STAT 453 Final Project - Analysis/Figures

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Based on your simulation results, describe your findings. In particular, pros and cons of the CRM and BOIN

Phase I trials are designed to test the safety, side effects, best dose, and formulation method for drugs. One of the most important things one would like to determine during a Phase I trial is the Maximum Tolerated Dose, also known as the MTD, which is defined as the dose that has the probability of toxicity equal to the target rate ϕ, which is often equal to a value such as 0.2 or 0.3. There are three main methods of dose finding that we discussed in class - 3+3, CRM, and BOIN. The 3+3 method is a conventional, algorithmic based way of finding the MTD, and it is quite easy and cheap to implement. However, it does not perform at the level that some other methods do, making it less favorable. This particular project focuses on CRM and BOIN designs. In class, we learned that BOIN and CRM have comparable average performance, but BOIN does have some favorable properties. First of all, BOIN is much easier to implement than CRM and is far more transparent. Second, BOIN is shown to have a lower variance, and therefore a higher reliability, which is critically important in practice.

To compare BOIN and CRM for this project, we ran simulation studies using software from MD Anderson that tested the performance of these methods at different dose levels, target toxicity rates, cohort sizes, and sample sizes. In each of these different "scenarios," we wanted to see how BOIN and CRM compared in terms of selection accuracy, allocation accuracy, and safety for current and future trials. The first metric we wanted to look at was selection accuracy - that is, the selection percentage of the MTD. The first case we looked at was when the Toxcity = 0.2, Number of Dose Levels = 5. We tested this at two different cohort sizes. When Cohort Size = 1, BOIN had a higher selection accuracy than CRM in 19/20 trials, and when cohort size = 3, BOIN had a higher selection accuracy than CRM in 16/20 trials. When we increased the target toxicity to $\phi = 0.3$, we saw similar results - BOIN outperforms CRM in terms of selection percentage more often than not, both for cohort sizes 1 and 3. The next condition we varied was the number of dose levels, which we lowered from 5 to 3. When the target = 0.2 and the Number of Dose Levels = 3 and cohort size = 1, BOIN won out 80% of the time. Increasing the cohort size to 3 did not change this finding. When we increased $\phi = 0.3$, BOIN still outperformed CRM consistently. What these experiements tell us is that if selection percentage is particularly important to the study, then the BOIN method is preferable to the CRM method. The CRM method did do better in some scenarios when the DLT rates in the scenarios I created were low compared to the target, so perhaps in extreme cases like this, the CRM could do better than BOIN. However, it seems reasonable to conclude that BOIN outperforms CRM in terms of selection accuracy.

The next metric we looked at is the allocation accuracy, which is the number of patients assigned to the MTD. Again, the first case we looked at was when the target Toxcity = 0.2 and Number of Dose Levels = 5. We tested this at two different cohort sizes. When Cohort Size = 1, BOIN had a higher allocation accuracy than CRM in 13/20 scenarios. After increasing the cohort size to 3, BOIN still had a higher allocation accuracy than CRM in 13/20 scenarios. When we increased the target toxicity to 0.3, BOIN outperformed CRM 18/20 times at a cohort size of 1. When we tested the case when Target Toxcity = 0.3, Number of Dose Levels = 5, and Cohort Size = 3 however, CRM did better in 14/20 scenarios. After increasing the dose levels to 3 and the toxicity to 0.2, BOIN had higher allocation accuracy when the cohort size equals 1 and CRM had higher allocation accuracy when cohort size = 3. This same pattern held when we increased the toxicity again to 0.3. From this, we can say that BOIN does better in terms of allocation accuracy when cohort size is lower and CRM does when cohort size is higher.

Next, we measured the average number of patients assigned to the doses above the MTD (safety for patients in current trial). We want this number to be lower because that means less people are exposed to potentially

toxic doses. When the Target Toxcity = 0.2, Number of Dose Levels = 5, Cohort Size = 1, BOIN assigned more patients to doses above the MTD than CRM 14 out of 20 times. When the cohort size increased to 3, CRM assigned more patients to doses above the MTD than BOIN 19/20 times. After we increased the target toxicity levels, we see the same pattern, CRM assigned more patients to doses above the MTD than BOIN when cohort size is higher, and BOIN assigned more patients to doses above the MTD than CRM when cohort size is lower. When we lower the dose levels to 3, the same pattern emerges. In general, CRM assigned more patients to doses above the MTD than BOIN when cohort size is higher and BOIN assigned more patients to doses above the MTD than CRM when cohort size is lower. There are some exceptions to this rule. If all the DLT rates are higher than the target, BOIN often assigns more patients assigned to the doses above the MTD than CRM, but the results are very close.

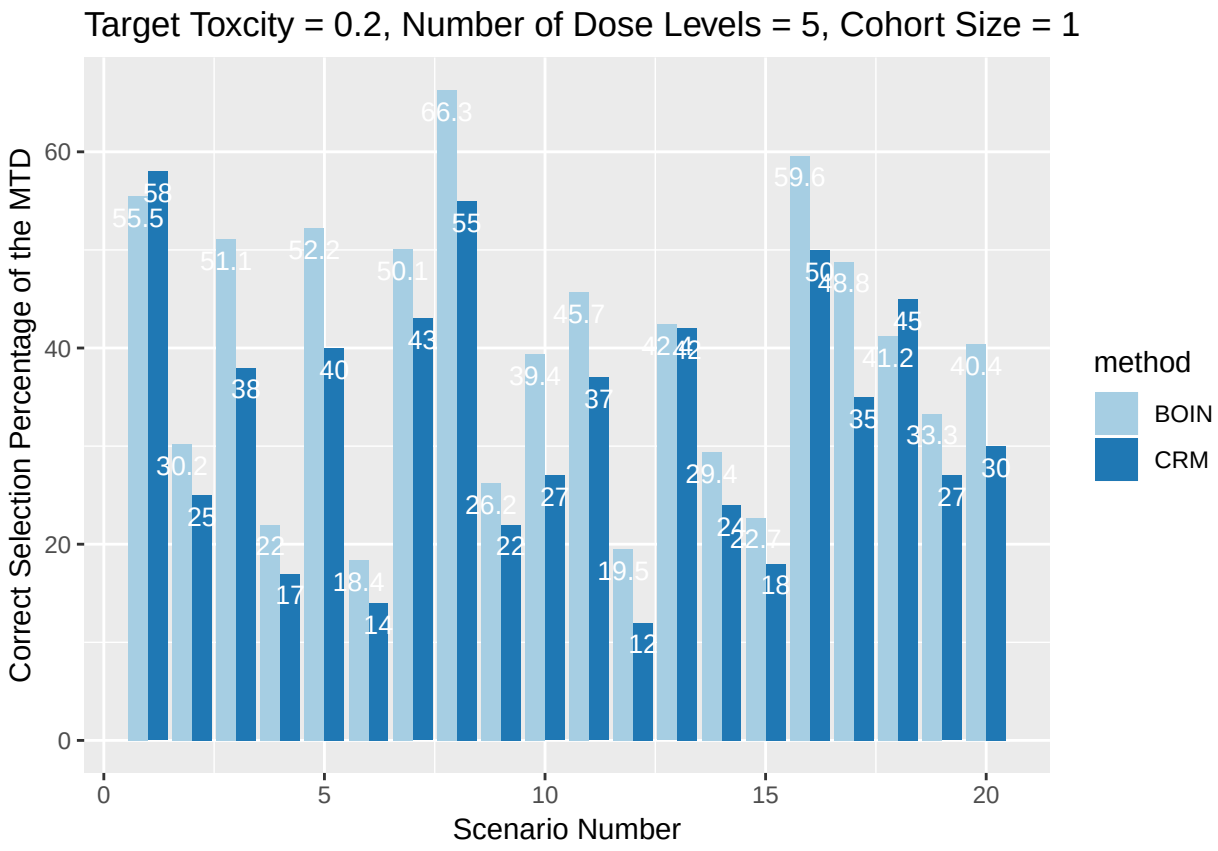
The last thing we looked at was the average selection percentage of the doses above the MTD. We want this number to be lower because that means less people are exposed to potentially toxic doses in future trials. When Target Toxcity = 0.2, Number of Dose Levels = 5, and Cohort Size = 1, BOIN assigned more patients to doses above the MTD than CRM in general, but when cohort size = 3, CRM assigned more patients to doses above the MTD than BOIN. We see the same pattern when we increase the target toxicity level. Even after lowering the number of doses, the same pattern emerges. BOIN assigned more patients to doses above the MTD than CRM when cohort size was small, but when cohort size is large, CRM assigned more patients to doses above the MTD than BOIN. When dealing with larger cohort sizes, it may be advantages to use BOIN and when dealing with smaller cohort sizes, it may be advantageous to use CRM, but the differences are quite minor.

Throughout these analysis, the differences in performance between CRM and BOIN were quite small. While on average BOIN may have done better in some settings and CRM may have done better in others, the actual margin between the two was often minuiscule. When selection percentage and allocation accuracy is very important, it seems advantageous to use BOIN, as BOIN outperforms CRM quite often in terms of these metrics. When loking at safety and future studies, BOIN and CRM are quite similar. While the actual performance of these two methods seems comparable in many settings, our findings show that BOIN often ourtperforms CRM in the majority of the scenarios. Since BOIN is often easier to implement in practice and is usually less variable, it seems to me that BOIN is the better method than CRM.

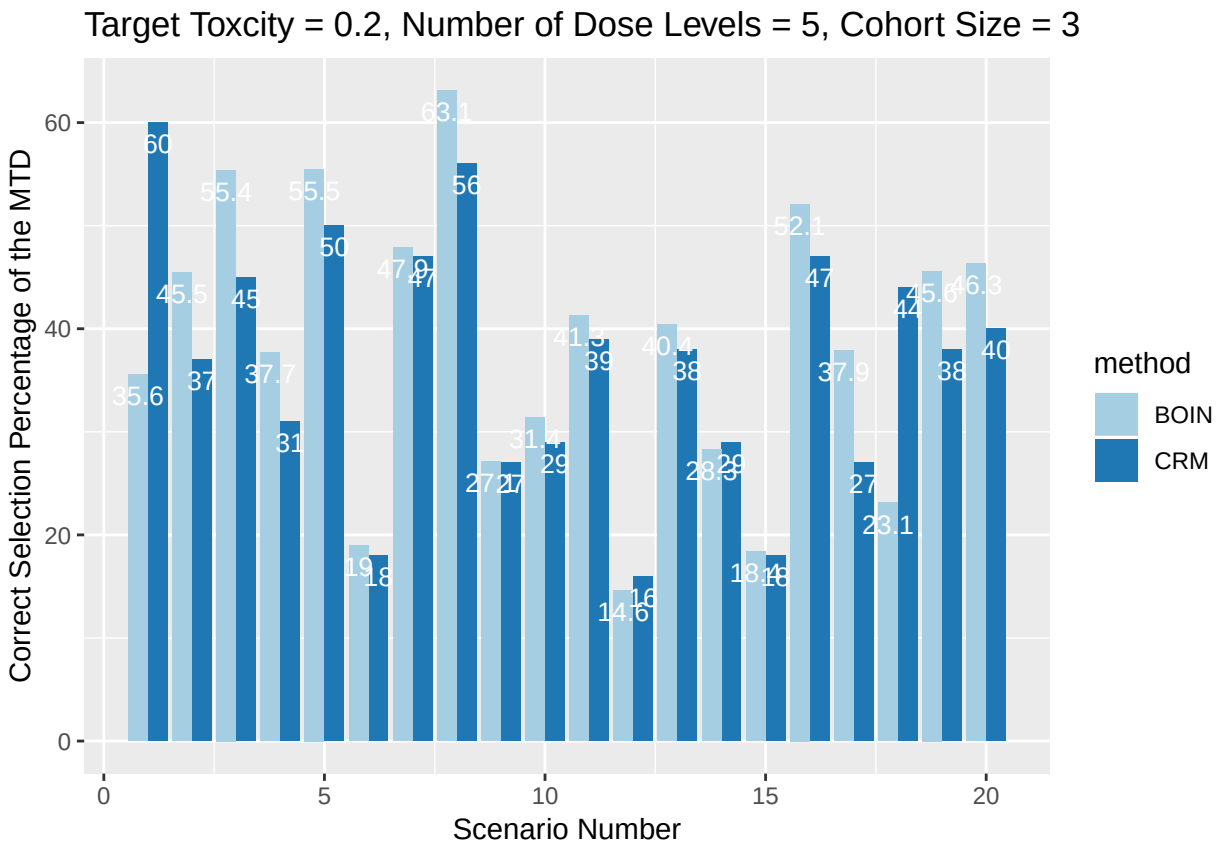
Figures to show the correct selection percentage of the MTD (selection accuracy)

Case 1: Target = 0.2 and the Number of Dose Levels = 5

Cohort Size = 1

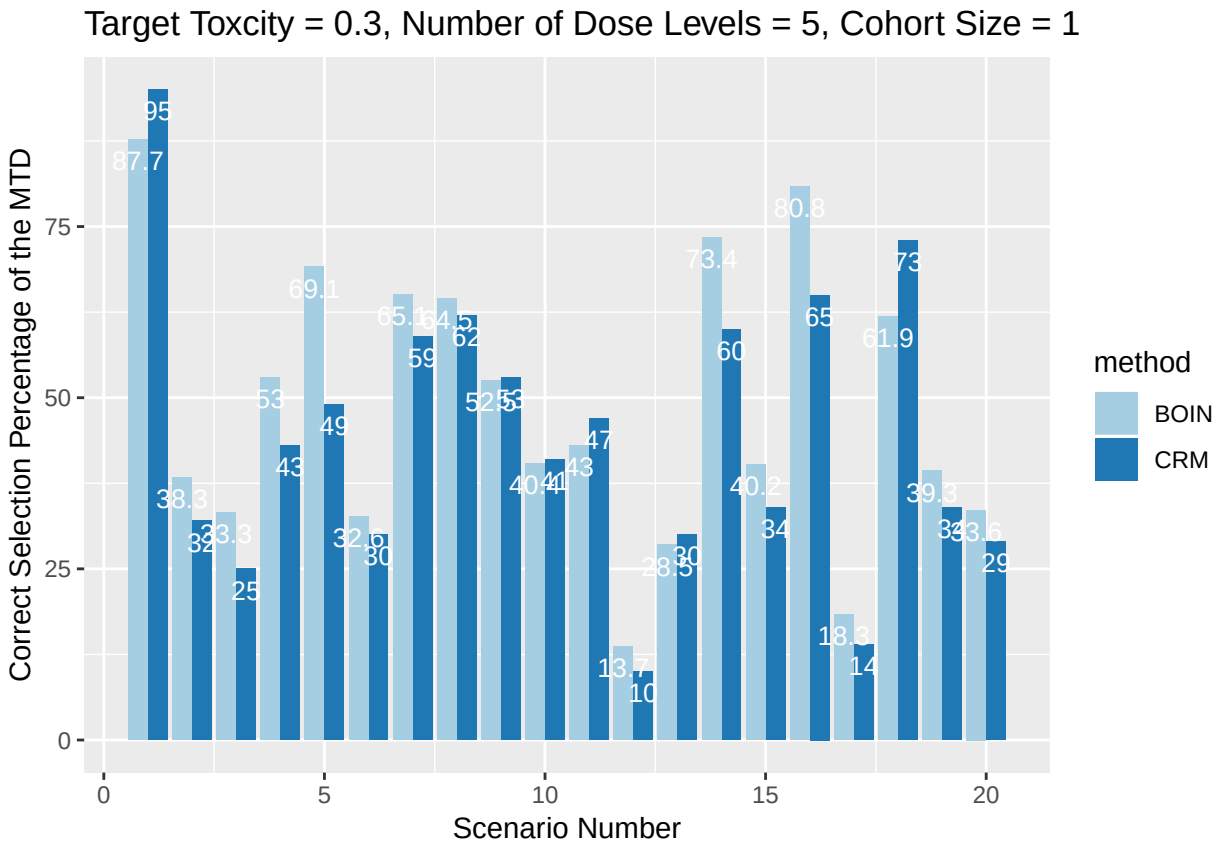


Cohort Size = 3



Case 2: Target = 0.3 and the Number of Dose Levels = 5

Cohort Size = 1



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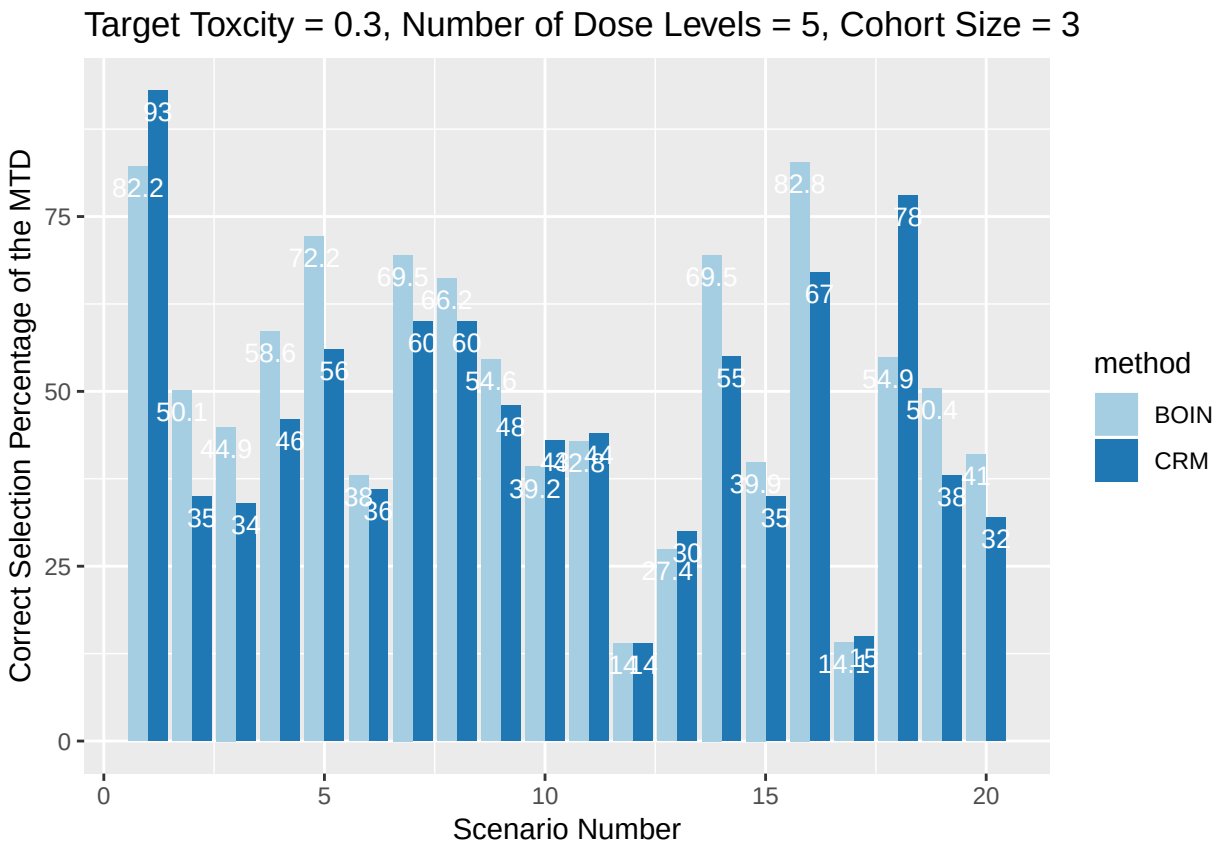
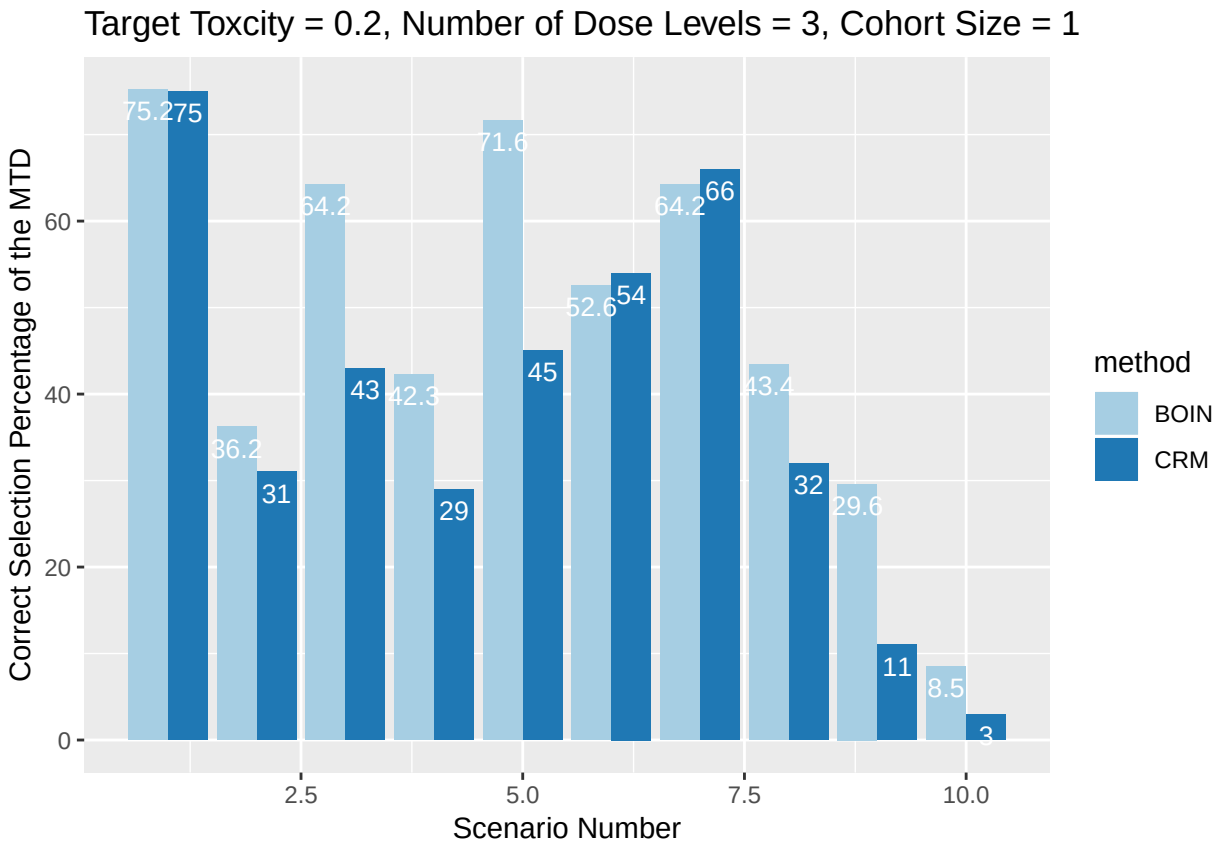


Case 3: Target = 0.2 and the Number of Dose Levels = 3

Cohort Size = 1



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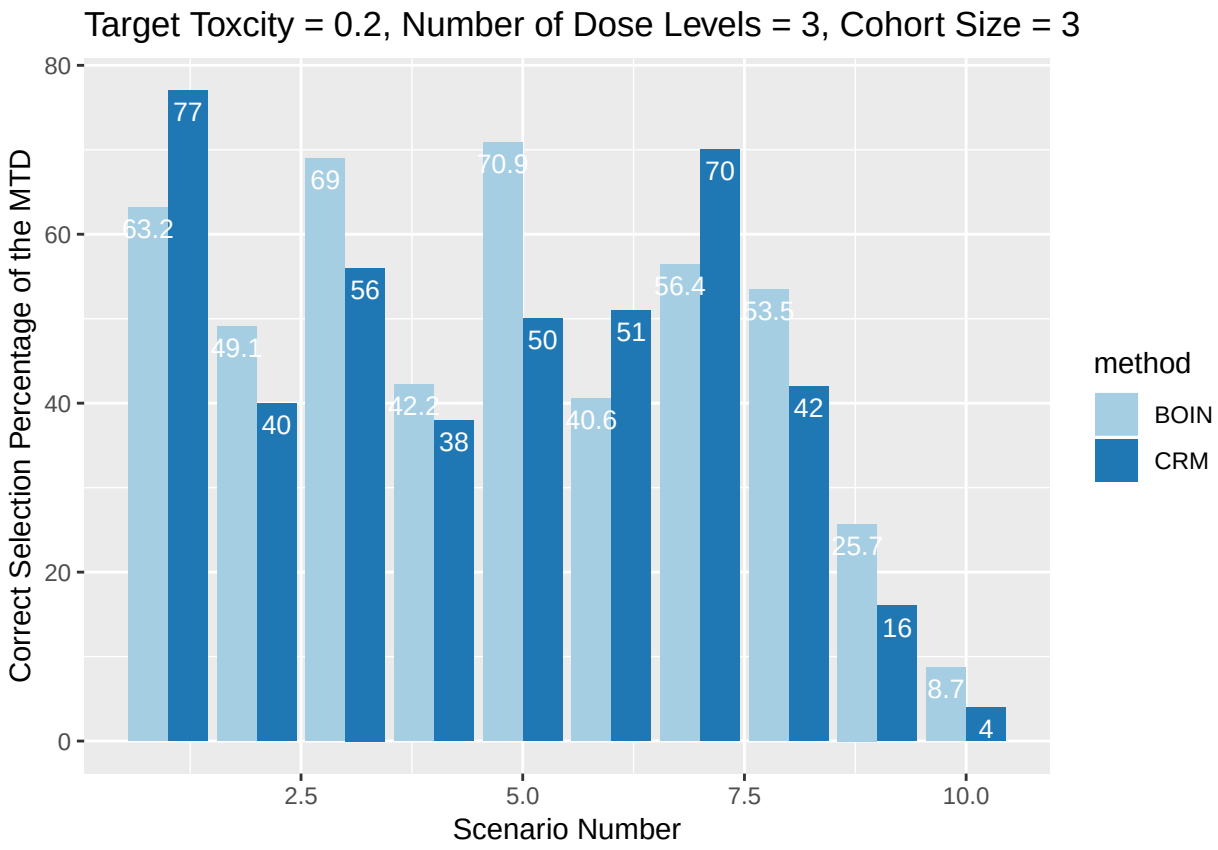
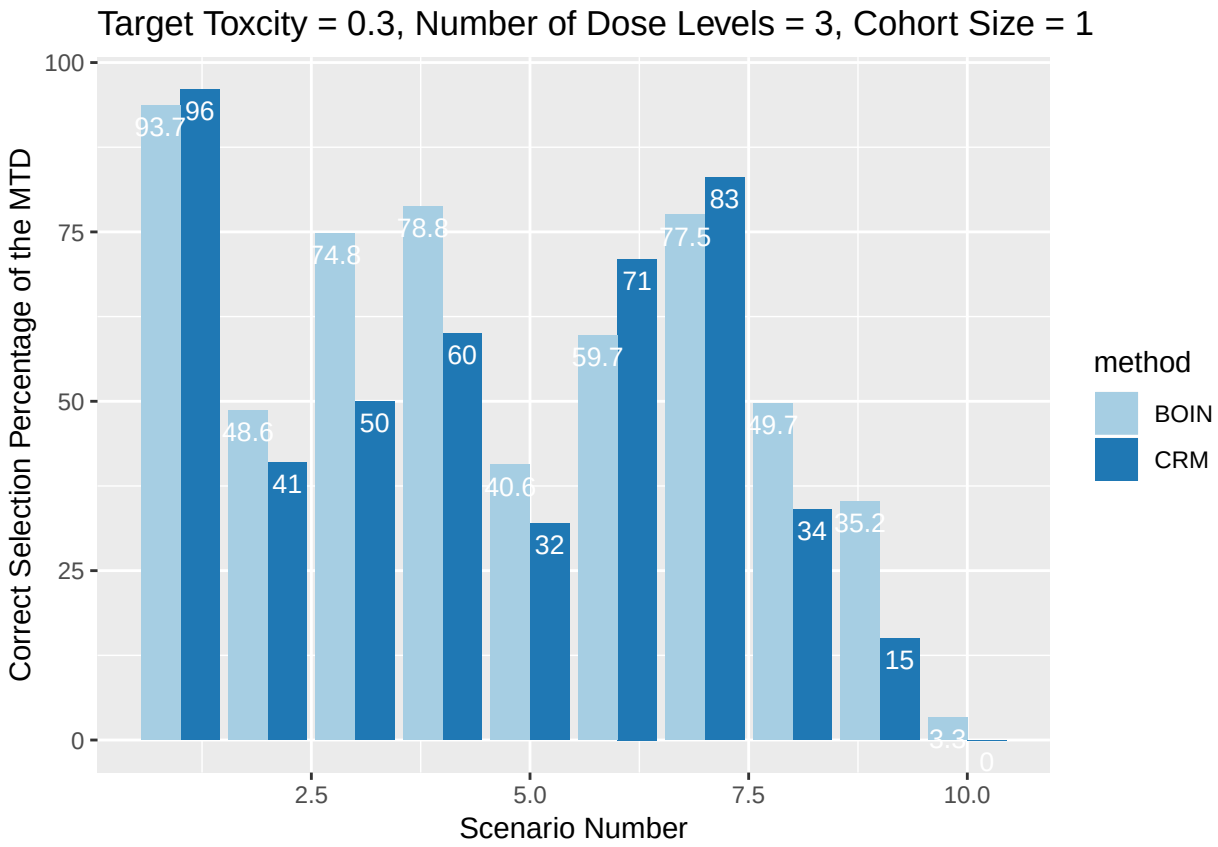


Case 4: Target = 0.3 and the Number of Dose Levels = 3

Cohort Size = 1



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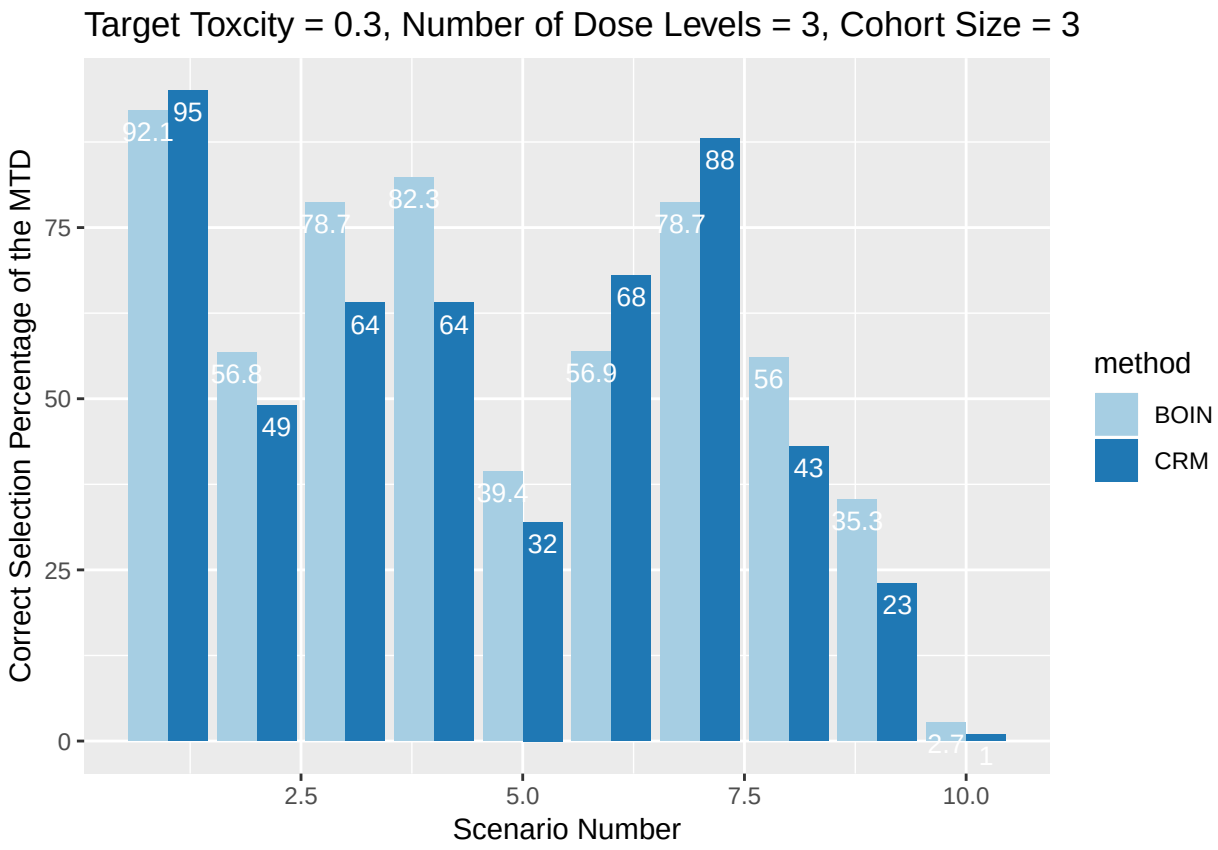
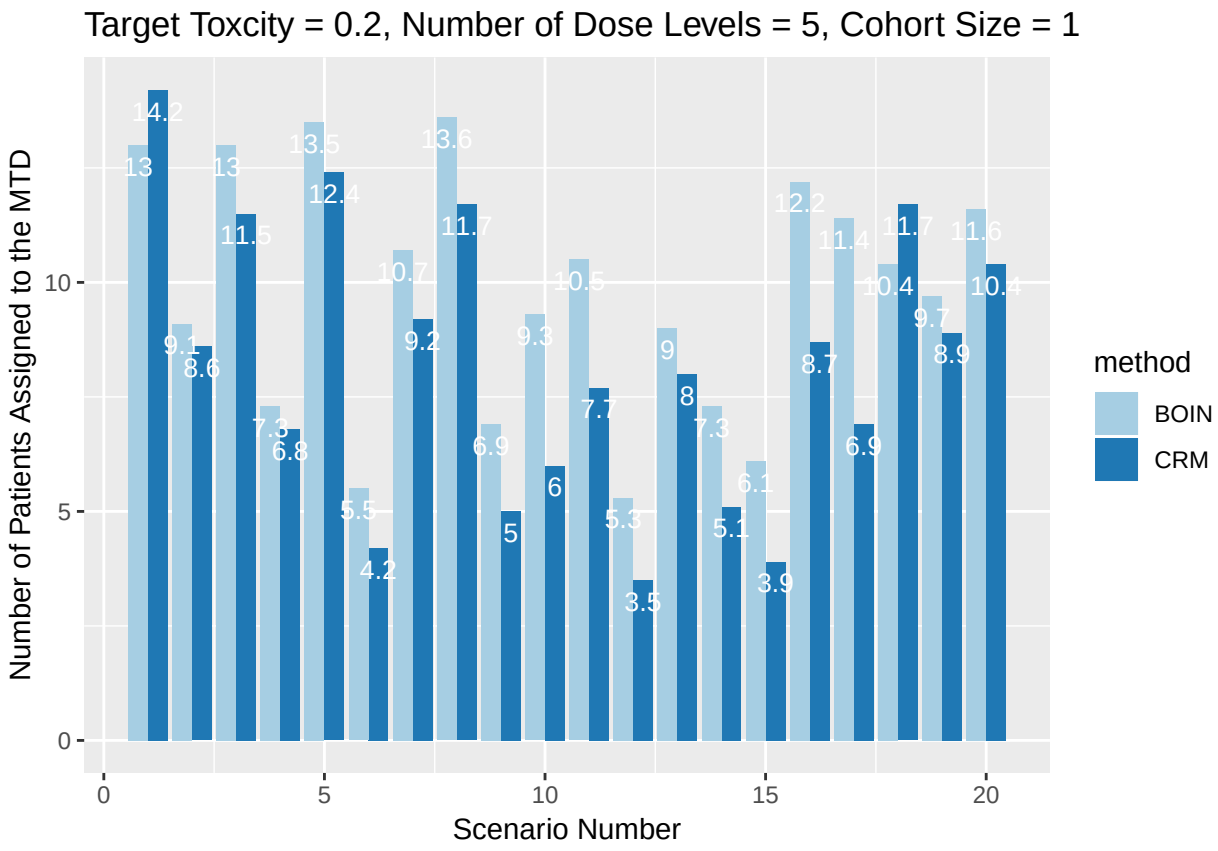


Figures to show the number of patients assigned to the MTD (allocation accuracy)

Case 1: Target = 0.2 and the Number of Dose Levels = 5

Cohort Size = 1



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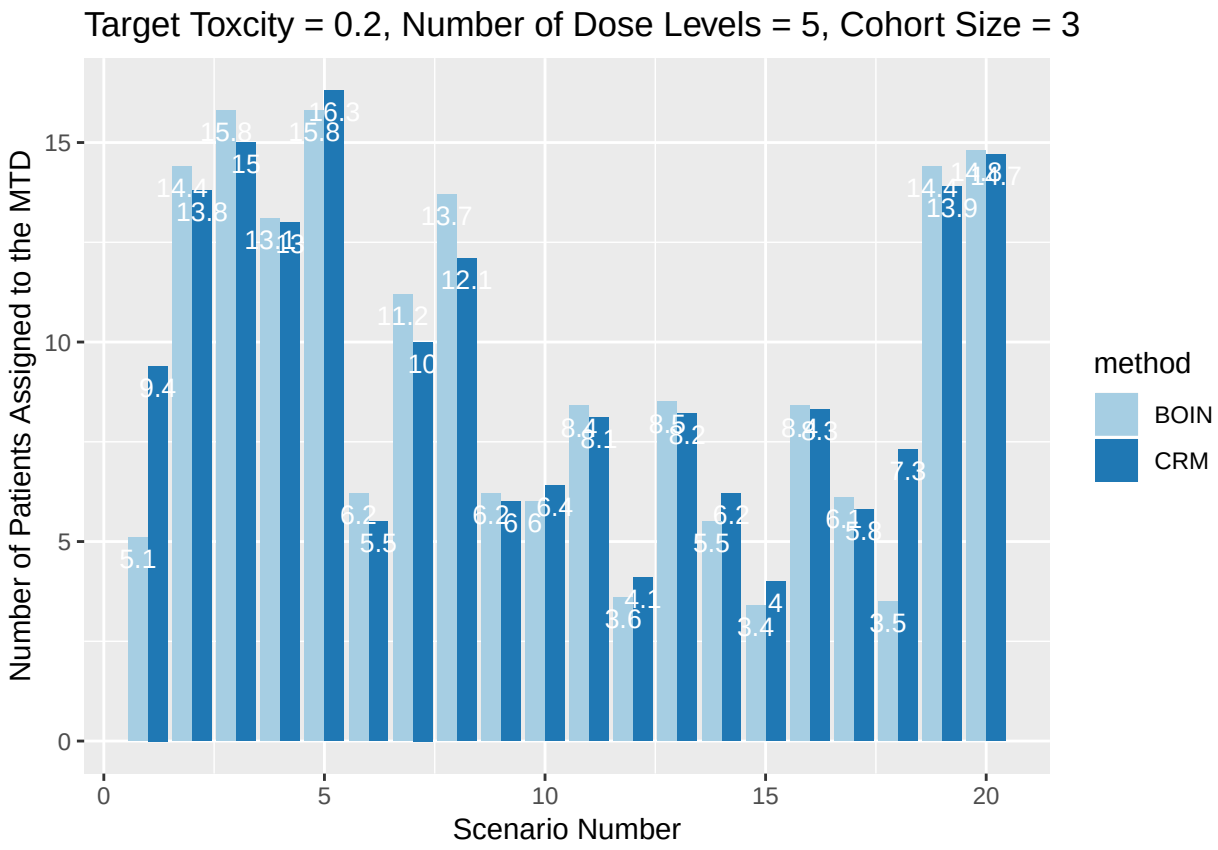
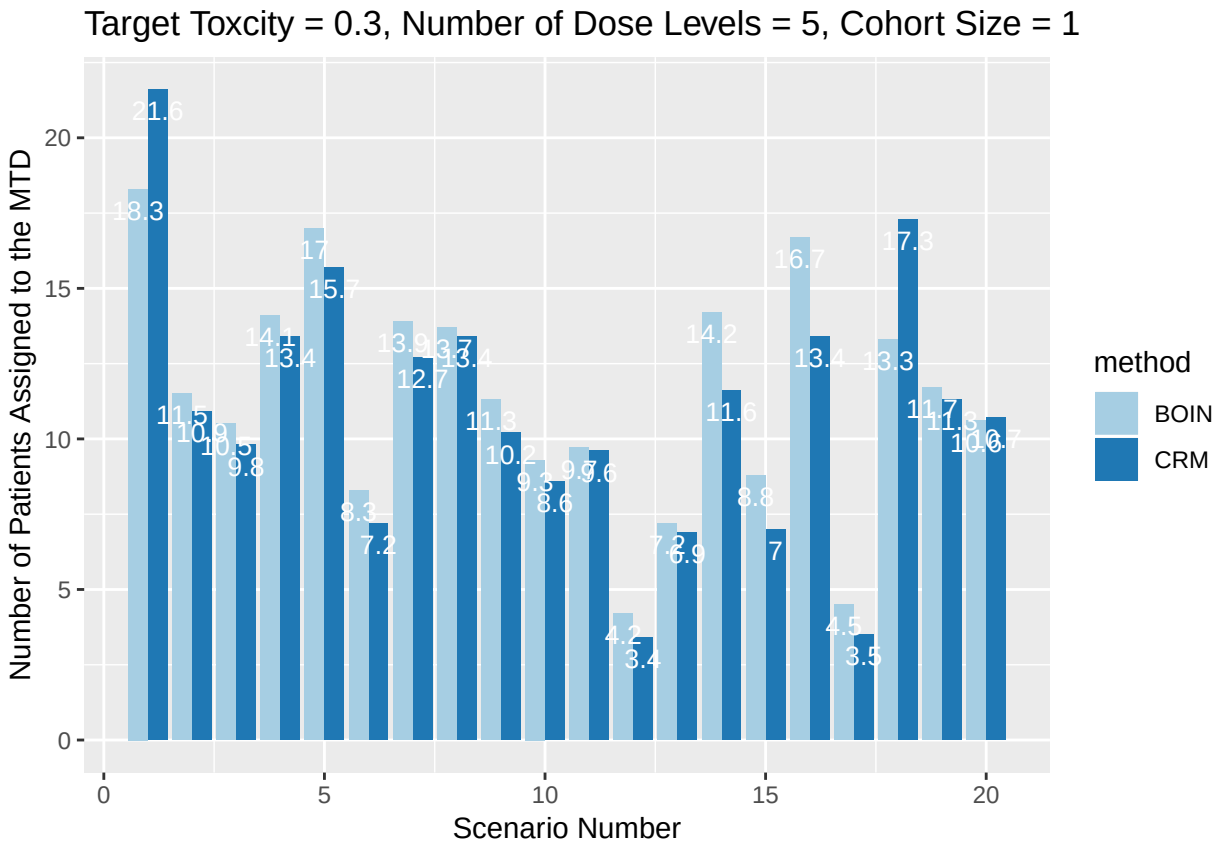


Case 2: Target = 0.3 and the Number of Dose Levels = 5

Cohort Size = 1



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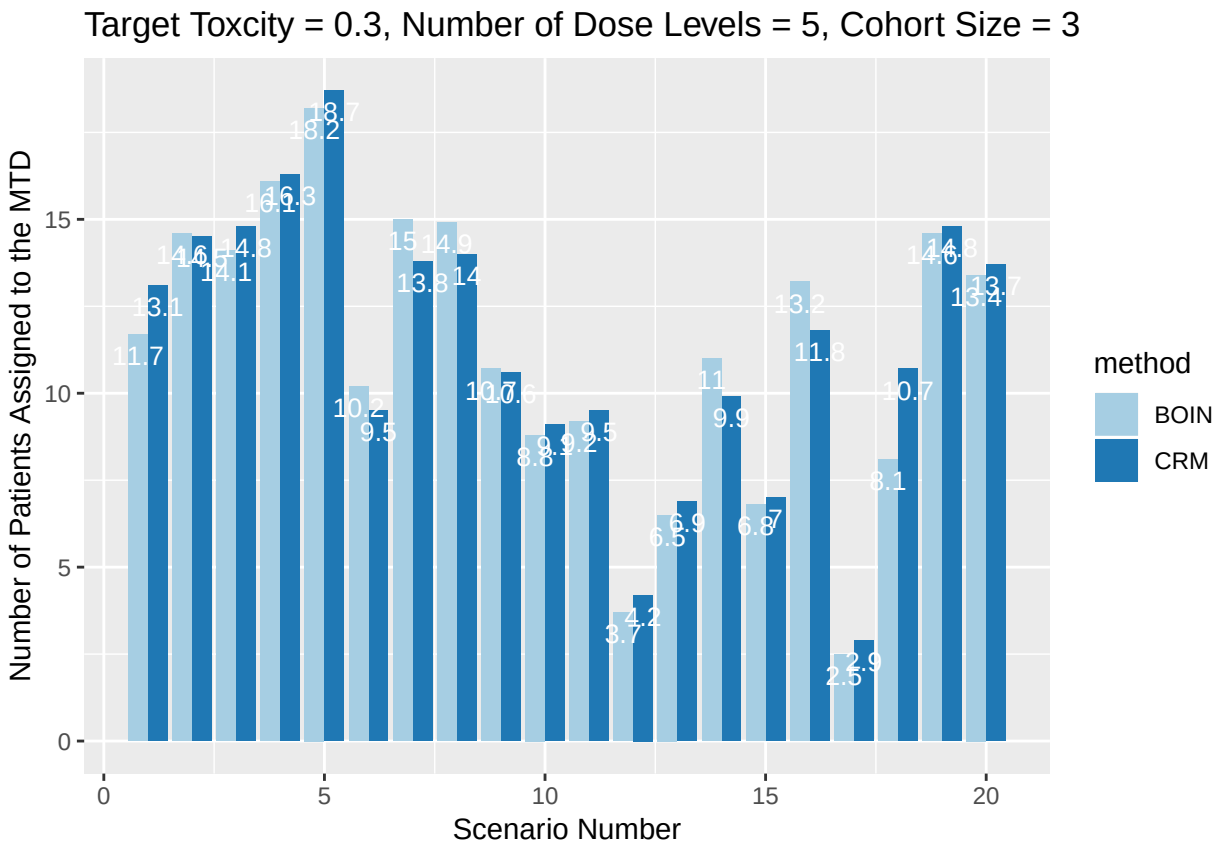
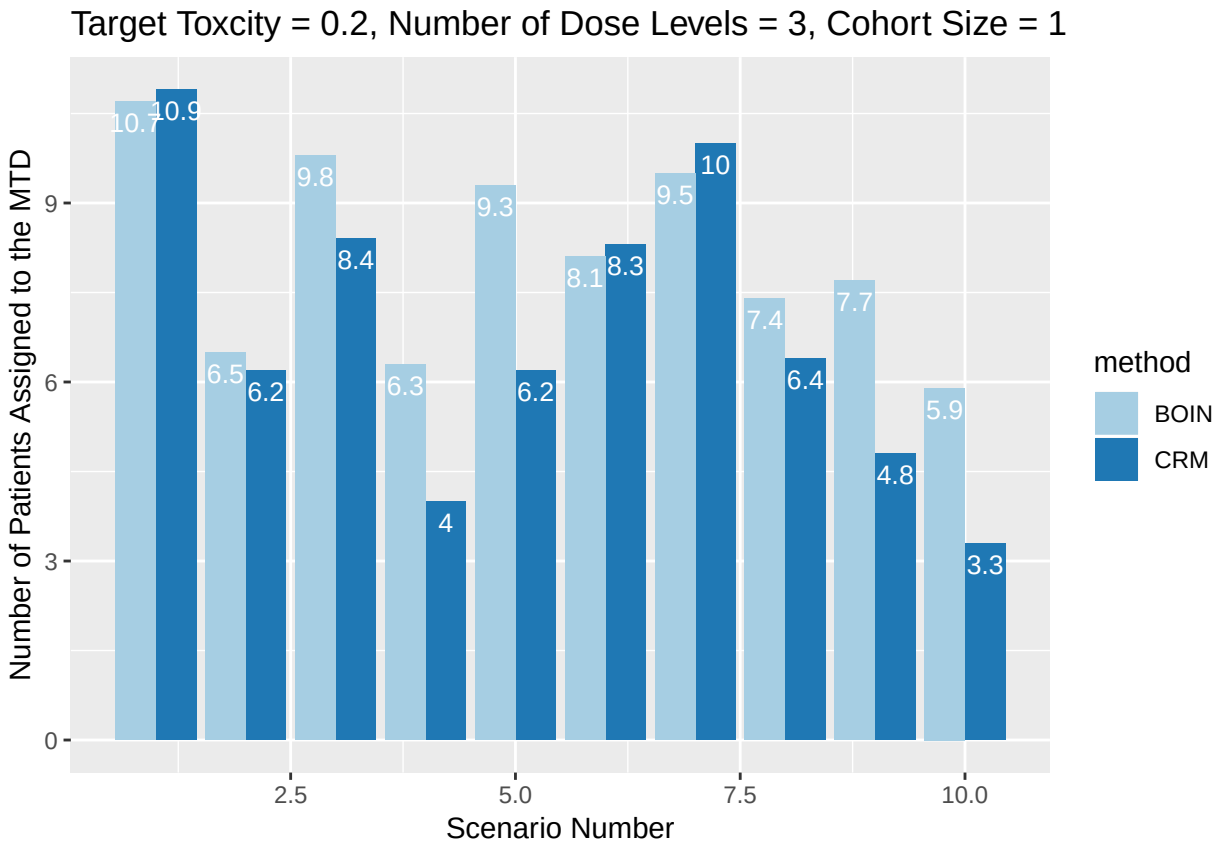


Case 3: Target = 0.2 and the Number of Dose Levels = 3

Cohort Size = 1



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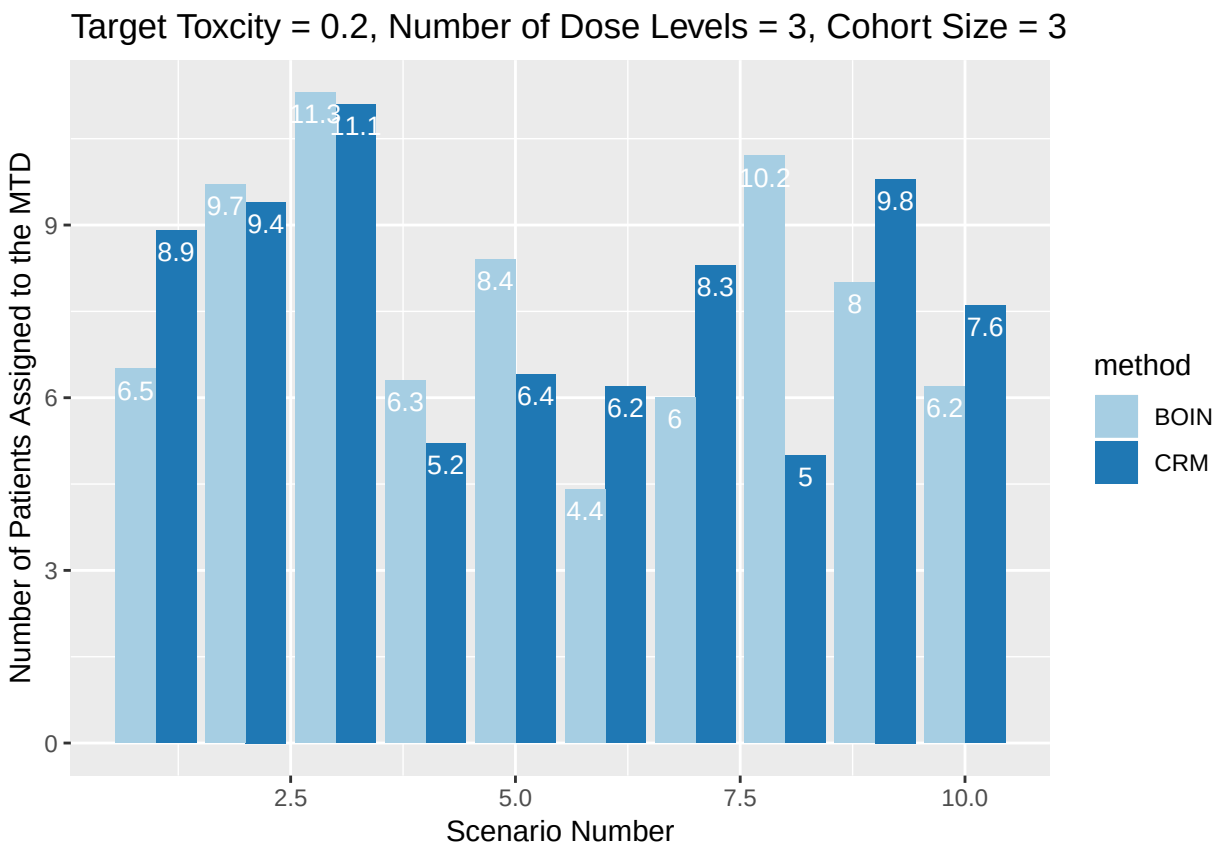
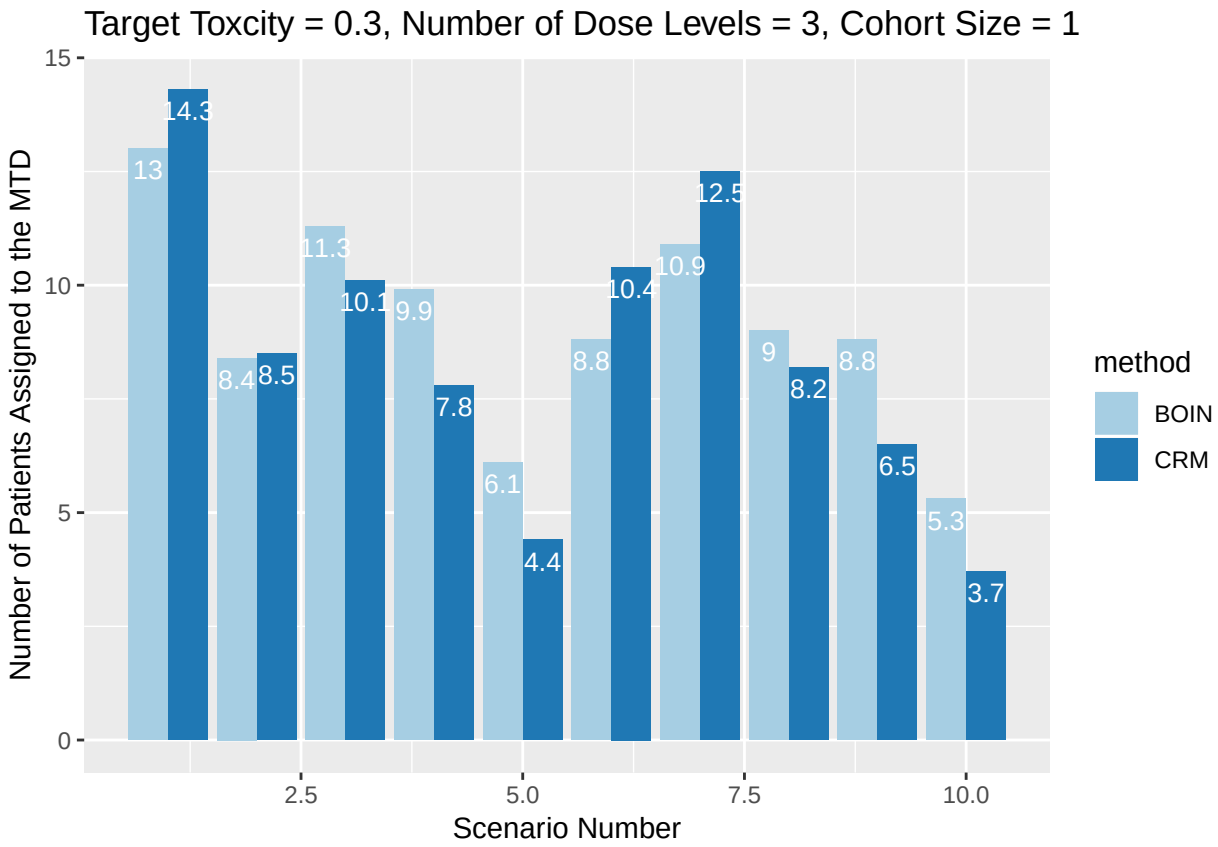


Case 4: Target = 0.3 and the Number of Dose Levels = 3

Cohort Size = 1



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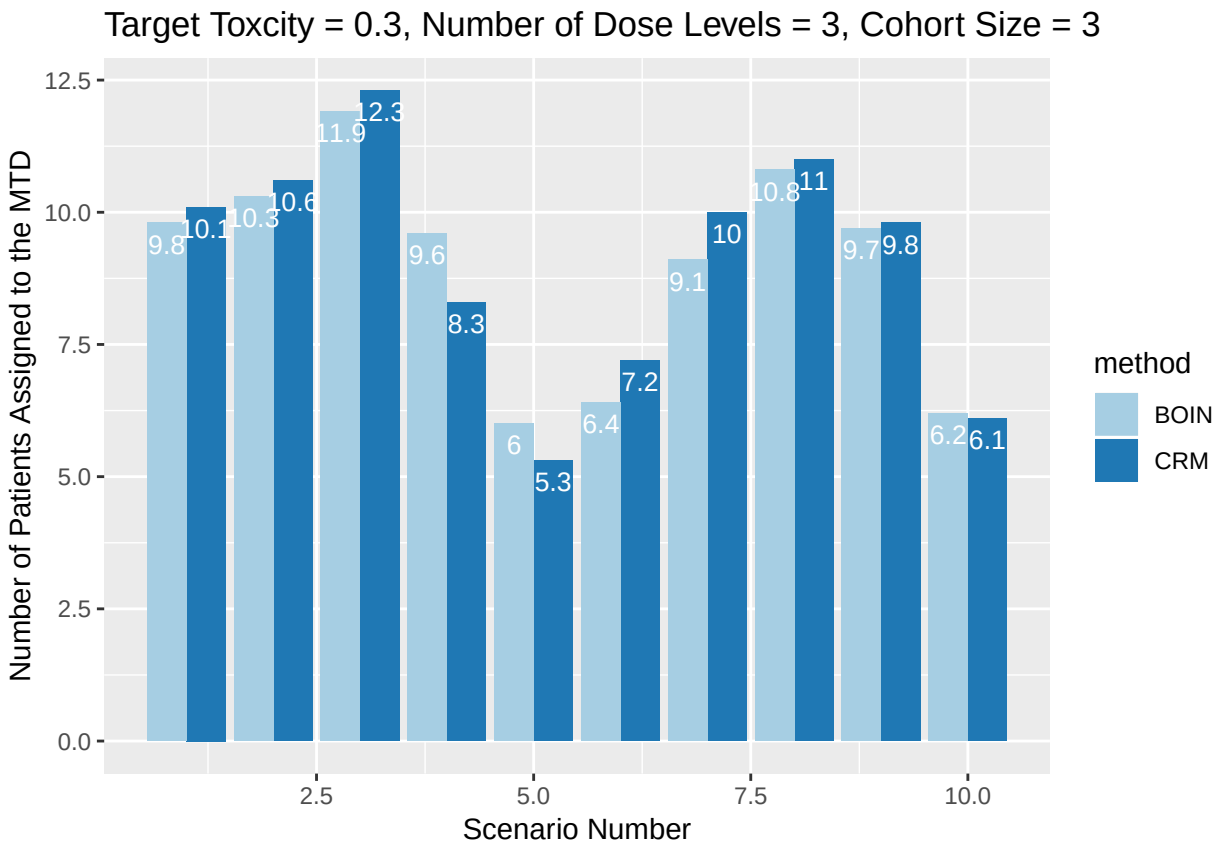
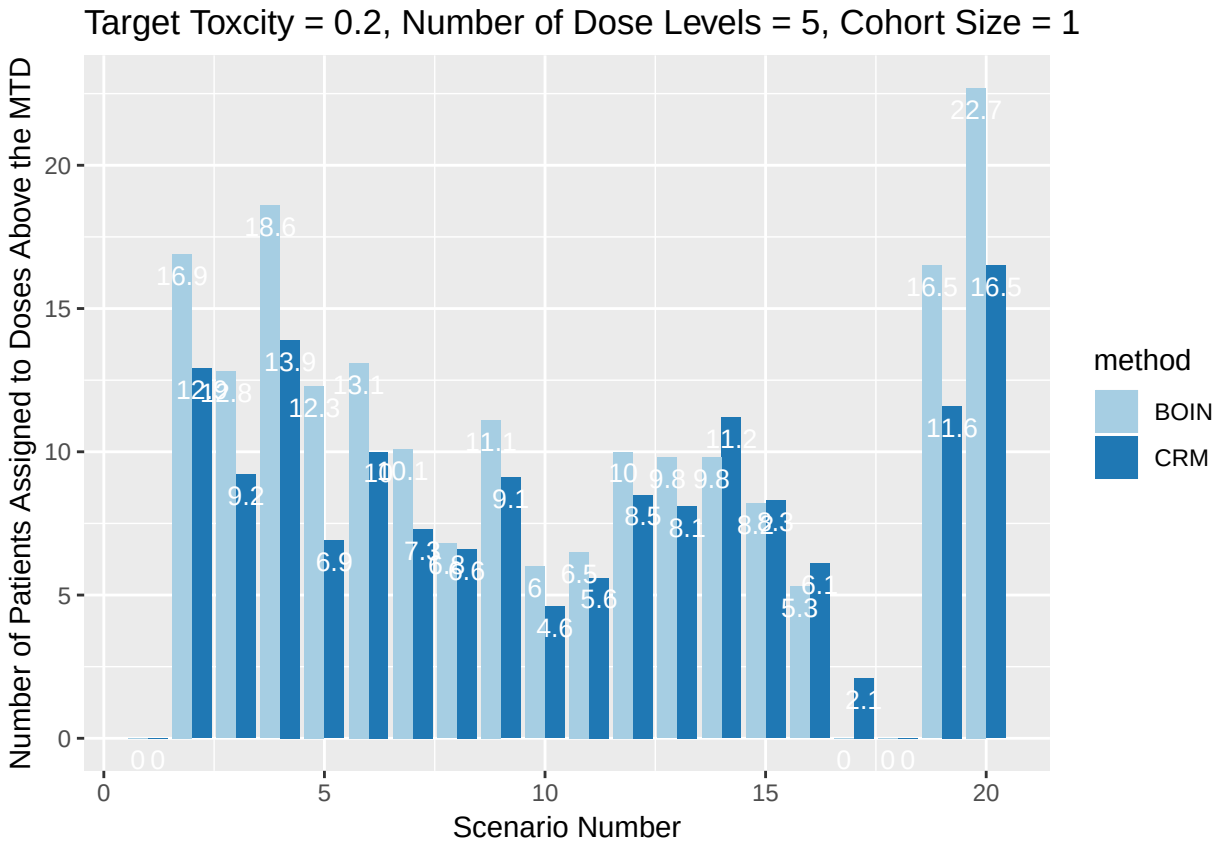


Figures to show the average number of patients assigned to the doses above the MTD (safety for patients in current trial)

Case 1: Target = 0.2 and the Number of Dose Levels = 5

Cohort Size = 1



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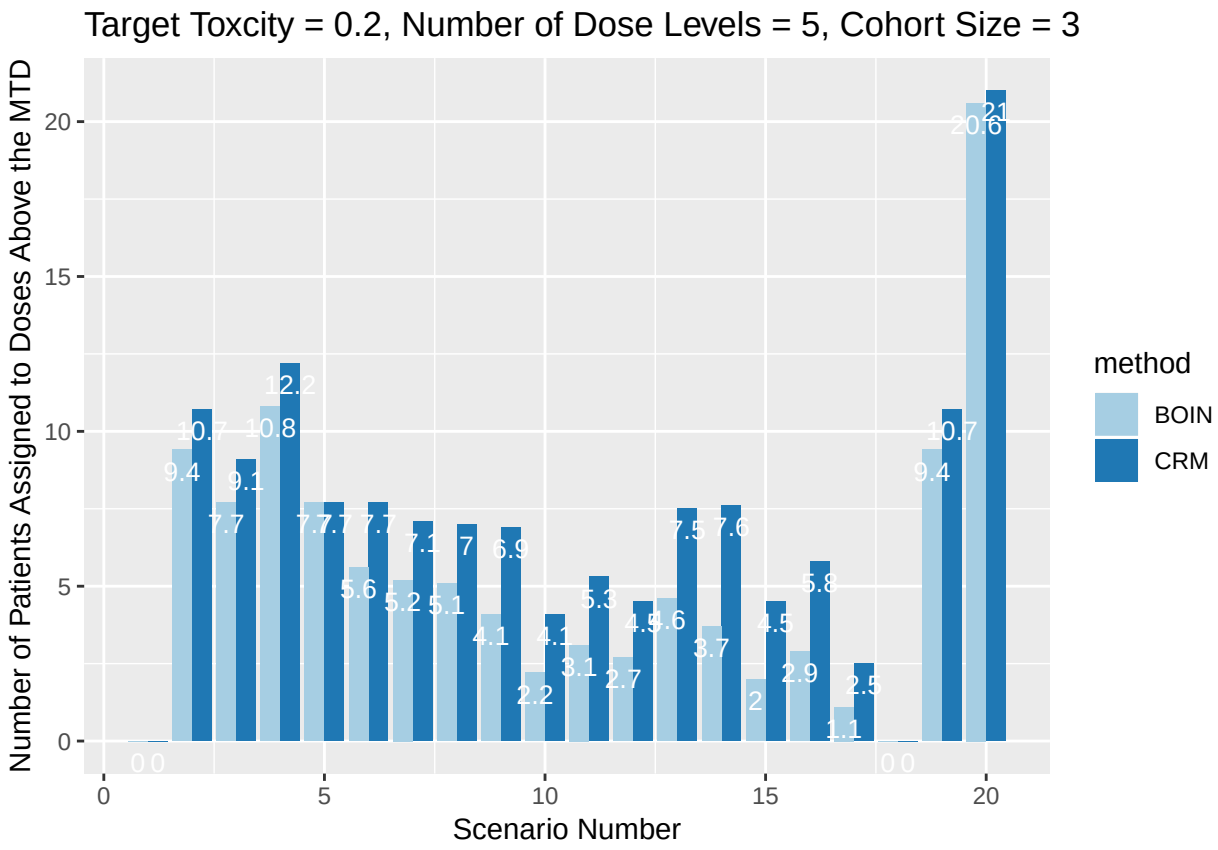
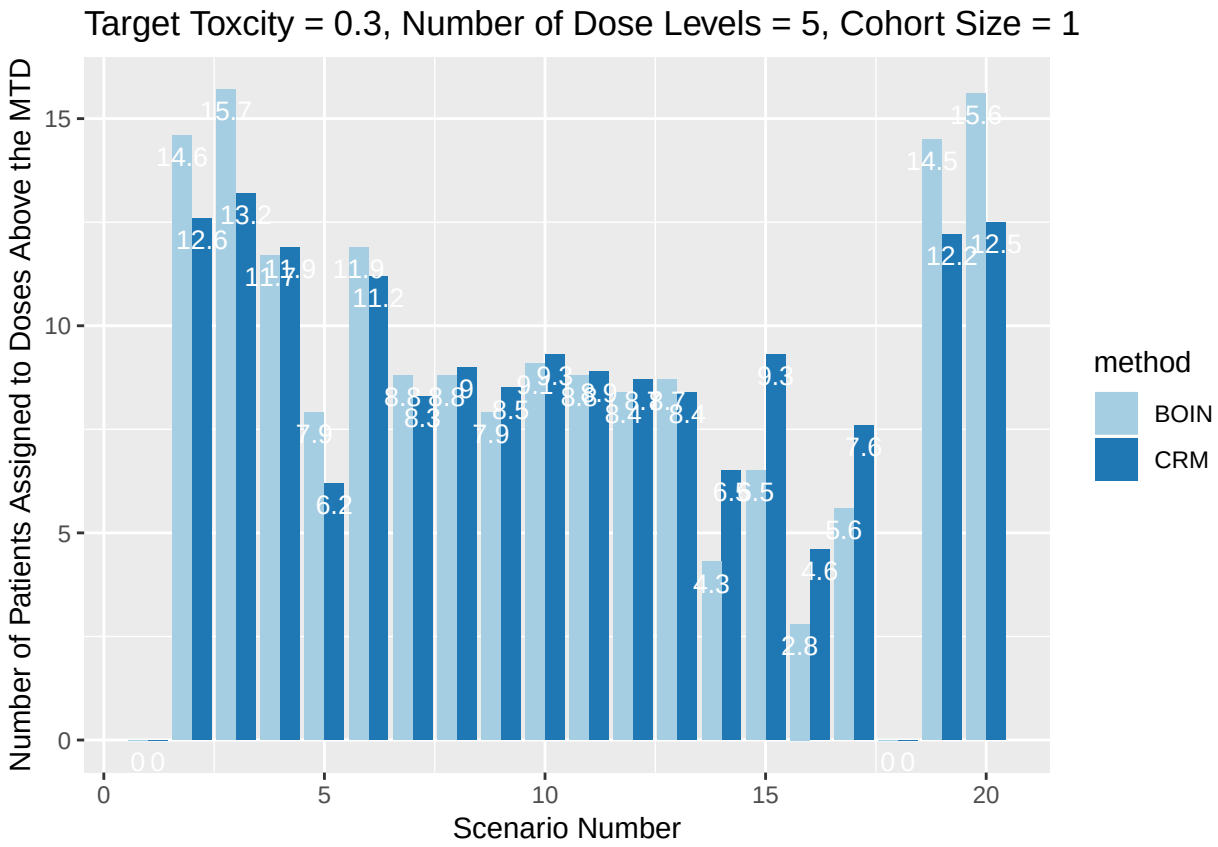


Case 2: Target = 0.3 and the Number of Dose Levels = 5

Cohort Size = 1



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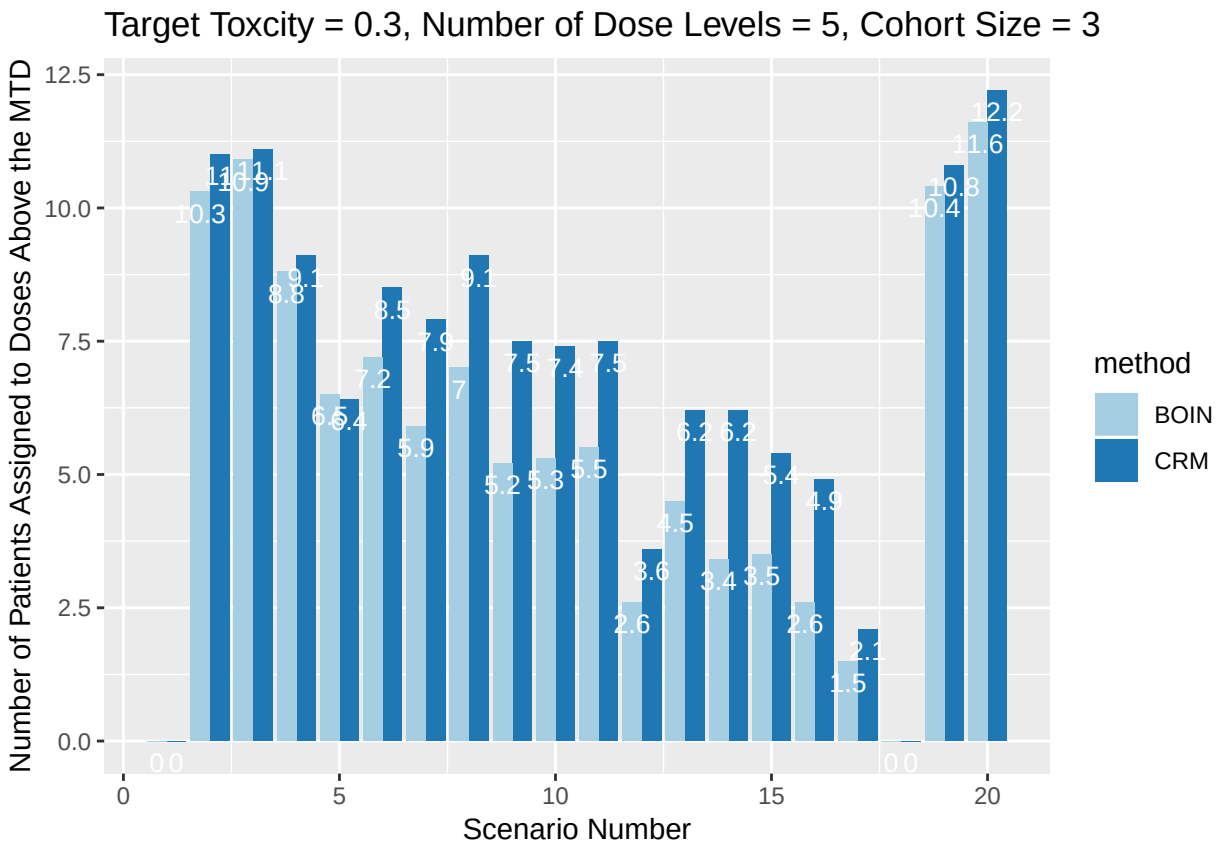
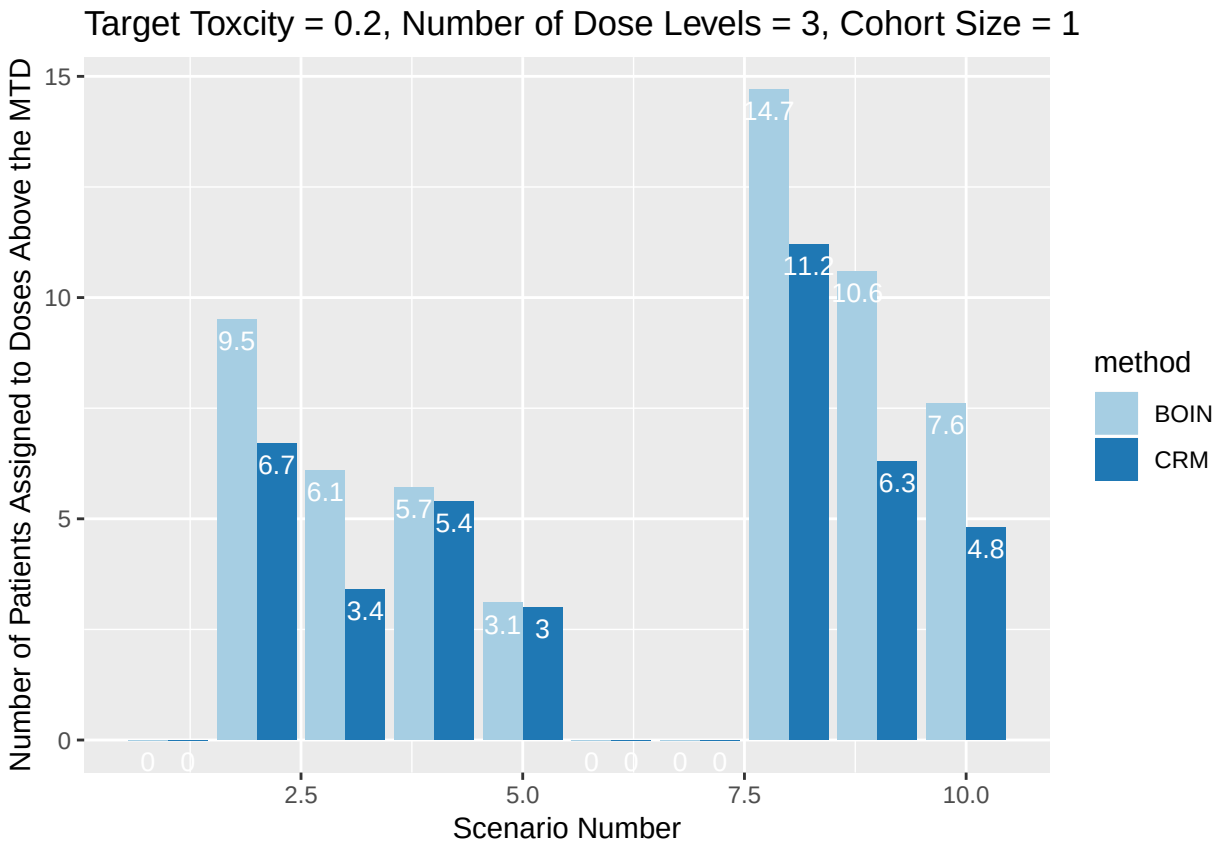


Case 3: Target = 0.2 and the Number of Dose Levels = 3

Cohort Size = 1



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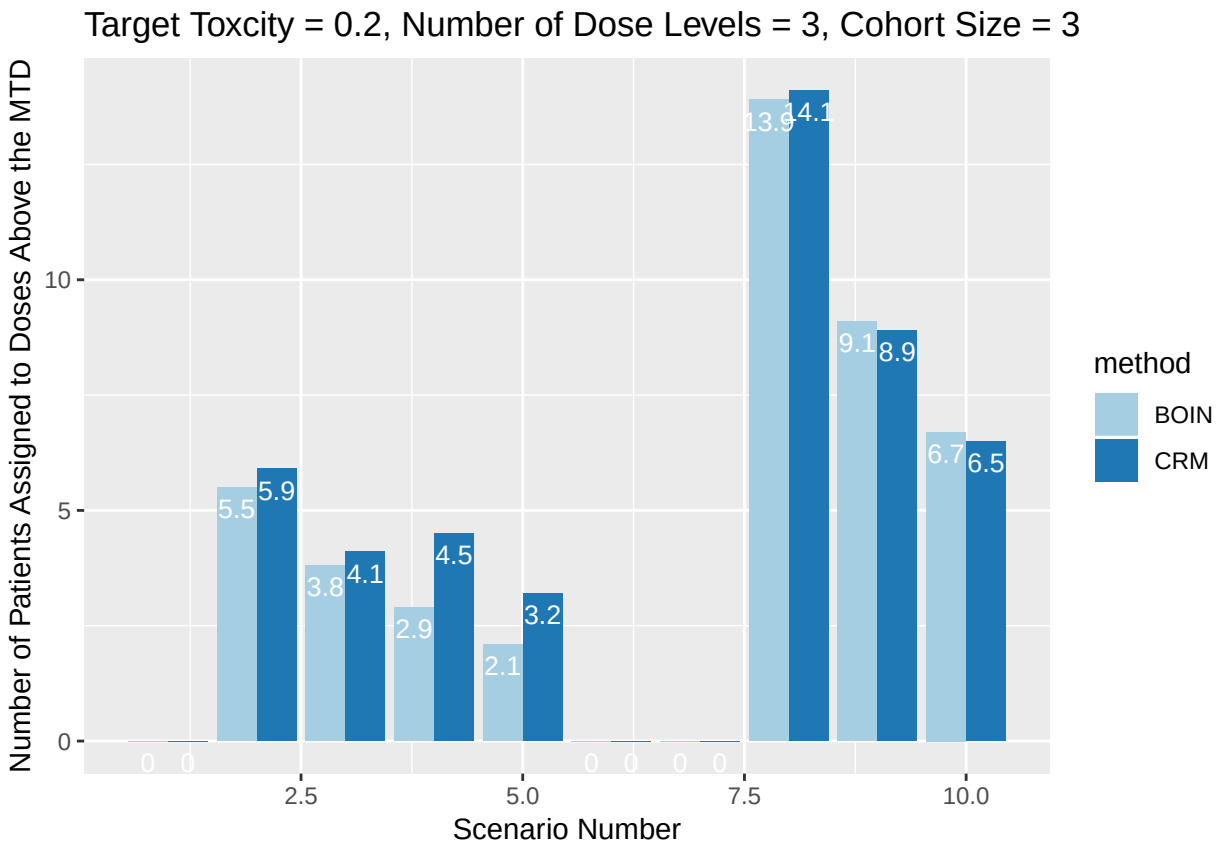
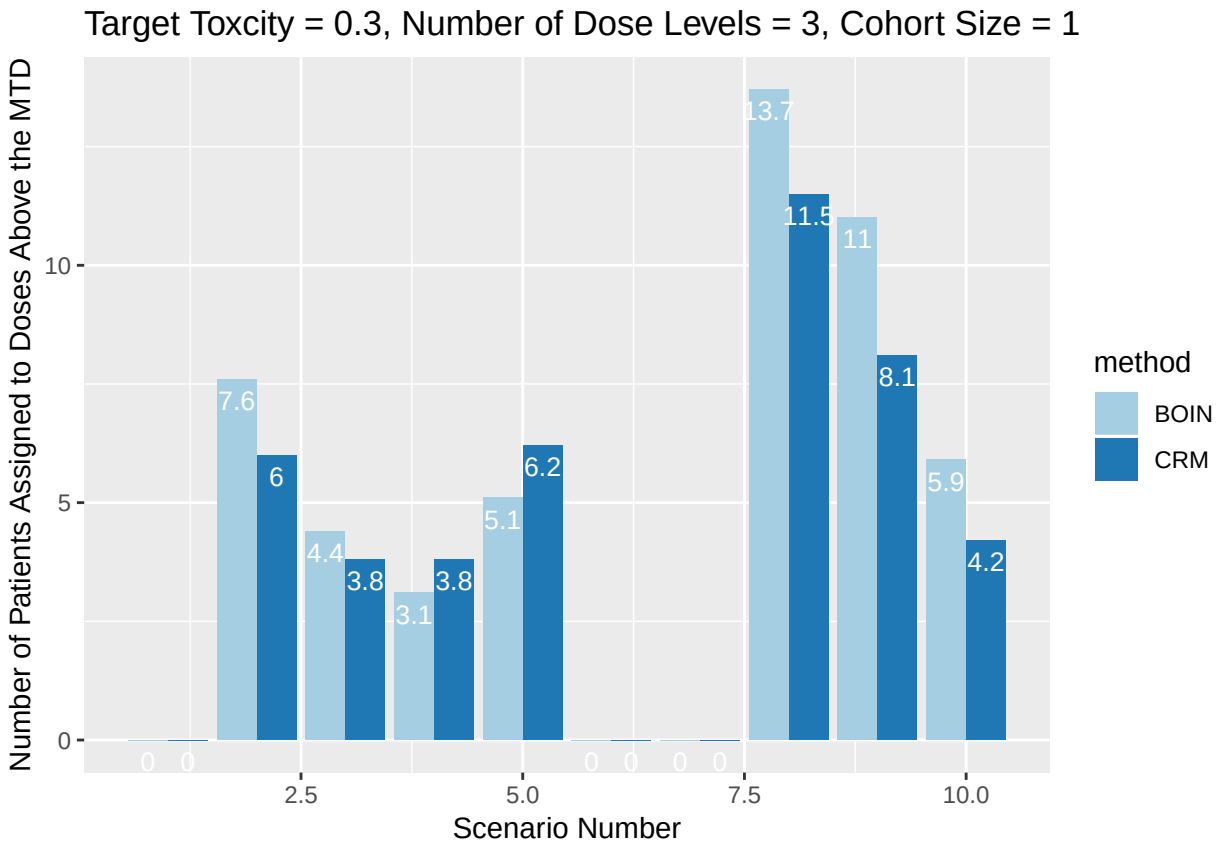


Case 4: Target = 0.3 and the Number of Dose Levels = 3

Cohort Size = 1



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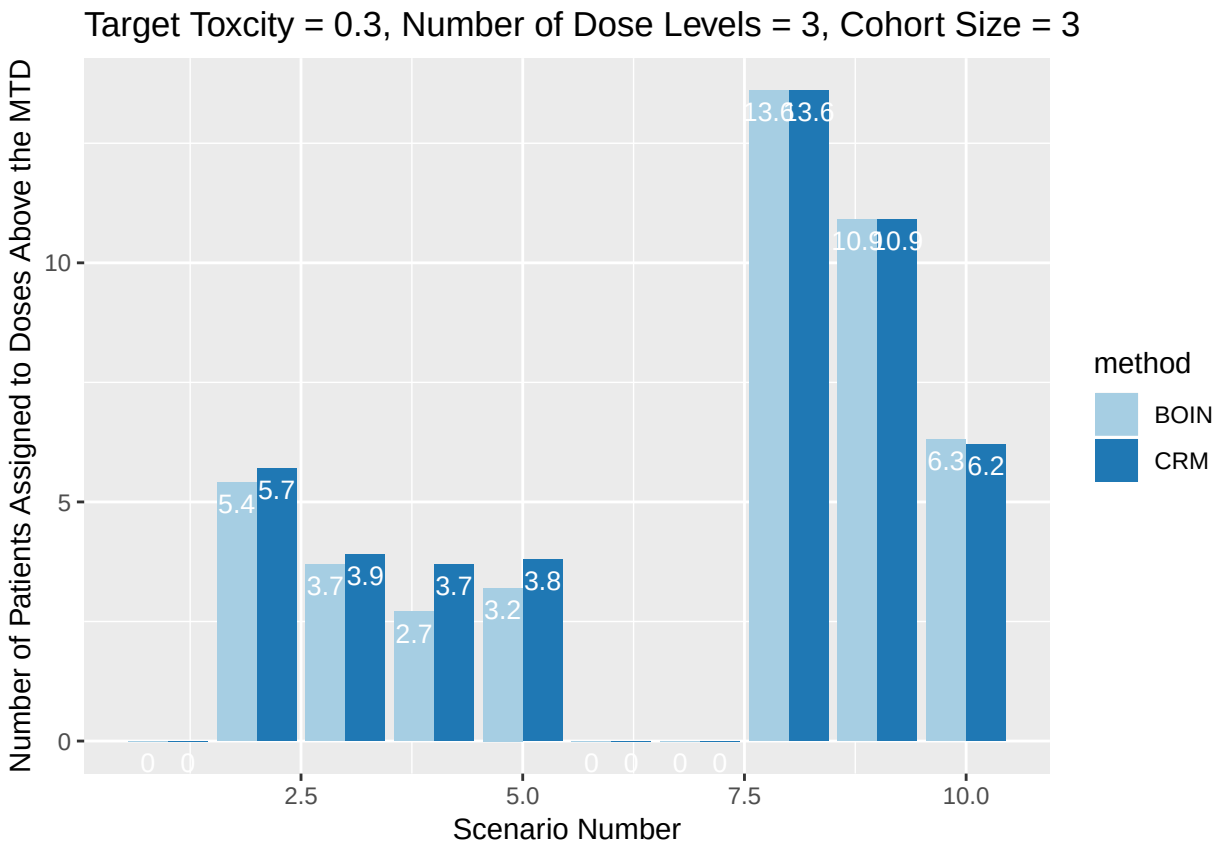
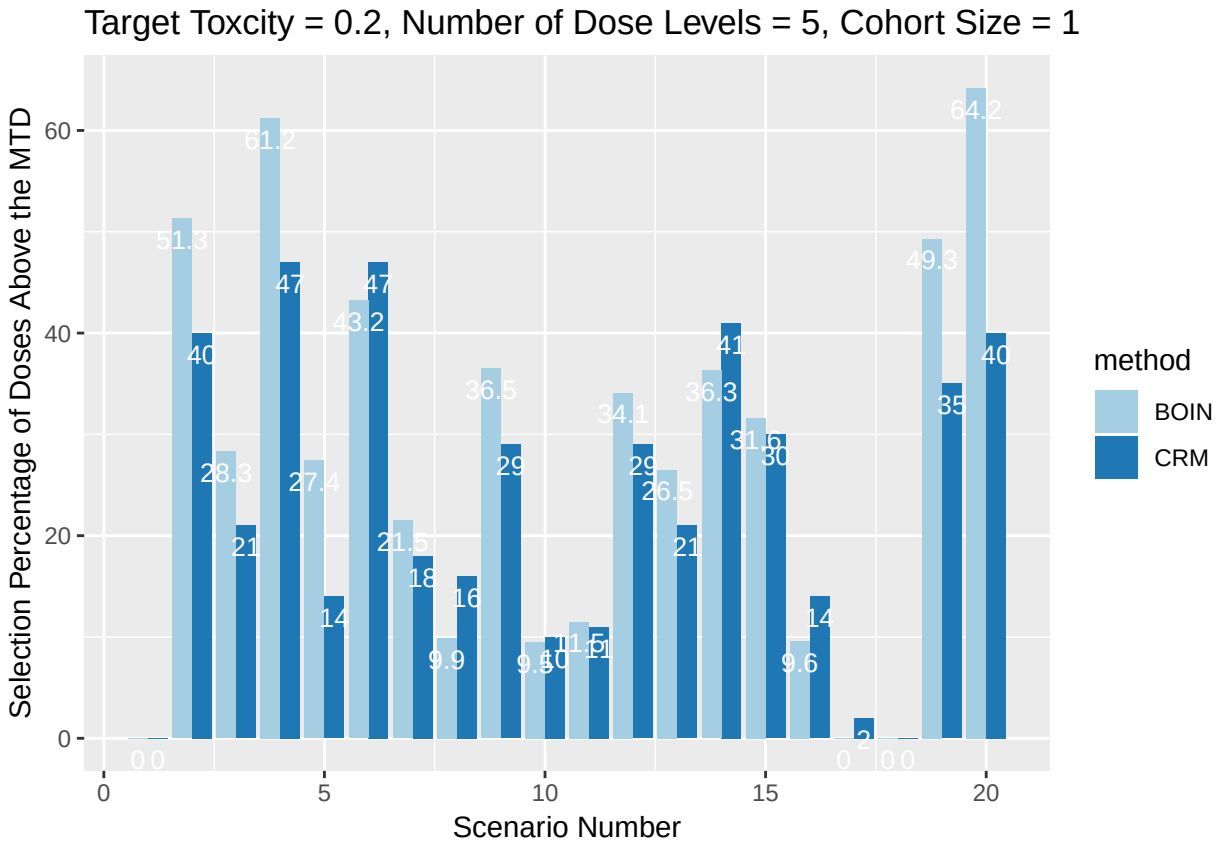


Figures to show the average selection percentage of the doses above the MTD (safety for patients for future trial)

Case 1: Target = 0.2 and the Number of Dose Levels = 5

Cohort Size = 1



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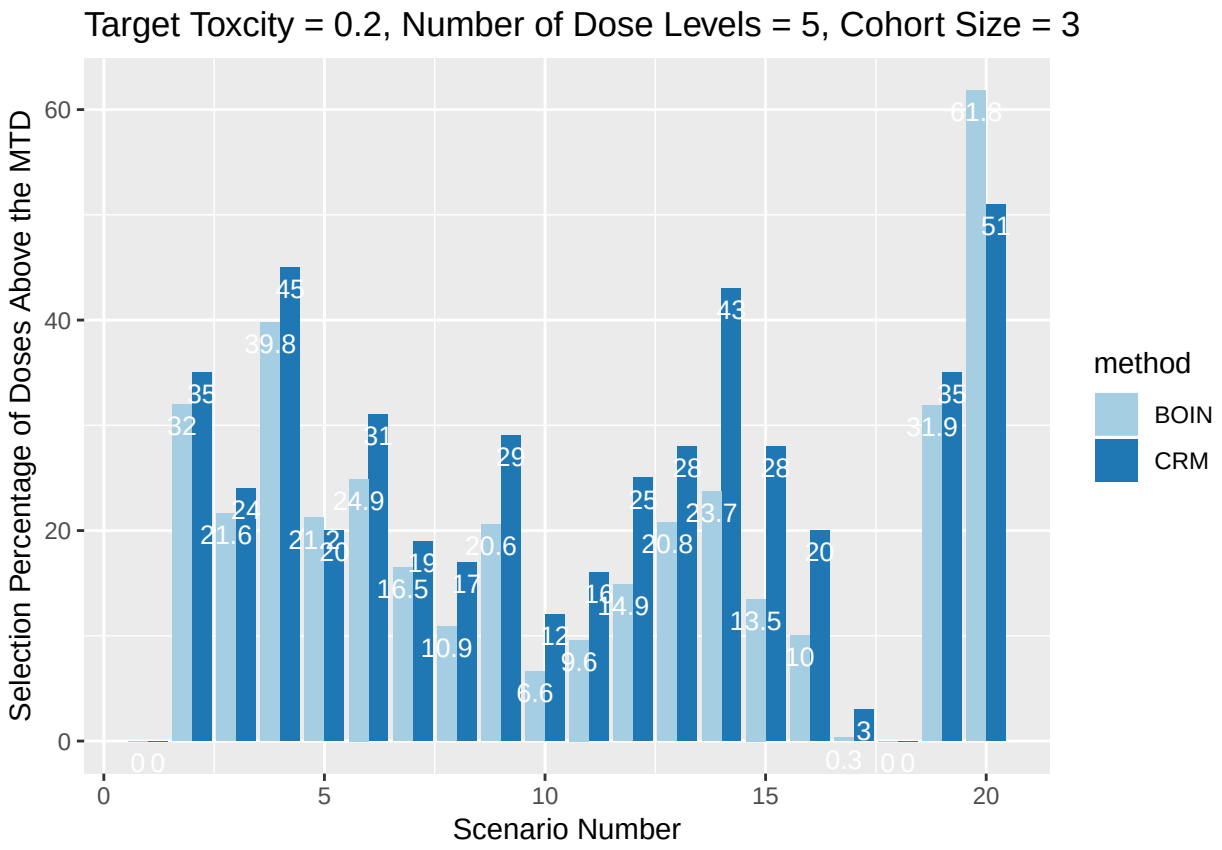
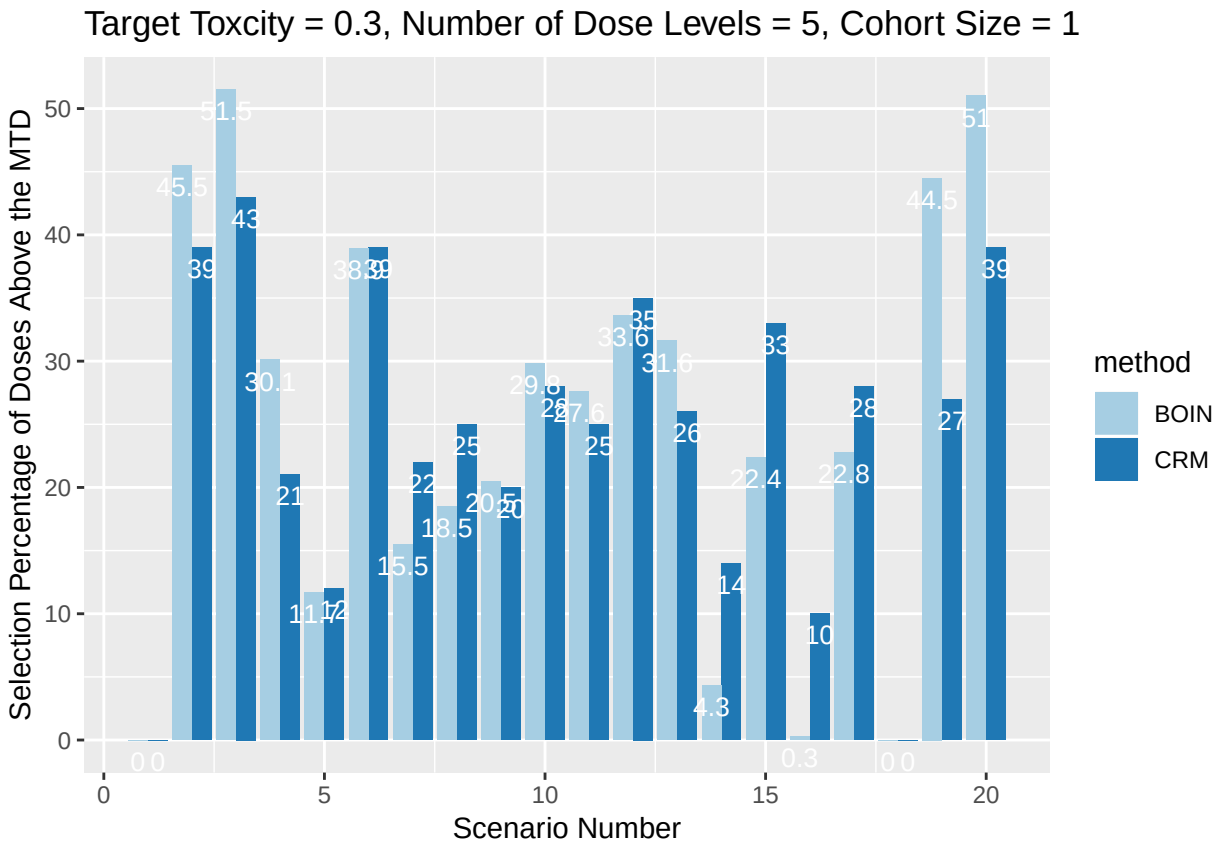


Case 2: Target = 0.3 and the Number of Dose Levels = 5

Cohort Size = 1



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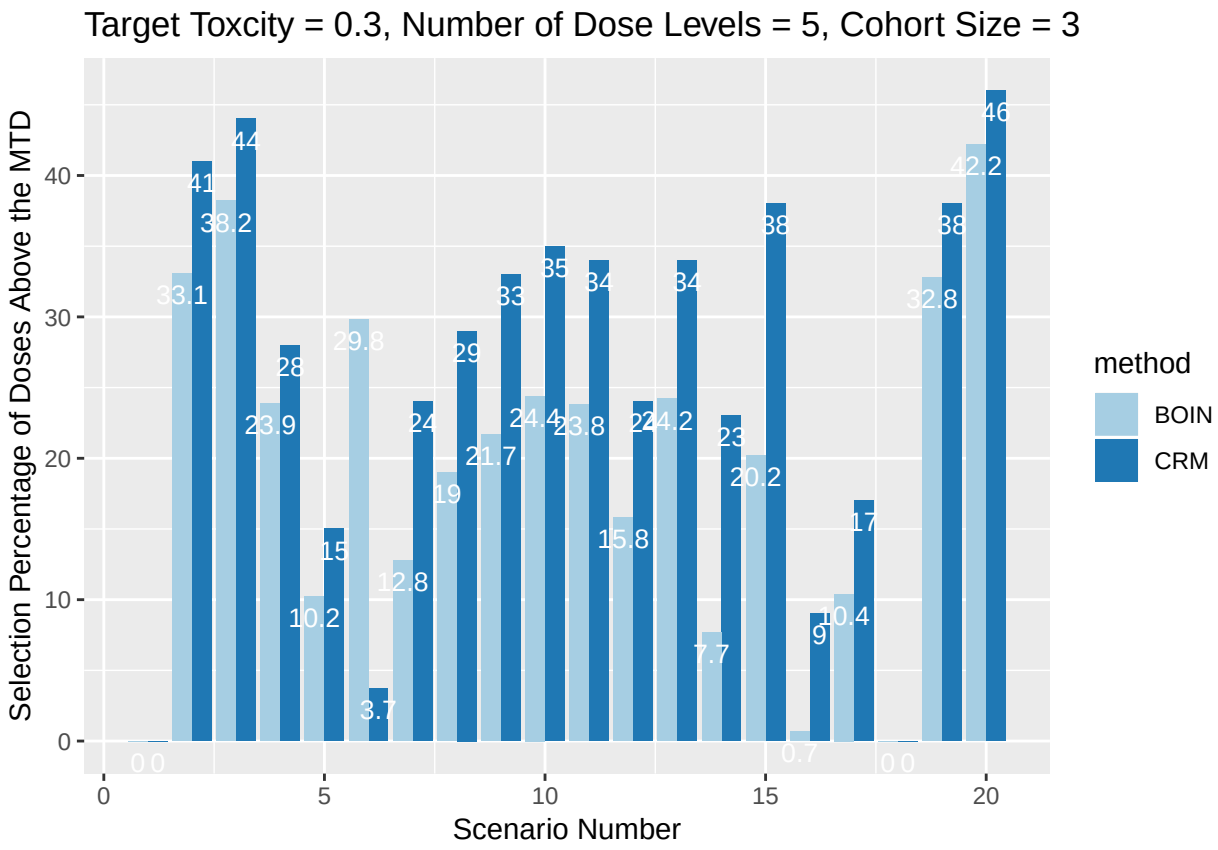
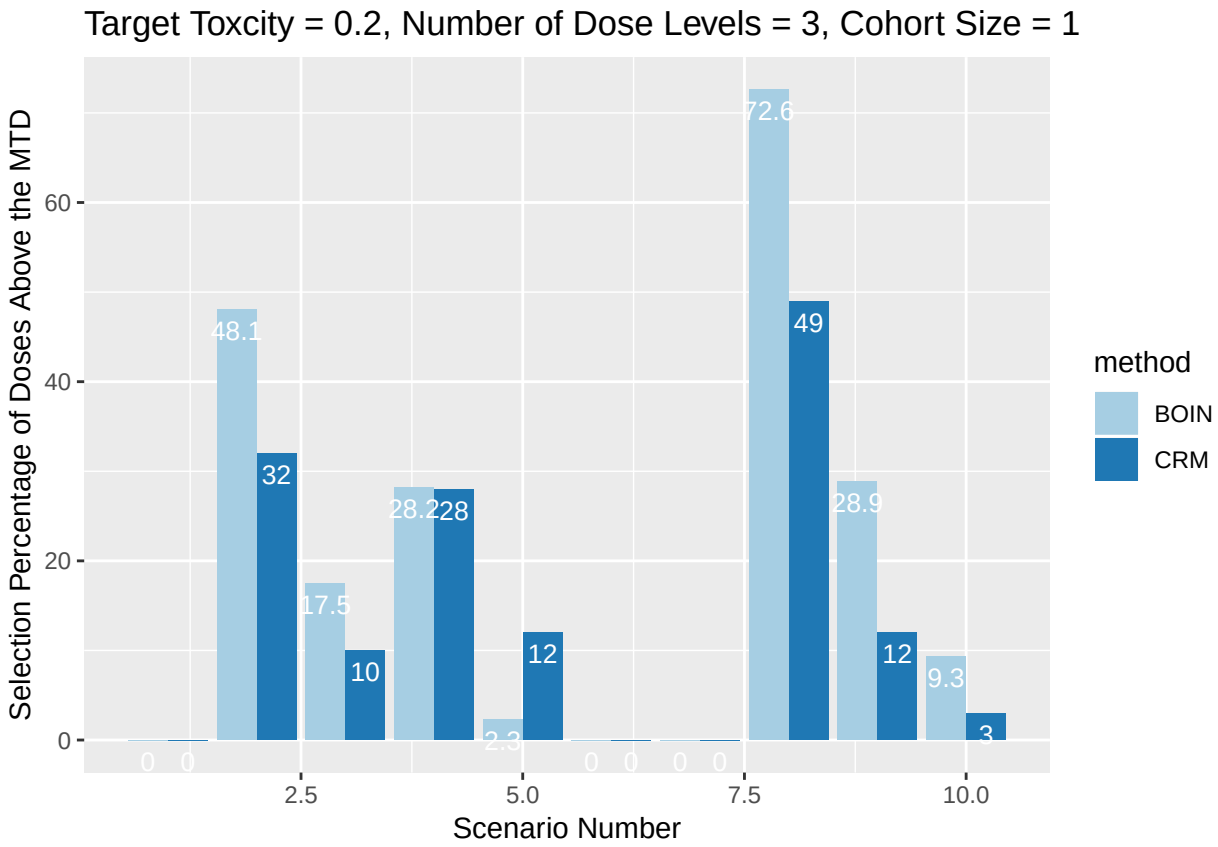


Case 3: Target = 0.2 and the Number of Dose Levels = 3

Cohort Size = 1



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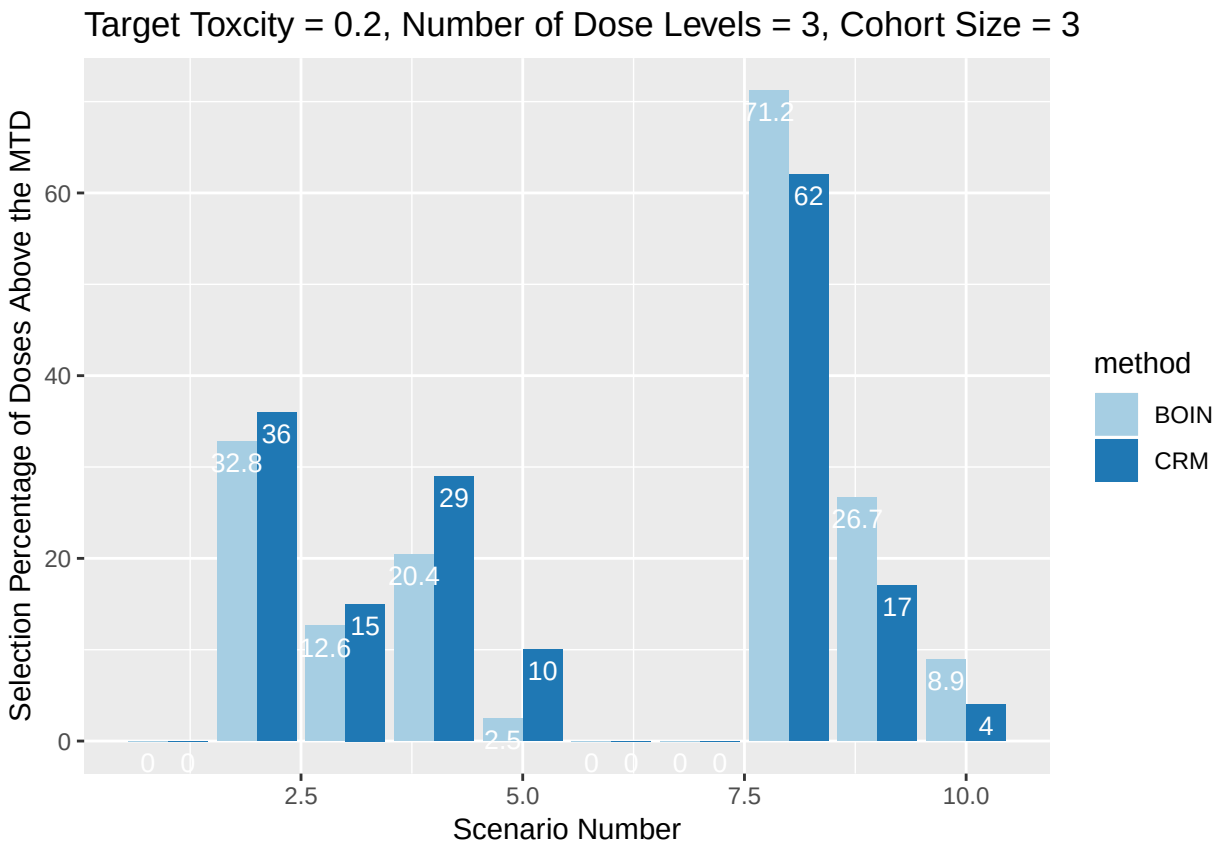
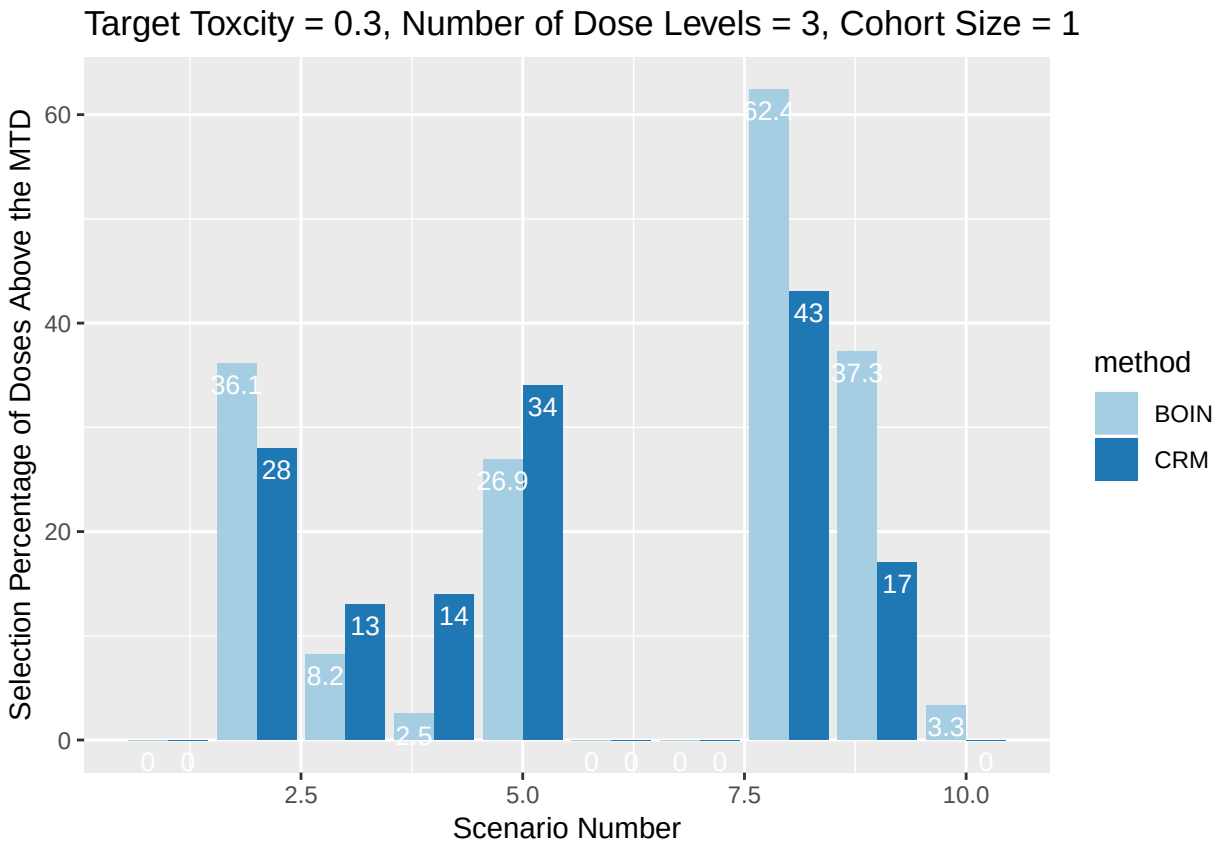


Case 4: Target = 0.3 and the Number of Dose Levels = 3

Cohort Size = 1



Cohort Size = 3