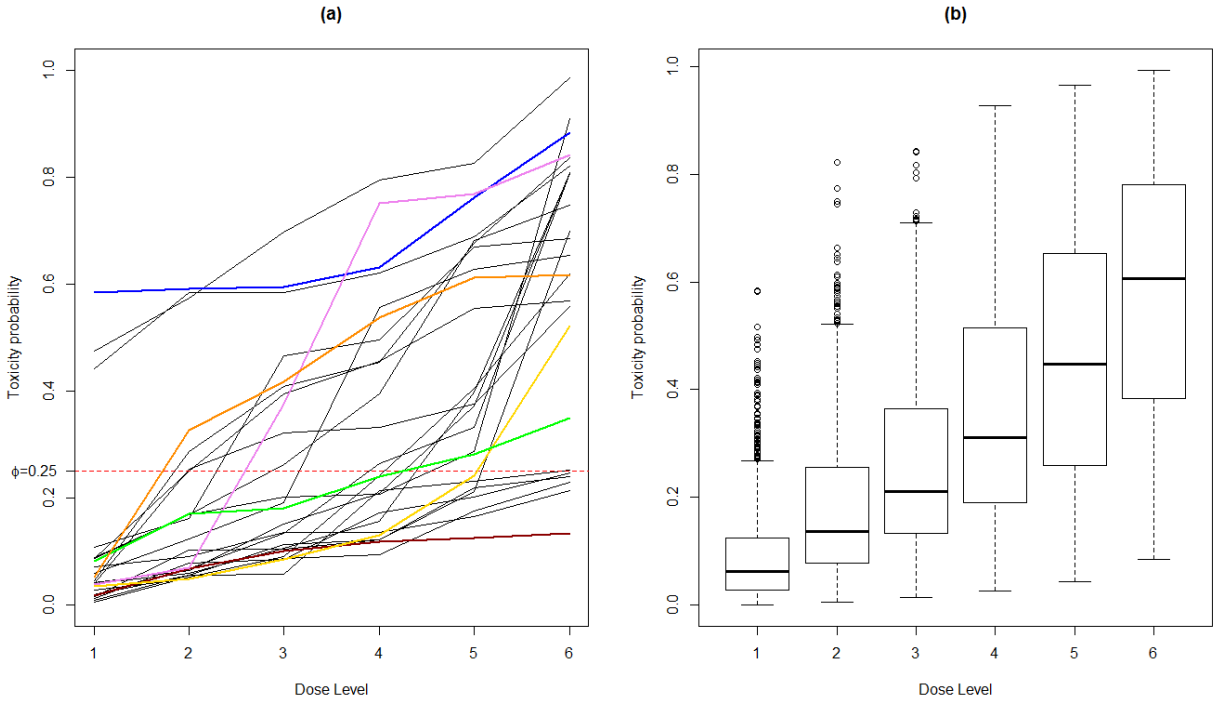


**Figure S1**. Relation between dose level and toxicity. (a) 25 randomly selected dose-toxicity curves with 6 picked curves showing different shapes; (b) distribution of the DLT probabilities by dose level from the 1000 scenarios.

## Appendix C: Simulation Results of Eight Representative Scenarios with the Target DLT Probability of 0.25.

**Table S2.** Simulation results for eight representative scenarios selected from 1000 randomly generated scenarios with the target DLT probability of 0.25. The doses in bold are the MTD. In scenario 7, all doses are overly toxic, no dose should be selected as the MTD.

| Scenario | Dose level | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 |
| 1 | **0.26** | 0.34 | 0.47 | 0.64 | 0.66 | 0.77 |
| 2 | 0.18 | **0.25** | 0.32 | 0.36 | 0.60 | 0.69 |
| 3 | 0.09 | 0.16 | **0.23** | 0.34 | 0.51 | 0.74 |
| 4 | 0.07 | 0.12 | 0.17 | **0.27** | 0.34 | 0.55 |
| 5 | 0.03 | 0.13 | 0.17 | 0.19 | **0.26** | 0.31 |
| 6 | 0.04 | 0.05 | 0.09 | 0.14 | 0.15 | **0.24** |
| 7 | 0.34 | 0.42 | 0.46 | 0.49 | 0.58 | 0.62 |
| 8 | **0.13** | 0.41 | 0.45 | 0.58 | 0.75 | 0.76 |

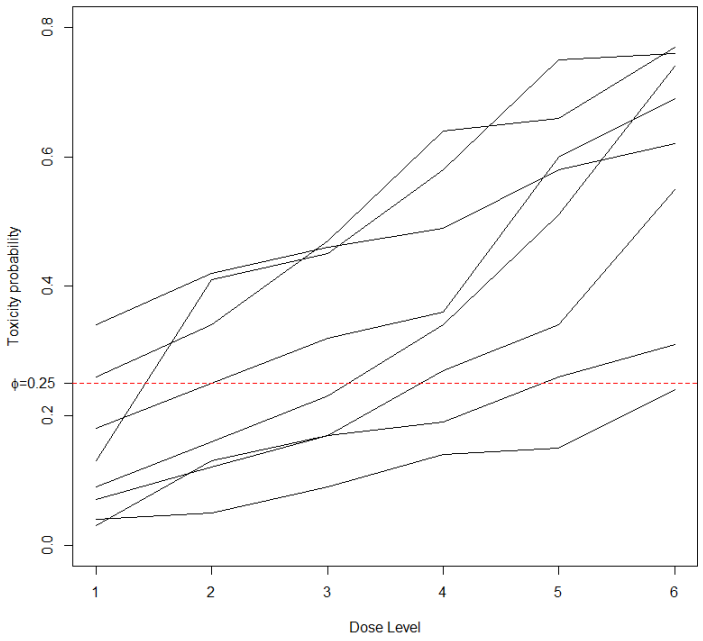


**Figure S2**. The curves of eight representative scenarios selected from 1000 randomly generated scenarios.

**Table S3.** Operating characteristics of the designs under eight representative scenarios shown in Table S2.

| **A1. Percentage of correct selection of MTD (%)** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Scenario | | | | | | | |
| Design | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| 3+3 | 31.50 | 24.65 | 27.30 | 21.75 | 13.65 | 31.40 | 64.75 | 64.10 |
| Benchmark* | 69.00 | 38.15 | 49.60 | 42.20 | 27.95 | 82.60 | N/A | 56.65 |
| CRM | 55.10 | 41.00 | 48.45 | 42.25 | 23.80 | 39.90 | 45.65 | 51.95 |
| CRM-DS | 56.05 | 40.75 | 48.50 | 45.00 | 31.50 | 50.20 | 43.55 | 51.70 |
| BLRM | 6.65 | 21.40 | 37.05 | 18.65 | 12.20 | 24.60 | 96.15 | 15.15 |
| BLRM-NOC | 51.70 | 36.70 | 47.05 | 47.65 | 31.10 | 64.85 | 39.85 | 45.90 |
| EWOC | 41.70 | 54.45 | 60.25 | 19.95 | 6.80 | 0.75 | 0 | 61.95 |
| mTPI | 55.40 | 37.90 | 39.85 | 38.10 | 21.90 | 48.40 | 45.20 | 69.70 |
| BOIN | 61.50 | 39.35 | 42.55 | 38.75 | 23.65 | 45.70 | 46.20 | 68.80 |
| Keyboard | 61.40 | 39.40 | 42.55 | 38.75 | 23.65 | 45.70 | 46.20 | 68.75 |
| **A2. Percentage of patients treated at MTD (%)** | | | | | | | | |
| | Scenario | | | | | | | |
| Design | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| 3+3 | 35.68 | 24.49 | 23.40 | 17.47 | 10.23 | 19.77 | 0 | 59.65 |
| CRM | 59.11 | 33.88 | 32.84 | 25.65 | 13.93 | 18.48 | 0 | 54.26 |
| CRM-DS | 59.65 | 26.92 | 32.40 | 34.20 | 18.85 | 35.42 | 0 | 50.65 |
| BLRM | 13.43 | 20.66 | 27.64 | 15.25 | 9.12 | 12.85 | 0 | 17.20 |
| BLRM-NOC | 48.67 | 31.57 | 34.98 | 31.22 | 20.44 | 31.18 | 0 | 42.30 |
| EWOC | 29.01 | 39.84 | 55.42 | 17.84 | 2.55 | 0.09 | 0 | 39.65 |
| mTPI | 59.53 | 33.87 | 29.84 | 23.47 | 12.22 | 20.68 | 0 | 56.25 |
| BOIN | 61.85 | 31.62 | 28.27 | 21.41 | 12.07 | 19.23 | 0 | 60.51 |
| Keyboard | 61.81 | 31.65 | 28.28 | 21.41 | 12.07 | 19.23 | 0 | 60.46 |
| **B1. Percentage of selecting doses with DLT probability ≥ 33% as MTD (%)** | | | | | | | | |
| | Scenario | | | | | | | |
| Design | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| 3+3 | 19.85 | 5.65 | 16.65 | 10.70 | 0 | 0 | 35.25 | 18.75 |
| CRM | 26.30 | 5.70 | 24.55 | 13.55 | 0 | 0 | 54.35 | 47.50 |
| CRM-DS | 25.20 | 6.80 | 25.80 | 14.60 | 0 | 0 | 56.45 | 47.75 |
| BLRM | 6.60 | 0.85 | 5.70 | 4.55 | 0 | 0 | 3.85 | 8.70 |
| BLRM-NOC | 35.90 | 13.75 | 38.95 | 23.60 | 0 | 0 | 60.15 | 52.90 |
| EWOC | 58.30 | 1.55 | 6.90 | 1.05 | 0 | 0 | 100 | 38.05 |
| mTPI | 27.70 | 7.45 | 27.25 | 18.45 | 0 | 0 | 54.80 | 29.70 |
| BOIN | 21.55 | 7.35 | 25.30 | 16.15 | 0 | 0 | 53.80 | 30.50 |
| Keyboard | 21.65 | 7.35 | 25.30 | 16.15 | 0 | 0 | 53.80 | 30.55 |
| **B2. Percentage of patients treated at doses with DLT probability ≥ 33% (%)** | | | | | | | | |
| | Scenario | | | | | | | |
| Design | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| 3+3 | 23.02 | 5.77 | 15.82 | 9.88 | 0 | 0 | 44.51 | 26.01 |
| CRM | 29.78 | 5.61 | 19.94 | 10.66 | 0 | 0 | 74.52 | 45.34 |
| CRM-DS | 29.51 | 13.50 | 29.60 | 15.91 | 0 | 0 | 75.14 | 48.95 |
| BLRM | 14.69 | 2.57 | 10.07 | 5.80 | 0 | 0 | 18.34 | 20.53 |
| BLRM-NOC | 44.47 | 14.27 | 32.27 | 19.50 | 0 | 0 | 79.00 | 56.82 |
| EWOC | 70.98 | 3.03 | 8.67 | 0.68 | 0 | 0 | 100 | 60.35 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| mTPI | 29.94 | 5.92 | 18.81 | 11.08 | 0 | 0 | 74.08 | 43.30 |
| BOIN | 27.87 | 6.15 | 17.94 | 11.06 | 0 | 0 | 73.98 | 38.95 |
| Keyboard | 27.91 | 6.15 | 17.94 | 11.06 | 0 | 0 | 73.98 | 39.00 |

**C1. Percentage of trials overdosing more than 50% patients above the MTD (%)**

| | Scenario | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Design | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| 3+3 | 21.35 | 17.10 | 16.75 | 9.95 | 7.40 | 0 | 40.50 | 19.00 |
| CRM | 25.10 | 20.45 | 17.40 | 8.30 | 3.95 | 0 | 69.05 | 34.90 |
| CRM-DS | 24.50 | 29.65 | 25.10 | 11.15 | 17.60 | 0 | 70.15 | 39.40 |
| BLRM | 10.55 | 10.20 | 6.50 | 2.75 | 0.95 | 0 | 8.55 | 14.05 |
| BLRM-NOC | 41.80 | 42.45 | 31.95 | 16.65 | 7.60 | 0 | 76.75 | 56.00 |
| EWOC | 72.25 | 41.50 | 3.60 | 0.05 | 0 | 0 | 100 | 56.15 |
| mTPI | 29.55 | 21.40 | 17.95 | 6.20 | 4.60 | 0 | 68.60 | 35.95 |
| BOIN | 21.45 | 15.55 | 10.00 | 2.80 | 1.35 | 0 | 68.65 | 24.35 |
| Keyboard | 21.45 | 15.55 | 10.00 | 2.80 | 1.35 | 0 | 68.65 | 24.35 |

**C2. Percentage of trials treating fewer than 6 patients at the MTD (%)**

| | Scenario | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Design | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| 3+3 | 32.35 | 50.10 | 49.50 | 55.80 | 70.45 | 50.40 | 0 | 18.15 |
| CRM | 12.95 | 32.35 | 28.70 | 40.60 | 64.25 | 58.85 | 0 | 7.45 |
| CRM-DS | 11.95 | 42.15 | 29.00 | 29.40 | 56.10 | 42.00 | 0 | 10.70 |
| BLRM | 80.55 | 58.55 | 45.80 | 62.20 | 75.20 | 66.45 | 0 | 72.95 |
| BLRM-NOC | 21.45 | 37.70 | 31.45 | 32.35 | 46.95 | 31.35 | 0 | 18.55 |
| EWOC | 52.80 | 30.05 | 13.80 | 57.05 | 92.60 | 99.95 | 0 | 38.05 |
| mTPI | 20.45 | 44.80 | 43.50 | 50.95 | 70.85 | 52.10 | 0 | 15.15 |
| BOIN | 7.35 | 25.75 | 27.50 | 37.35 | 58.35 | 47.50 | 0 | 2.60 |
| Keyboard | 7.45 | 25.75 | 27.50 | 37.35 | 58.35 | 47.50 | 0 | 2.90 |

**C3. Risk of irrational dose assignment (%)[§]**

| | | Scenario | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Design | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| 3+3 | 2/3 | Never happen | | | | | | | |
| | 3/6 | Never happen | | | | | | | |
| | 4/6 | Never happen | | | | | | | |
| CRM | 2/3 | 2.13 | 8.75 | 19.09 | 26.73 | 20.50 | 25.70 | 1.22 | 3.20 |
| | 3/6 | 24.68 | 31.22 | 26.25 | 27.02 | 29.50 | 32.42 | 15.48 | 38.27 |
| | 4/6 | 2.91 | 7.00 | 8.45 | 3.67 | 7.84 | 9.09 | 1.69 | 8.90 |
| CRM-DS | 2/3 | 2.24 | 4.79 | 2.60 | 0.59 | 3.26 | 1.33 | 4.09 | 3.70 |
| | 3/6 | 20.93 | 33.00 | 25.50 | 23.24 | 24.74 | 15.42 | 17.18 | 36.12 |
| | 4/6 | 5.94 | 3.51 | 6.15 | 4.07 | 10.39 | 5.88 | 0 | 10.53 |
| BLRM | 2/3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 3/6 | 0 | 0 | 0 | 1.08 | 0.63 | 0.92 | 0 | 0 |
| | 4/6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| BLRM-NOC | 2/3 | 30.92 | 35.75 | 38.12 | 37.07 | 42.06 | 39.87 | 31.26 | 47.65 |
| | 3/6 | 44.88 | 53.00 | 54.24 | 50.67 | 56.29 | 58.76 | 41.78 | 50.71 |
| | 4/6 | 5.85 | 6.99 | 7.34 | 5.96 | 5.71 | 12.50 | 6.12 | 13.39 |
| EWOC | 2/3 | 55.59 | 49.60 | 25.63 | 20.51 | 20.93 | 9.22 | 66.67 | 56.01 |
| | 3/6 | 57.50 | 52.03 | 29.91 | 20.99 | 26.32 | 0.10 | 63.17 | 63.31 |
| | 4/6 | 14.35 | 8.14 | 6.90 | 0 | 0 | 0 | 28.34 | 13.62 |
| | 2/3 | Never happen | | | | | | | |

| | | |
|---|---|---|
| mTPI | 3/6 | Never happen |
| | 4/6 | Never happen |
| BOIN | 2/3 | Never happen |
| | 3/6 | Never happen |
| | 4/6 | Never happen |
| Keyboard | 2/3 | Never happen |
| | 3/6 | Never happen |
| | 4/6 | Never happen |

*: The theoretical benchmark is obtained using the method of O'quigley, J., Paoletti, X., & Maccario, J. (2002). and Cheung, Y. K. (2014).

**Reference:**

O'quigley, J., Paoletti, X., & Maccario, J. (2002). Non-parametric optimal design in dose finding studies. *Biostatistics*, *3*(1), 51-56 (2)

Cheung, Y. K. (2014). Simple benchmark for complex dose finding studies. *Biometrics*, *70*(2), 389-397.

## Appendix D: Simulation results with target DLT probability of 0.25 and cohort size 1 for 1000 randomly generated scenarios

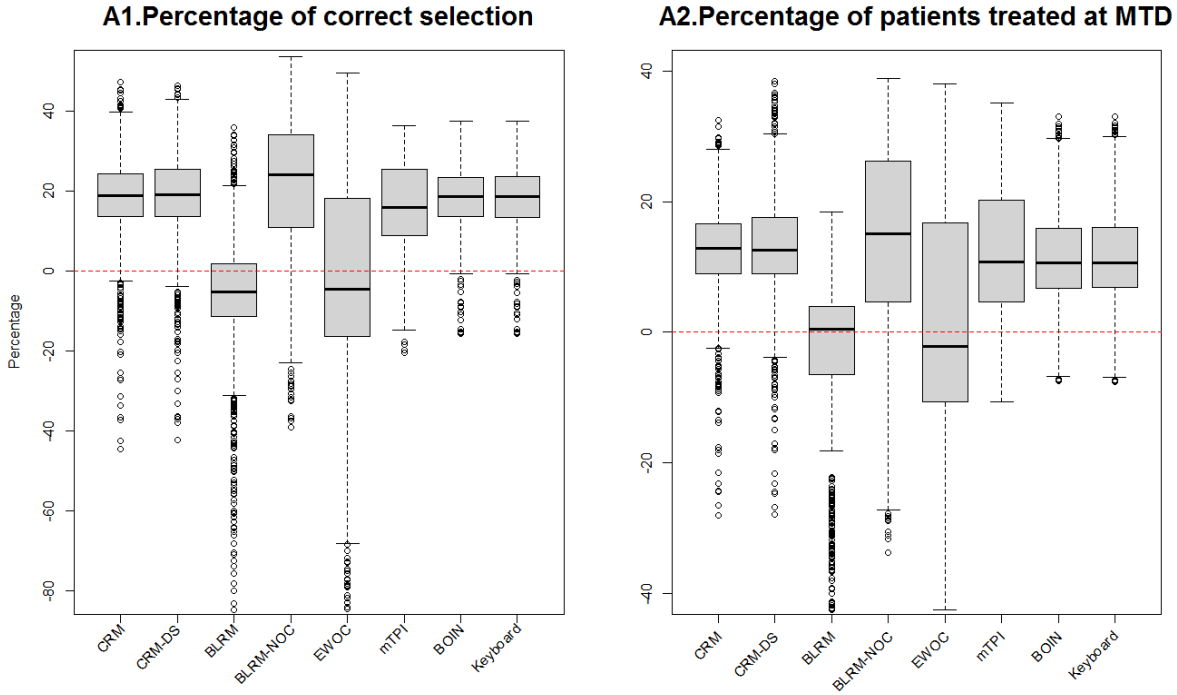


**Figure S3**. Comparison of accuracy metrics for the 8 designs with respect to the 3+3 design. A1. Percentage of correct selection of the MTD; A2. Percentage of patients treated at the MTD; A larger value indicates better performance; positive value means that the design outperforms the 3+3 design.

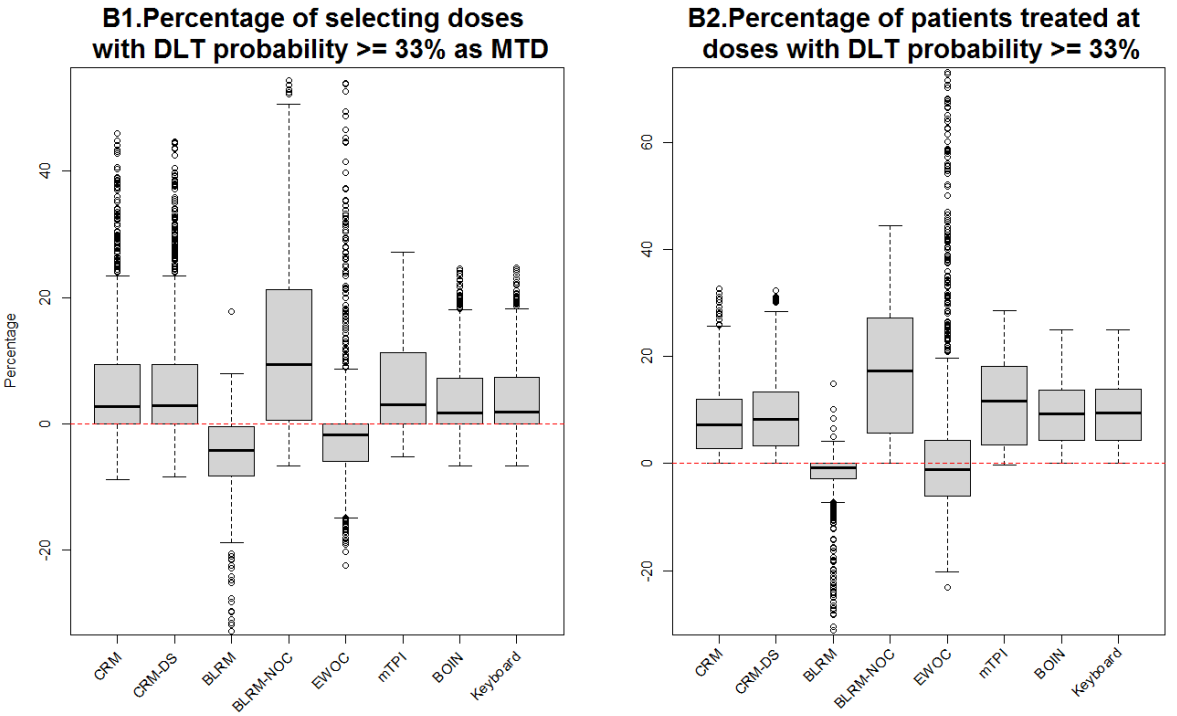


**Figure S4**. Comparison of safety metrics for the 8 designs with respect to the 3+3 design. B1. Percentage of selecting doses with DLT probability $\geq$ 33% as the MTD; B2. Percentage of patients treated at doses with DLT probability $\geq$ 33%; A smaller value indicates better performance; negative value means that the design outperforms the 3+3 design.

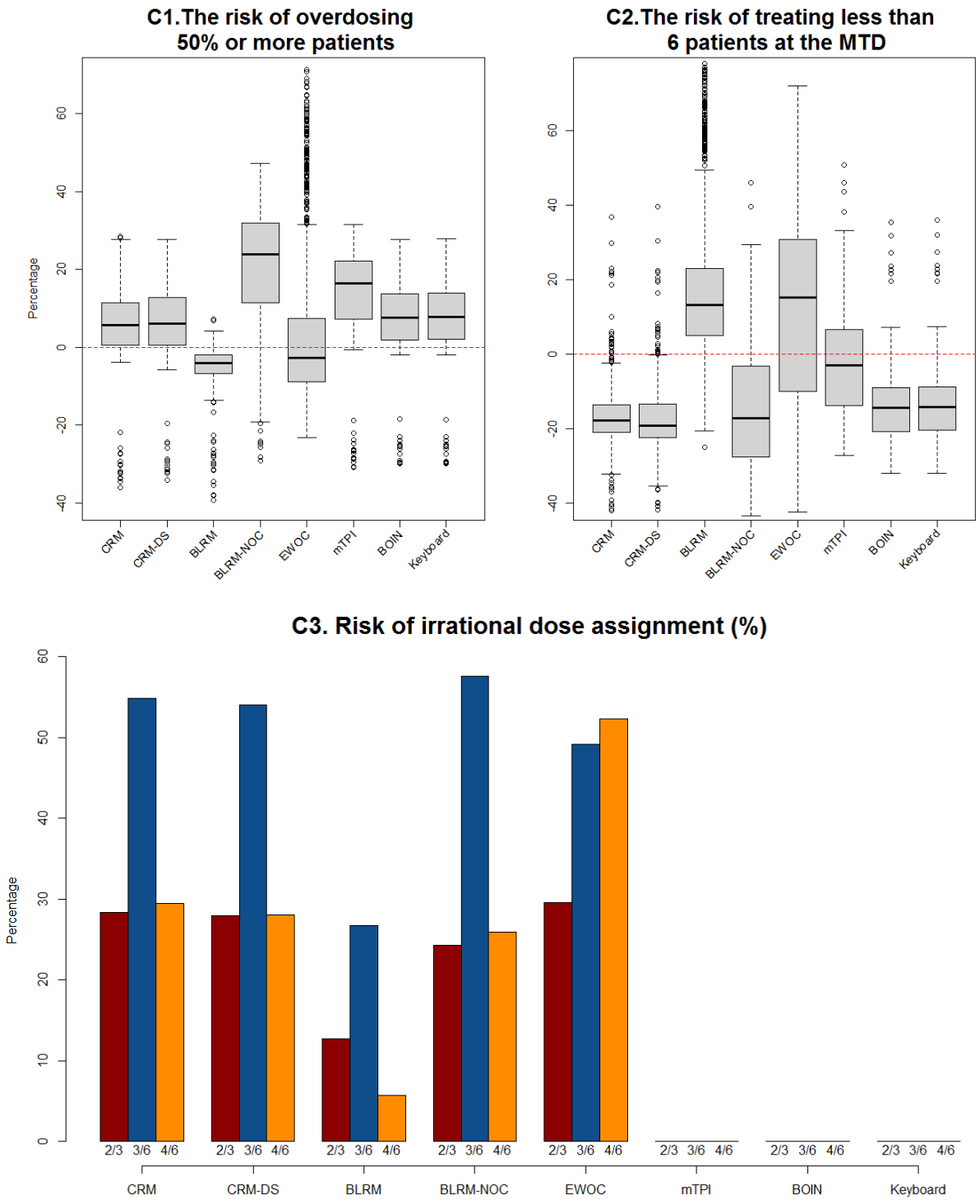


**Figure S5**. Comparison of reliability metrics for the 8 designs with respect to the 3+3 design. C1. Risk of overdosing 50% or more patients; C2. Risk of treating < 6 patients at the MTD; C3. Risk of irrational dose assignment. A smaller value indicates better performance; negative value means that the design outperforms the 3+3 design.

## Appendix E: Simulation results with target DLT probability of 0.20 for 1000 randomly generated scenarios

### (1) cohort size = 1 (Figures S6-8)

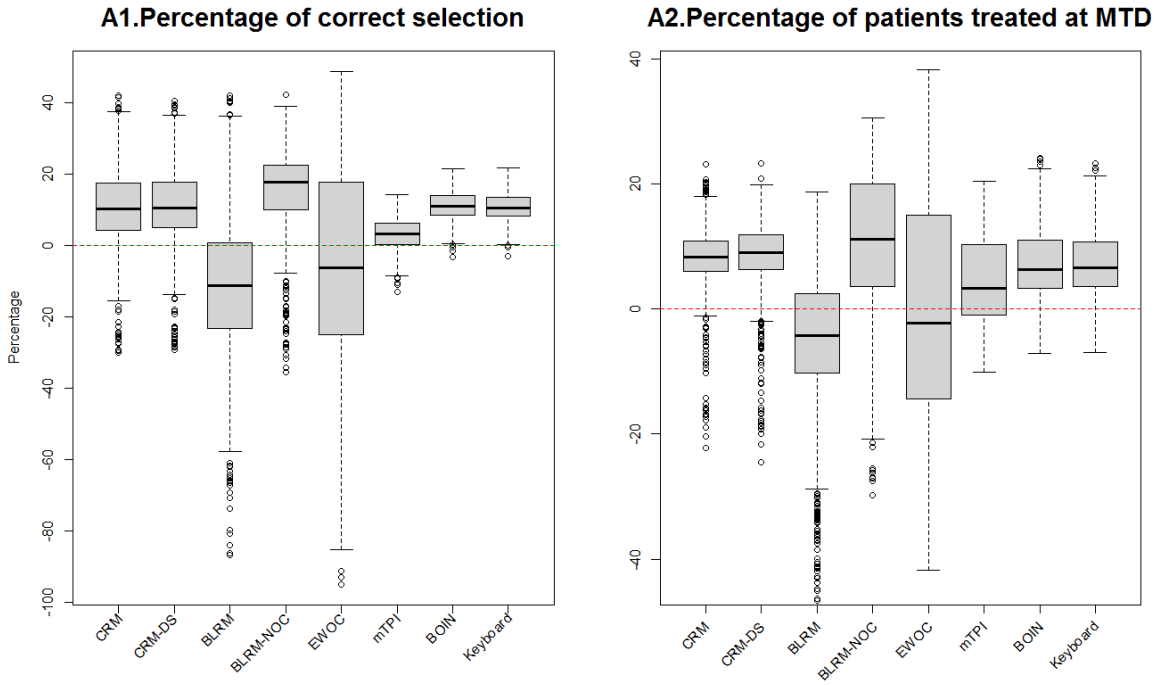


**Figure S6**. Comparison of accuracy metrics for the 8 designs with respect to the 3+3 design. A1. Percentage of correct selection of the MTD; A2. Percentage of patients treated at the MTD; A larger value indicates better performance; positive value means that the design outperforms the 3+3 design.

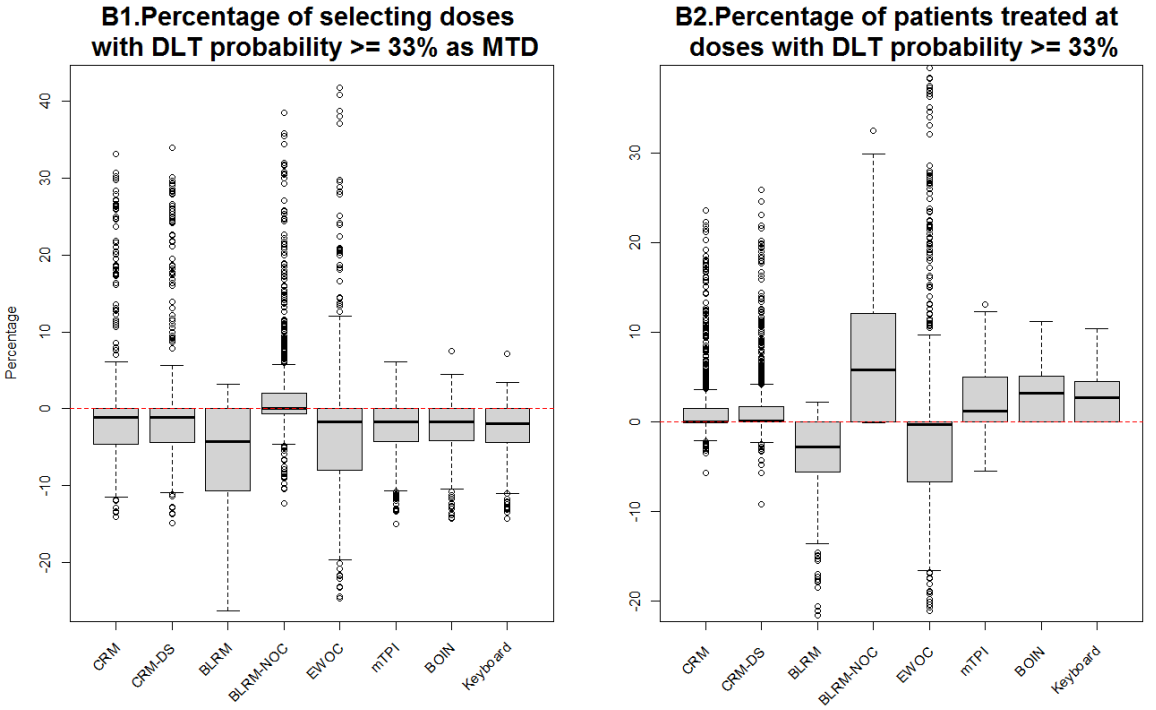


**Figure S7**. Comparison of safety metrics for the 8 designs with respect to the 3+3 design. B1. Percentage of selecting doses with DLT probability $\geq$ 33% as the MTD; B2. Percentage of patients treated at doses with DLT probability $\geq$ 33%; A smaller value indicates better performance; negative value means that the design outperforms the 3+3 design.

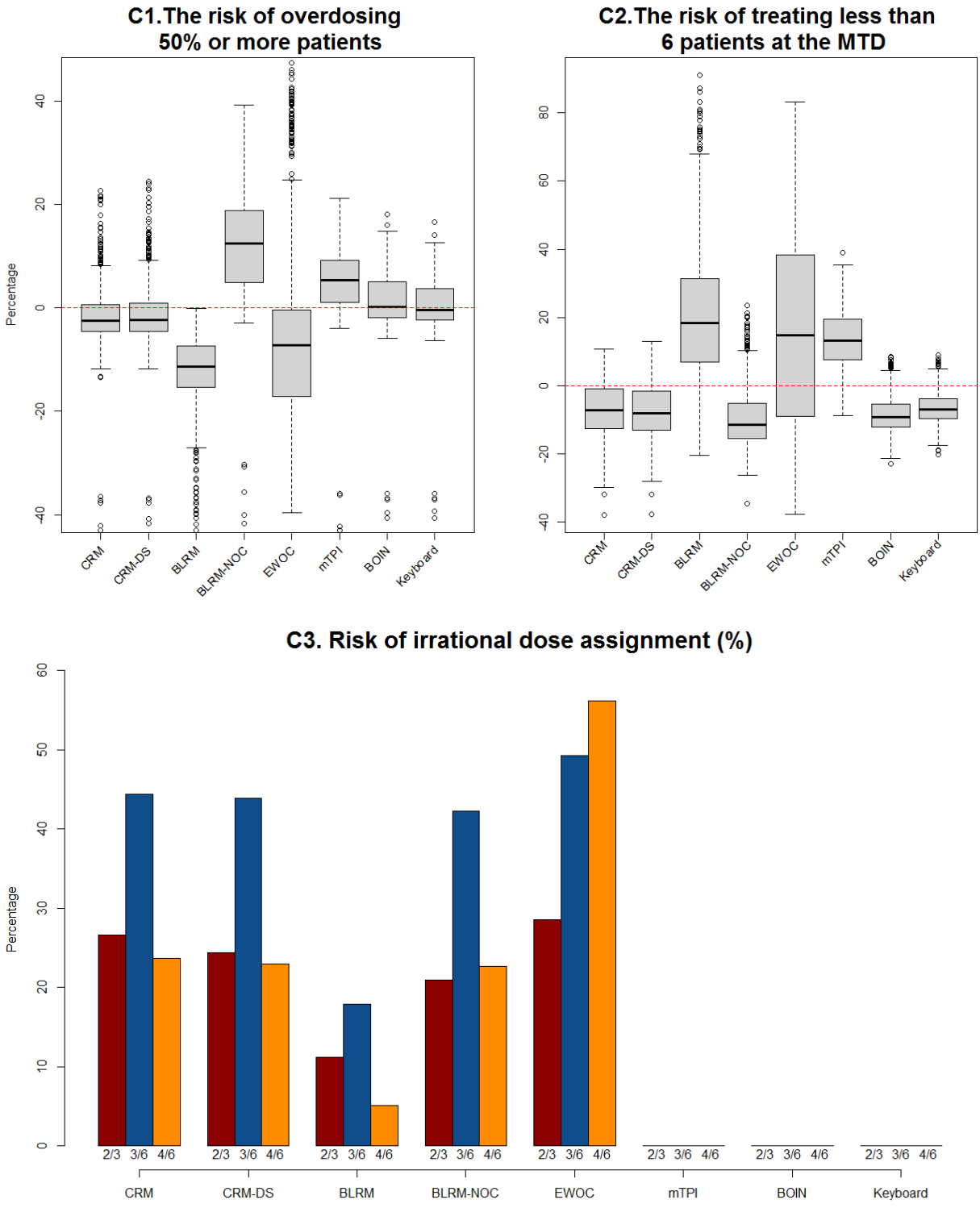


**Figure S8**. Comparison of reliability metrics for the 8 designs with respect to the 3+3 design. C1. Risk of overdosing 50% or more patients; C2. Risk of treating < 6 patients at the MTD; C3. Risk of irrational dose assignment. A smaller value indicates better performance; negative value means that the design outperforms the 3+3 design.

**(2) Cohort size = 3 (Figures S9-11)**

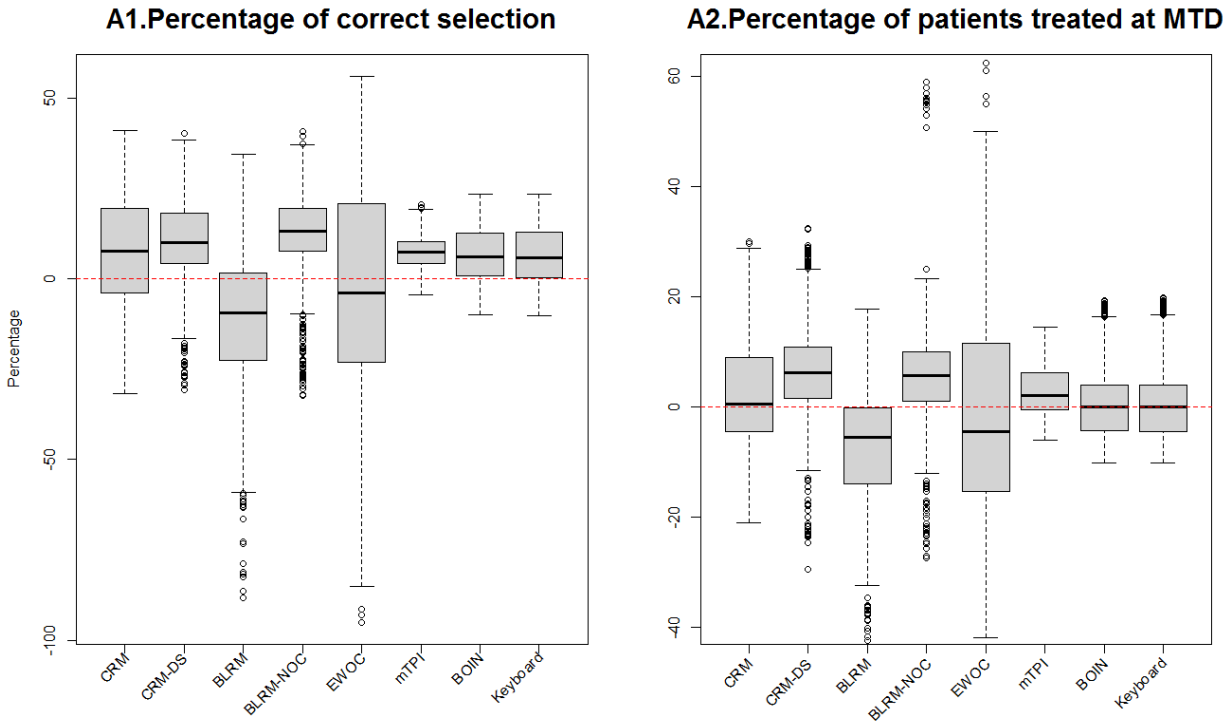


**Figure S9**. Comparison of accuracy metrics for the 8 designs with respect to the 3+3 design. A1. Percentage of correct selection of the MTD; A2. Percentage of patients treated at the MTD; A larger value indicates better performance; positive value means that the design outperforms the 3+3 design.

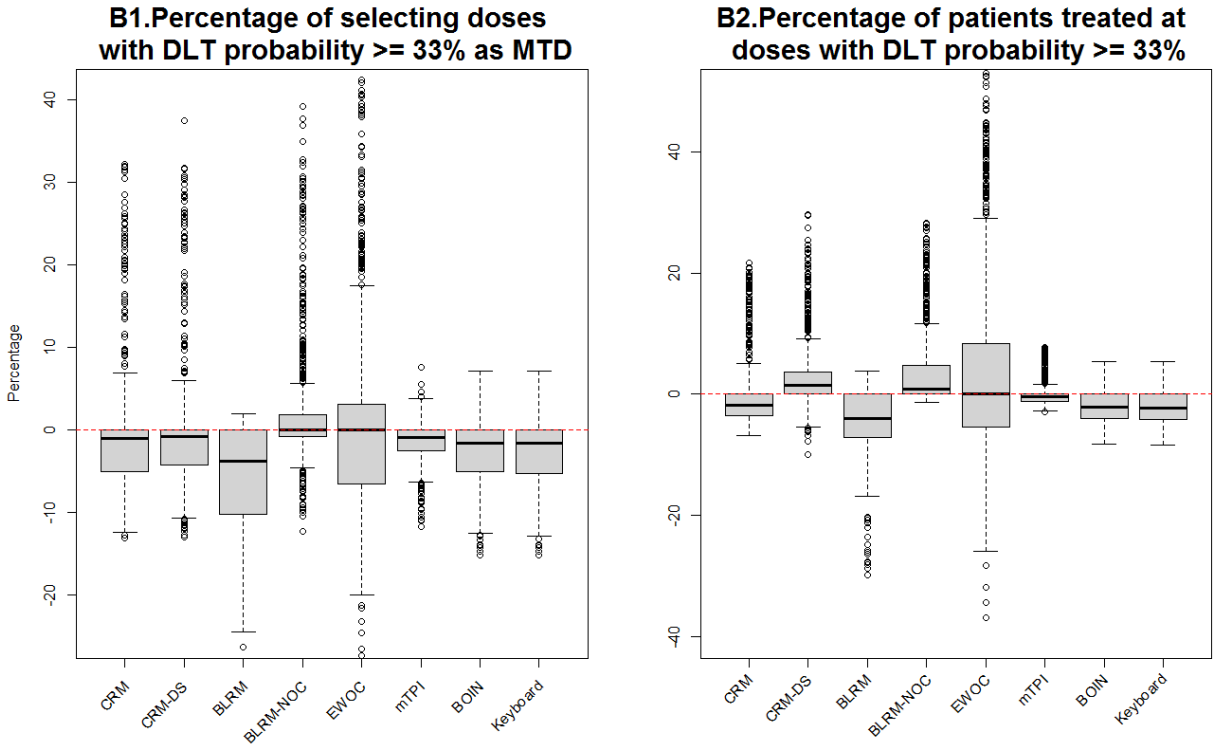


**Figure S10**. Comparison of safety metrics for the 8 designs with respect to the 3+3 design. B1. Percentage of selecting doses with DLT probability $\geq$ 33% as the MTD; B2. Percentage of patients treated at doses with DLT probability $\geq$ 33%; A smaller value indicates better performance; negative value means that the design outperforms the 3+3 design.

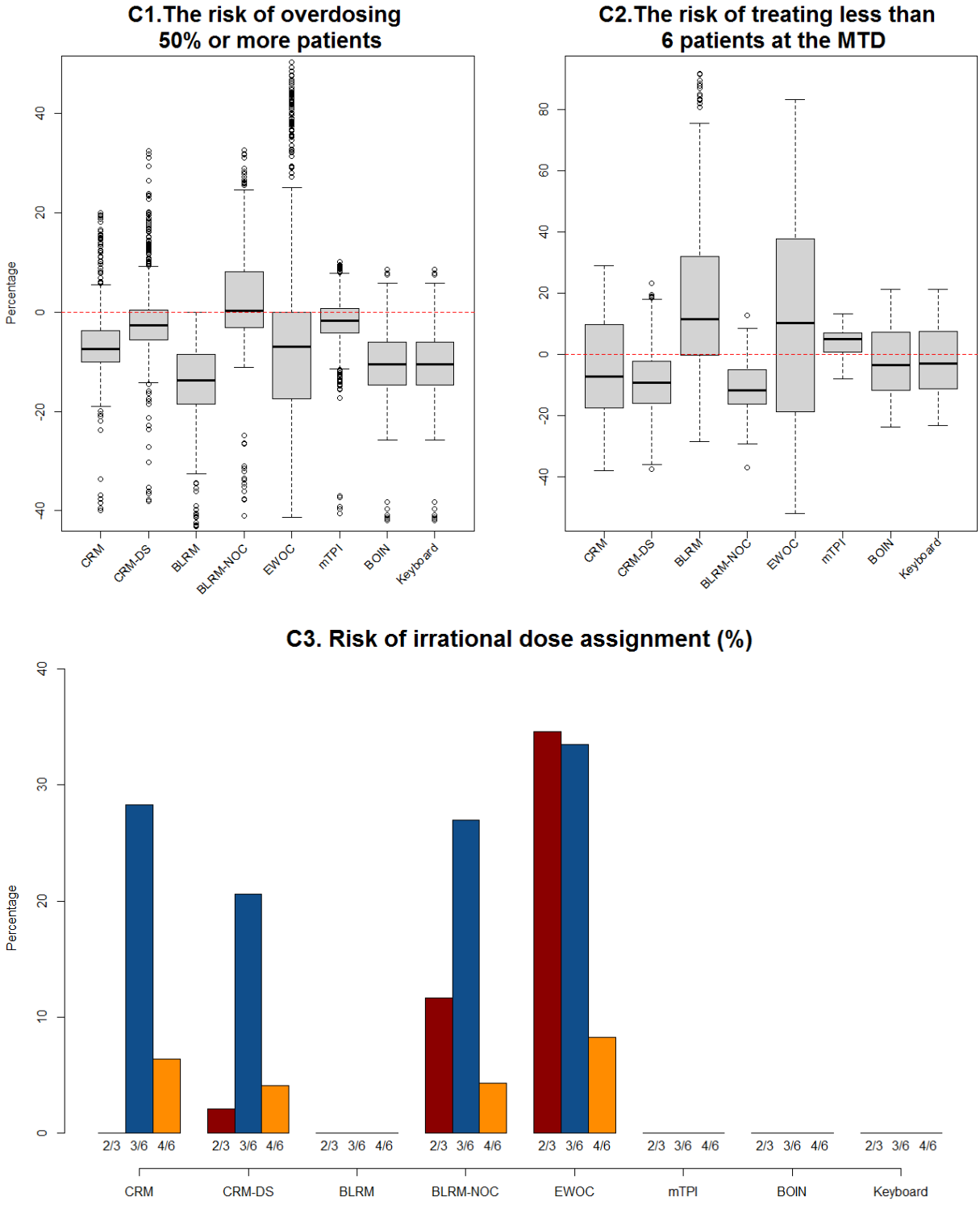


**Figure S11**. Comparison of reliability metrics for the 8 designs with respect to the 3+3 design. C1. Risk of overdosing 50% or more patients; C2. Risk of treating < 6 patients at the MTD; C3. Risk of irrational dose assignment. A smaller value indicates better performance; negative value means that the design outperforms the 3+3 design.

## Appendix F: Simulation results with target DLT probability of 0.30 for 1000 randomly generated scenarios

### (1) Cohort size = 1 (Figures S12-14)

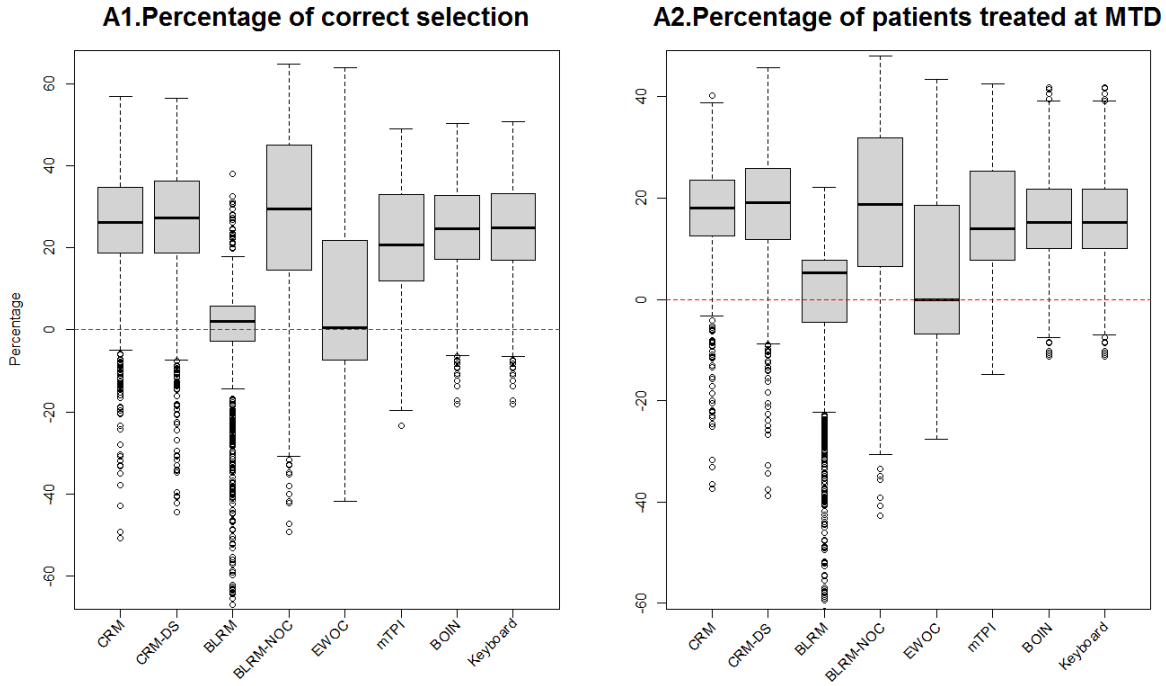


**Figure S12**. Comparison of accuracy metrics for the 8 designs with respect to the 3+3 design. A1. Percentage of correct selection of the MTD; A2. Percentage of patients treated at the MTD; A larger value indicates better performance; positive value means that the design outperforms the 3+3 design.

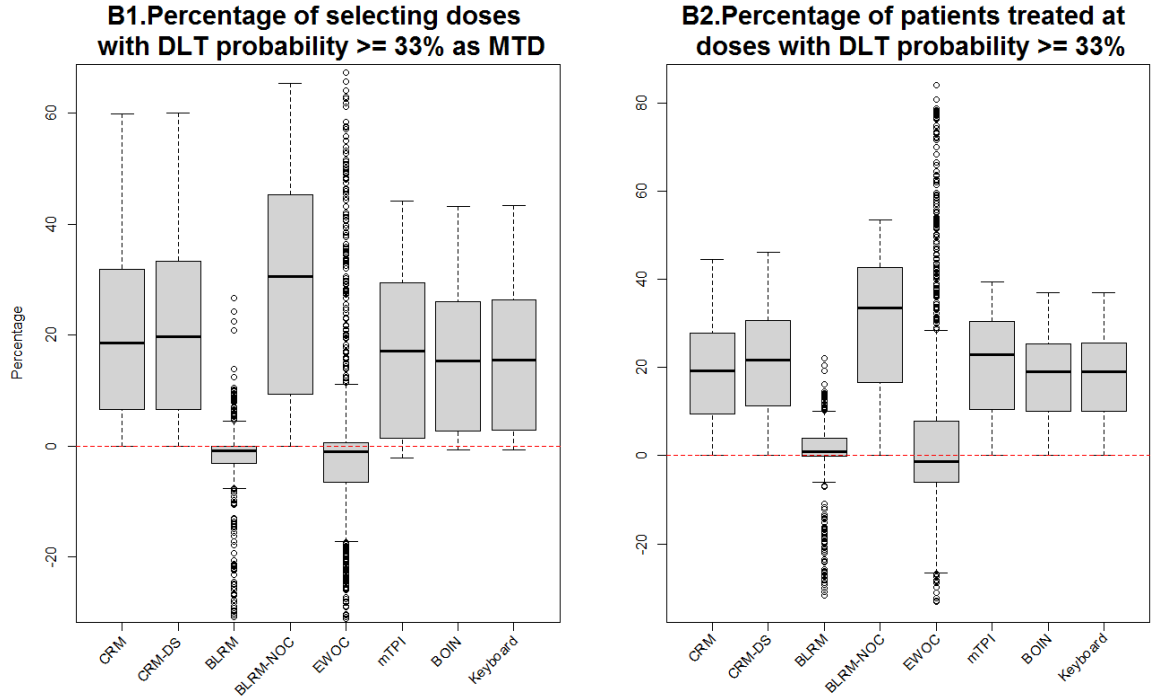


**Figure S13**. Comparison of safety metrics for the 8 designs with respect to the 3+3 design. B1. Percentage of selecting doses with DLT probability $\geq$ 33% as the MTD; B2. Percentage of patients treated at doses with DLT probability $\geq$ 33%; A smaller value indicates better performance; negative value means that the design outperforms the 3+3 design.

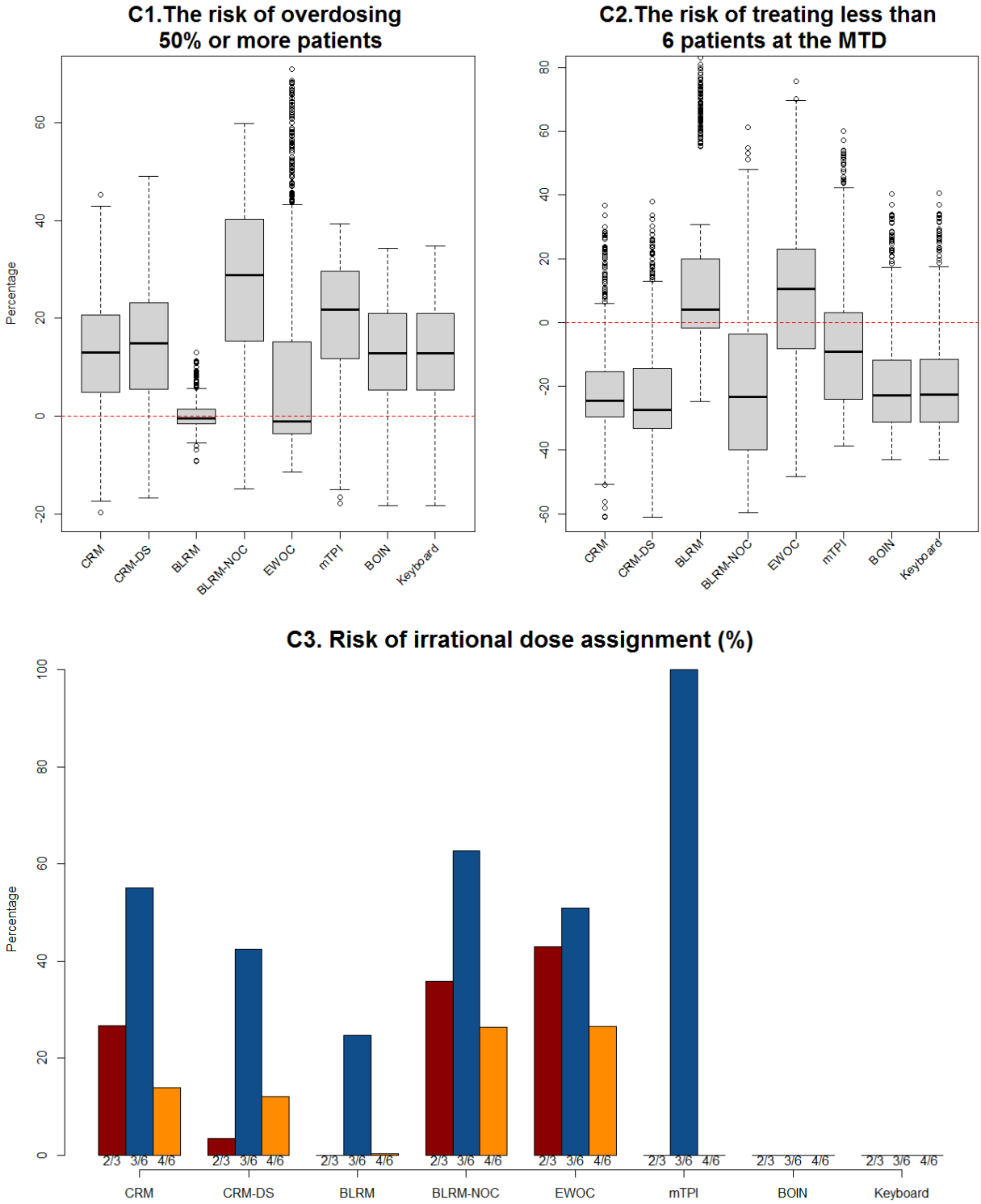


**Figure S14**. Comparison of reliability metrics for the 8 designs with respect to the 3+3 design. C1. Risk of overdosing 50% or more patients; C2. Risk of treating < 6 patients at the MTD; C3. Risk of irrational dose assignment. A smaller value indicates better performance; negative value means that the design outperforms the 3+3 design.

**(2) Cohort size = 3 (Figures S15-17)**

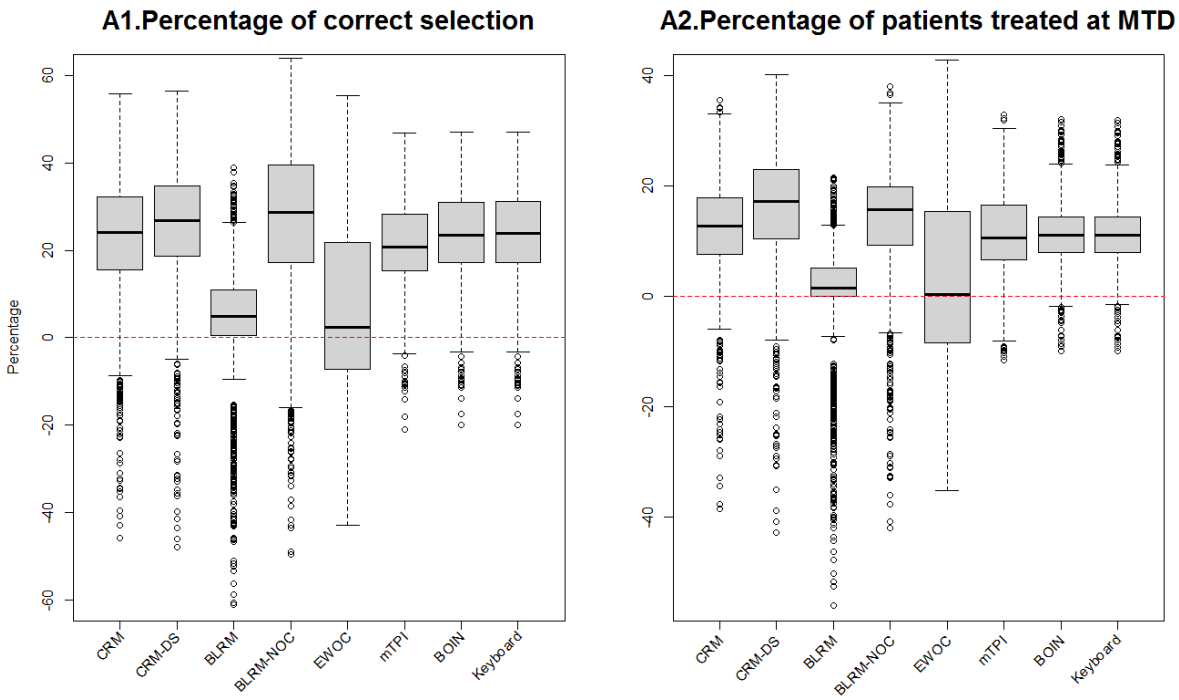


**Figure S15**. Comparison of accuracy metrics for the 8 designs with respect to the 3+3 design. A1. Percentage of correct selection of the MTD; A2. Percentage of patients treated at the MTD; A larger value indicates better performance; positive value means that the design outperforms the 3+3 design.

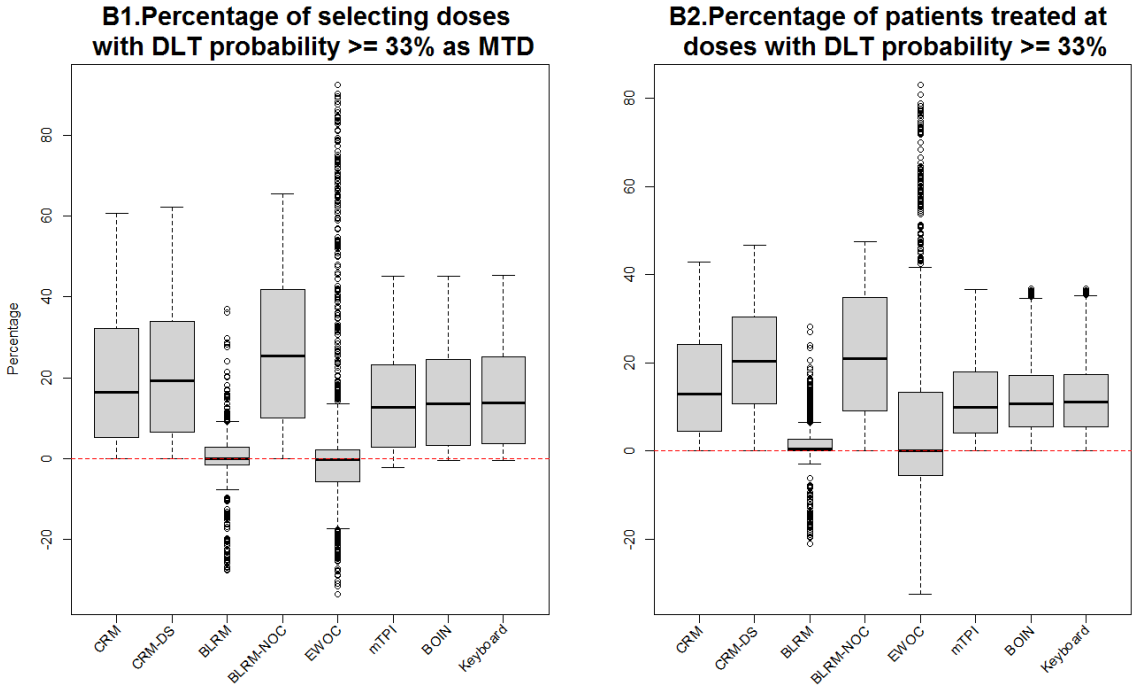


**Figure S16**. Comparison of safety metrics for the 8 designs with respect to the 3+3 design. B1. Percentage of selecting doses with DLT probability $\geq$ 33% as the MTD; B2. Percentage of patients treated at doses with DLT probability $\geq$ 33%; A smaller value indicates better performance; negative value means that the design outperforms the 3+3 design.

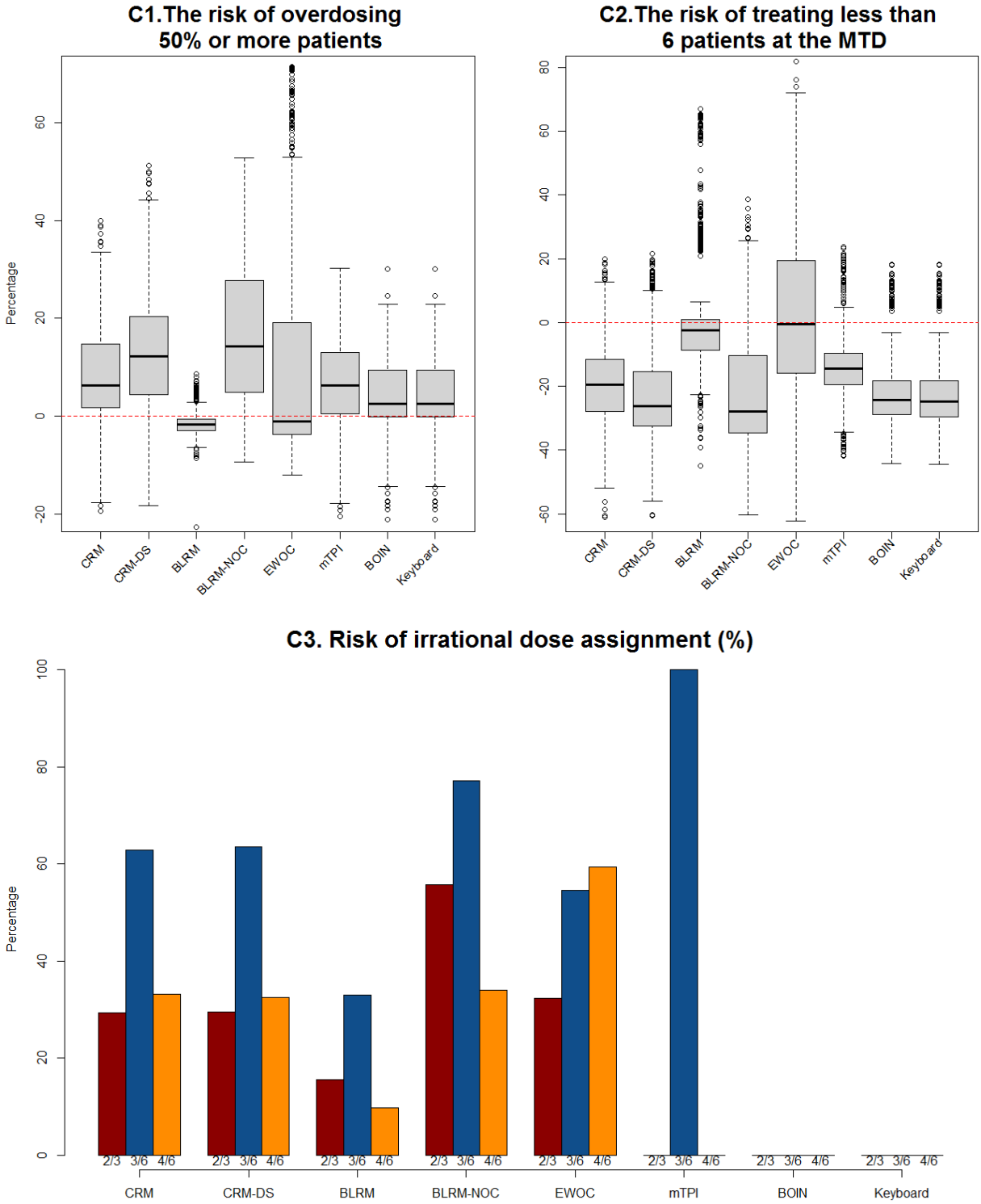


**Figure S17**. Comparison of reliability metrics for the 7 designs with respect to the 3+3 design. C1. Risk of overdosing 50% or more patients; C2. Risk of treating < 6 patients at the MTD; C3. Risk of irrational dose assignment. A smaller value indicates better performance; negative value means that the design outperforms the 3+3 design.