CFO suite User Guide

Contents

1 CFO designs for phase I clinical trial

The CFO suite is designed to perform real trials and single or multiple simulations. For real trials, it provides functions to determine the next cohort dose. It also facilitates the selection of the maximum tolerated dose (MTD) upon completion of dose assignments in a real trial. In the context of simulation trials, the CFO suite executes one or multiple simulations of a CFO-type design, obtaining relevant operating characteristics.

1.1 Real trial: Dose determination for next cohort

Click **Dose for Next Cohort** (shown in Figure 1), and enter design parameters (e.g., the target DLT rate, current dose level, ...).

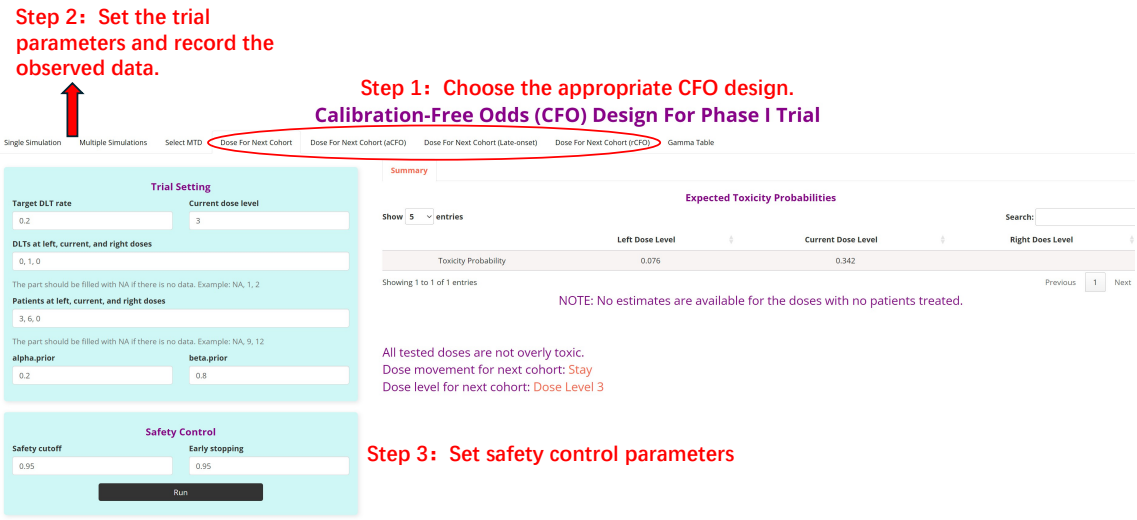

Figure 1: Main Interface of CFO Suite

1.1.1 Step-by-step instructions

(1) Choose the appropriate CFO design.

The App can be used in two scenarios: with late-onset toxicity or without late-onset toxicity. For scenarios without late-onset toxicity, the **Dose for Next Cohort** tab follows the standard CFO design, which offers two variants: aCFO and rCFO. For scenarios considering late-onset toxicity, the **Dose for Next Cohort (with Late-onset)** tab provides an appropriate adjustment.

(2) Set the trial parameters and record the observed data.

(2a) The CFO and rCFO designs

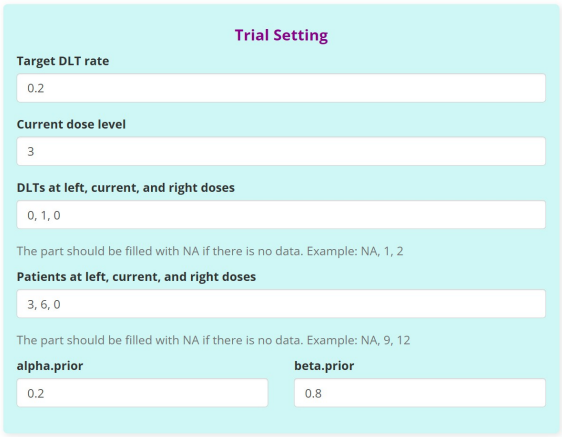

Figure 2: Trial configuration interface under **Dose for Next Cohort (CFO)** tab and **Dose for Next Cohort (rCFO)** tab

Remark 1: **DLTs at left, current, and right doses** should be filled in with the observed DLT results at different dose levels. For example, `0,1,0` indicates that one DLT outcome has been observed so far at the dose level used for the current cohort (the third dose level in this example), with no DLT outcomes at the adjacent left (dose level 2) or right (dose level 4) doses. When there is no data available on the left or right of the current dose—for example, if the current cohort is treated at the first dose level, meaning there is no lower dose— use `NA` for the missing data. For instance, if the current dose is 1 (with no dose to the left), the data is filled in as `NA,1,0`, which means one DLT was observed at the current dose, no DLT was observed at the right dose, and there is no dose level on the left. **Patients at left, current, and right doses** is also set in a similar way.

Remark 2: **alpha.prior** and **beta.prior** are used to set the prior distribution for the DLT rate. The beta distribution Beta(alpha.prior, beta.prior) is used here.

(2b) The aCFO design

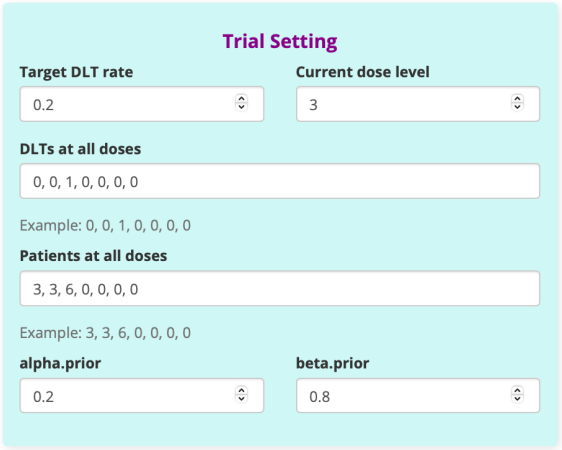

Figure 3: Trial configuration interface under the **Dose for Next Cohort (aCFO)** tab

The settings here are essentially the same as those in **Dose for Next Cohort.** The only difference is that you need to enter all observed data from the lowest to the highest dose level. As shown in the example in the figure 3, the vector `3, 3, 6, 0, 0, 0, 0` indicates that seven doses to be tested in the entire trial. Results from the first to the

current cohort show that 3 patients were treated at dose level 1, 3 at dose level 2, and 6 at dose level 3. The vector `0, 0, 1, 0, 0, 0, 0` shows that one DLT outcome was observed at dose level 3, while no DLT outcomes were observed at the other dose levels.

(2c) Designs with late-onset toxicity

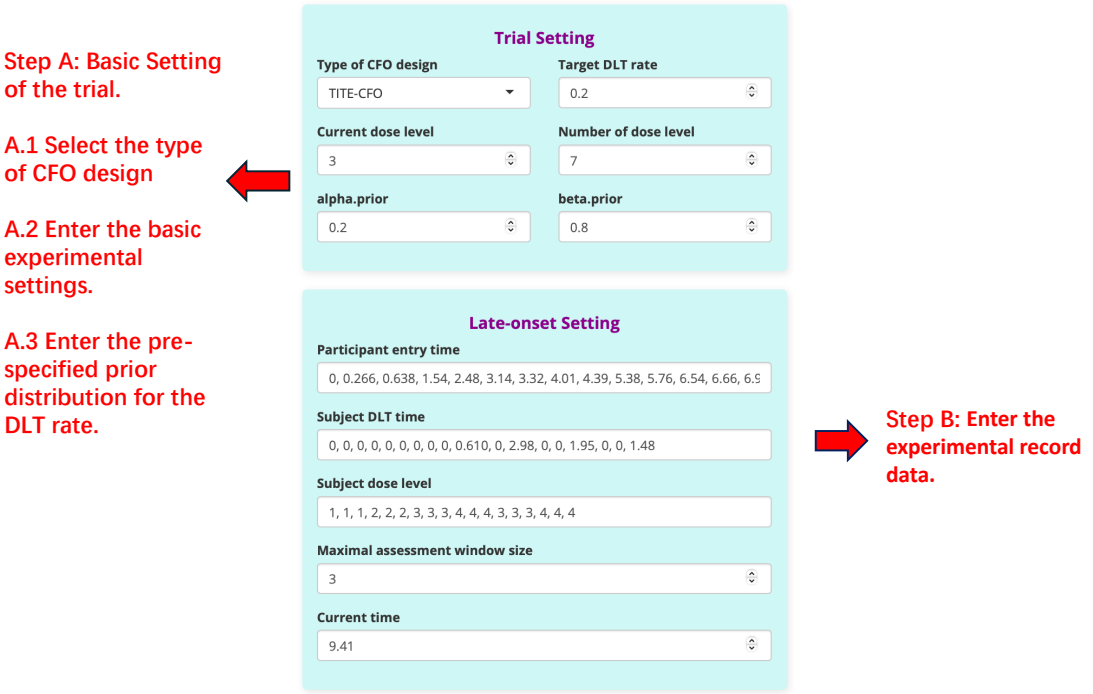

Figure 4: Trial configuration interface under the **Dose for Next Cohort (late-onset)** tab

The data encompasses all records from the first enrolled cohort up to the current cohort in the trial. This includes the entry time of each cohort and the dose level treated. If a DLT outcome occurs, the time from treatment to the observation of the DLT outcome should also be recorded.

(3) Set safety control parameters

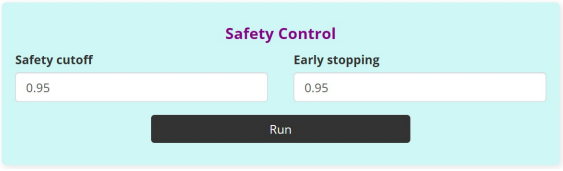

Figure 5: Safety control interface

For safety, early stopping and dose elimination rules are adopted. Any dose level identified as overly toxic, as well as all the higher dose levels, are eliminated. If the lowest dose level is overly toxic, the trial will be terminated according to the early stopping rule. The **Safety cutoff** and **Early stopping** tabs respectively set the thresholds for removing over-toxic doses from the trial and stopping the entire trial due to excessive drug toxicity.

1.1.2 Result Analysis

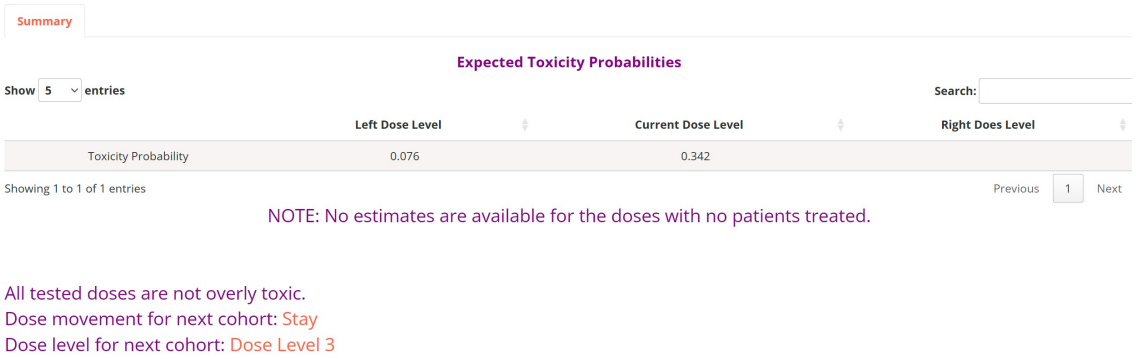

Figure 6: An example of determining the dose level for the next cohort using the CFO suite

The results are presented in two parts: the expected toxicity probability and the dose recommendation. The first part provides the estimates of the probability of toxicity for each dose level, based on observed data. The second part displays the dose escalation or de-escalation decision, along with the recommended dose for the next cohort. For example, as shown in Figure 6, the trial is recommended to continue at dose level 3. Additionally, none of the tested dose levels may be identified as excessively toxic.

If a dose level is deemed excessively toxic, the result shown in Figure 7 indicates that dose level 3 and higher doses are too toxic and should be excluded from the trial.

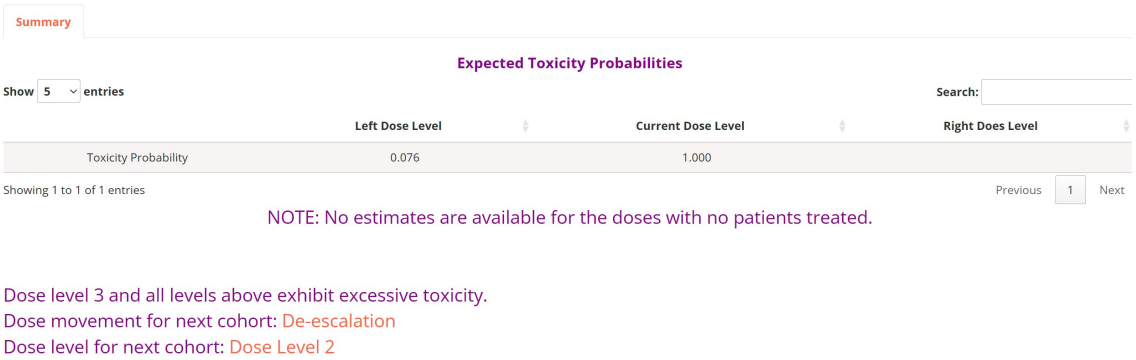

Figure 7: An example demonstrating an overly toxic scenario

1.2 Real trial: MTD selection

Figure 8: Main interface

1.2.1 Step-by-step instructions

(1) Choose **Select MTD** tab

Remark: Regardless of which CFO design is used, the final summarization of results is performed using the functionality provided in this tab for estimation.

(2) Enter the trial design and the recorded results

After the trial is completed, input the results for all tested doses, along with the pre-specified target and the prior distribution parameters for the DLT rate.

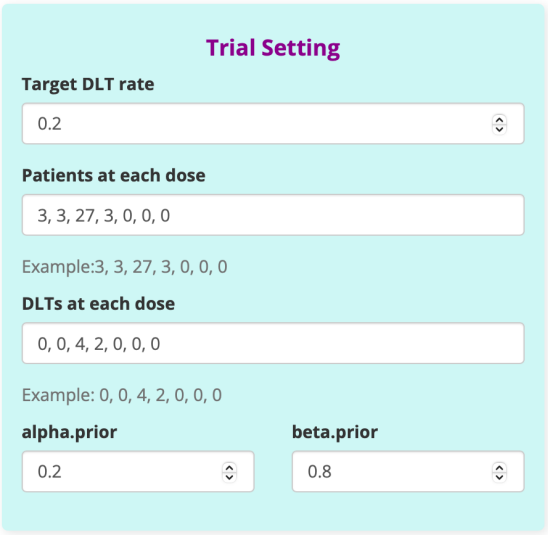

Figure 9: Trial configuration interface under the **Select MTD** tab

(3) Set the safety control threshold

Figure 10: Safety control interface

1.2.2 Results Analysis

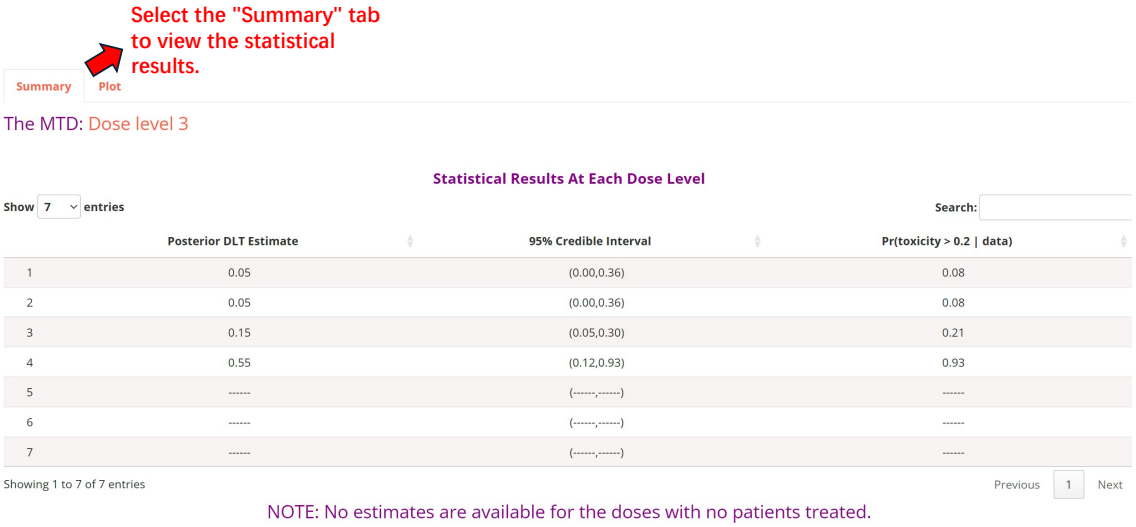

Figure 11: An example of selecting the MTD based on complete trial data using the CFO suite

Select the **Summary** tab to view the estimation results based on the observed data, including the final MTD and the corresponding estimates of the DLT rate at different dose levels. The **Statistical Results At Each Dose Level** table displays the DLT rate-related results. For dose levels that are not administered to any patients, no results are displayed, and these levels are represented by `------`. For a more intuitive visualization of the statistical results, relevant charts display the estimated DLT rate along with its confidence interval. To view this plot, select the **Plot** tab, as shown in Figure 12.

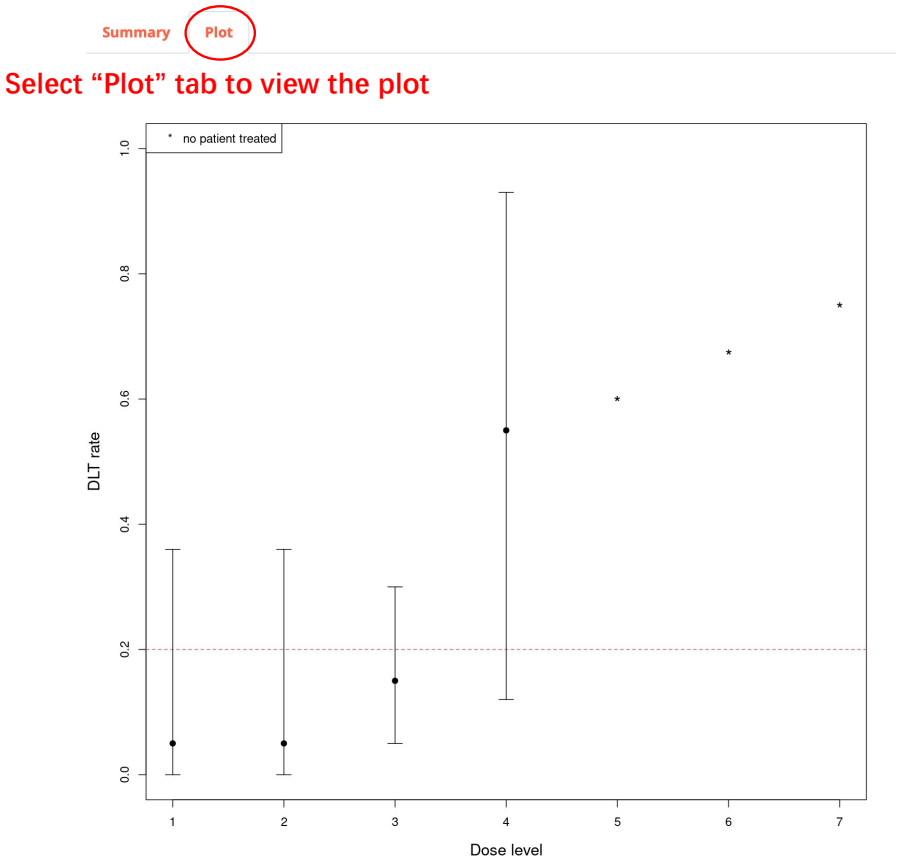

Figure 12: Plot displaying confidence intervals, mean estimates, and the target DLT rate indicated by a red dashed line

1.3 Simulation

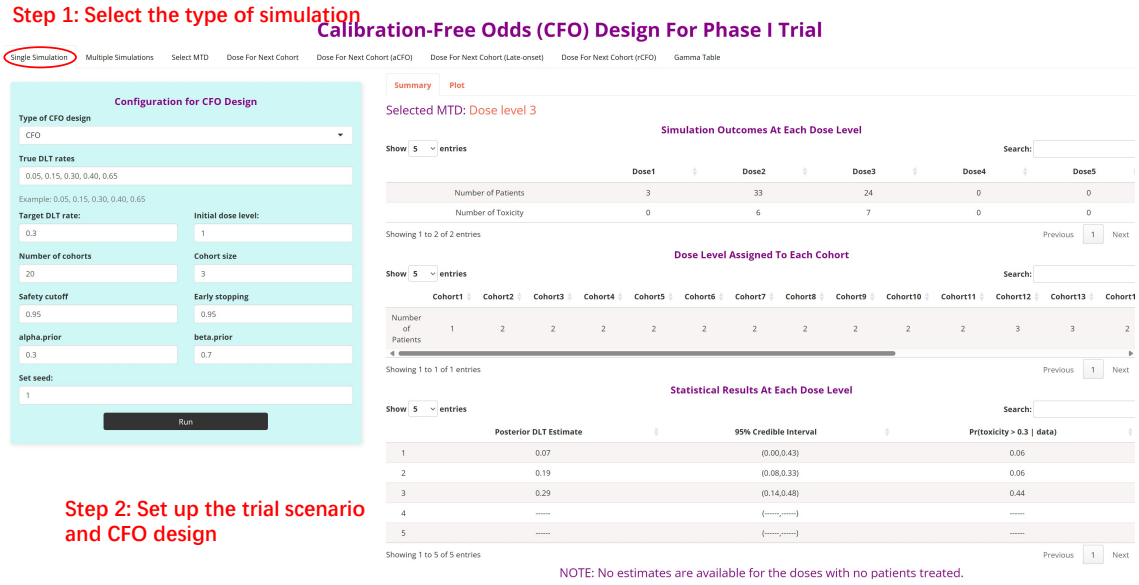

Figure 13: Main interface

1.3.1 Step-by-step instructions

(1) Select the type of simulation

Several simulation scenarios are available, including **Single Simulation** and **Multiple Simulation**, each corresponding to different needs. **Single Simulation** allows the use of the CFO design and its variants to perform a single simulation without late-onset toxicity. To conduct multiple simulations for a more comprehensive analysis, select the **Multiple Simulation** tab.

(2) Set up the trial scenario and CFO design

The CFO design parameter configuration interfaces under the **Multiple Simulation** and **Single Simulation** tabs are nearly identical, except that the "Number of simulations setting" is not required in the **Single Simulation** tab. The following instructions use the **Multiple Simulation** tab as an example.

Figure 14: CFO design parameter configuration interface under the **Multiple Simulation** tab

In the first step, select the CFO design you wish to use. This includes CFO designs that account for late-onset toxicities. Then, set the **seed** to initialize the random number generator, ensuring the reproducibility of the random process. Finally, specify the parameters for the prior distribution of the DLT rate, which follows a Beta distribution. When choosing `CFO`, `aCFO`, or `rCFO`, the CFO settings interface will appear as shown in Figure 15.

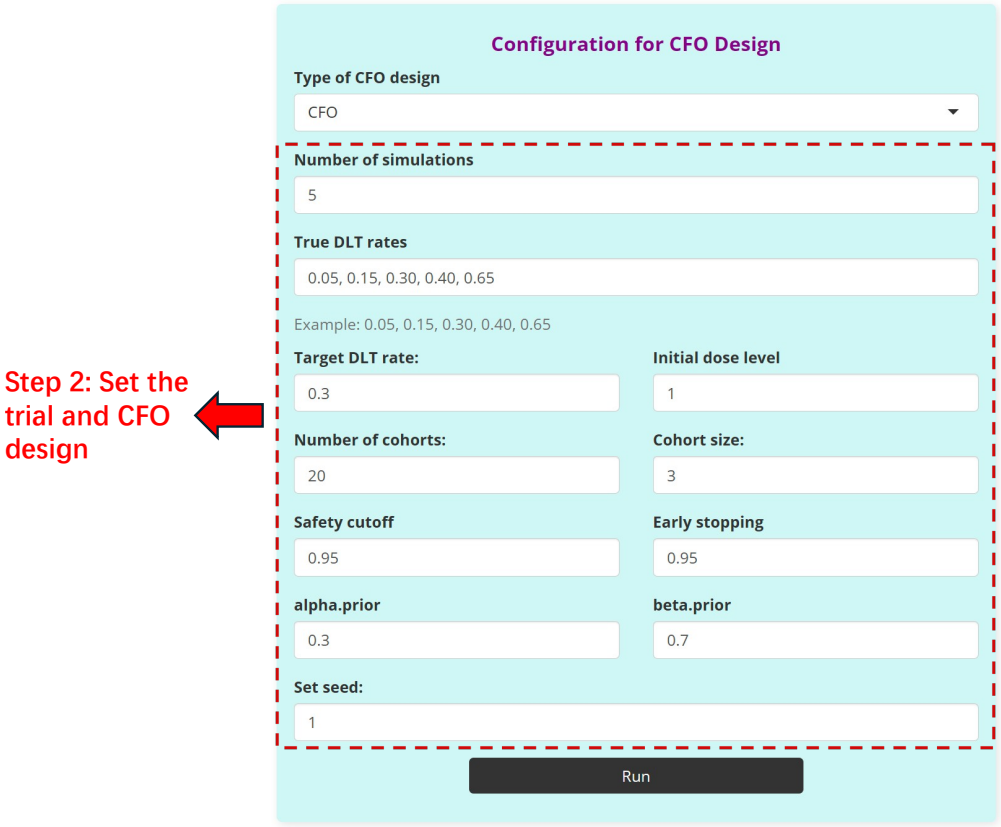

Figure 15: CFO design parameter configuration interface under the **Multiple Simulation** tab

If you select `TITE-CFO`, `TITE-aCFO`, `fCFO`, or `f-aCFO`, additional settings will be required. In this case, the CFO settings interface will appear as shown in the figure 16.

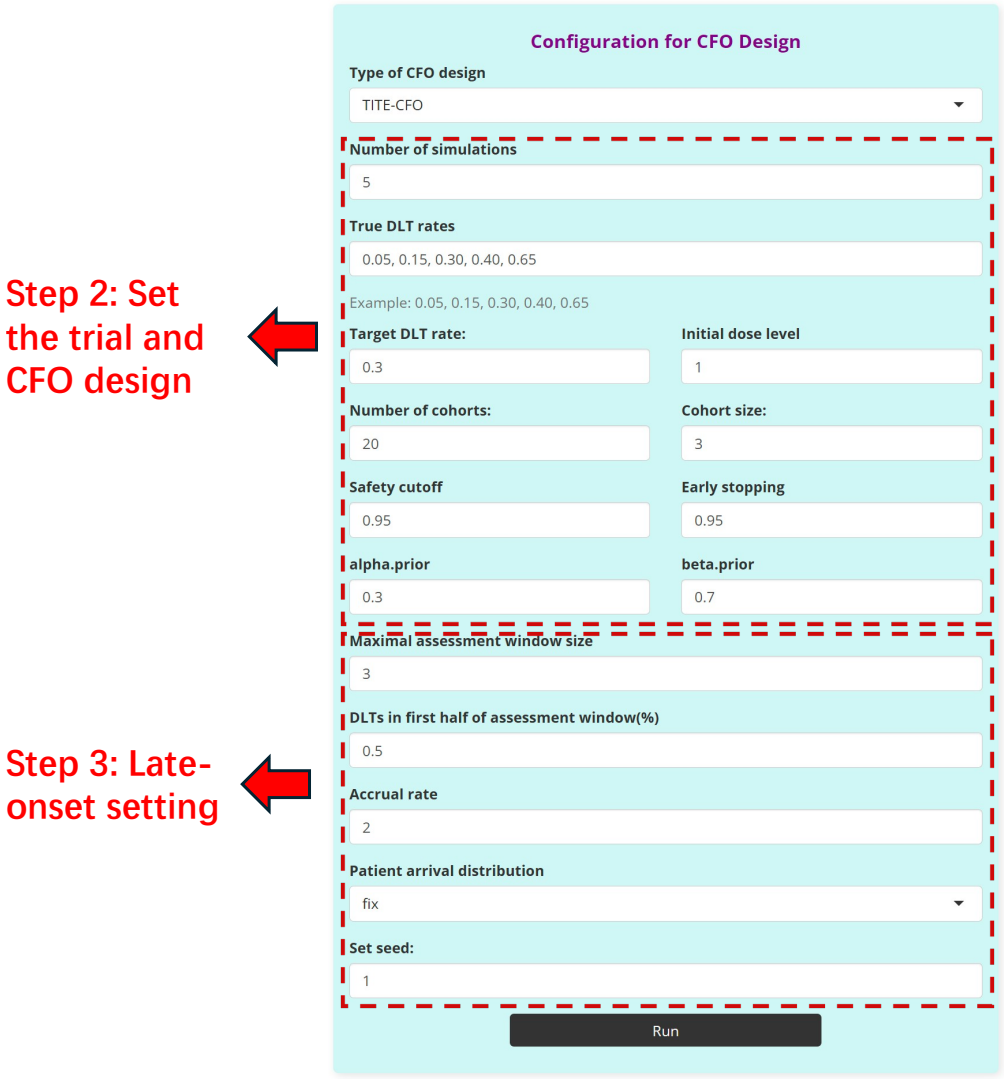

Figure 16: CFO design parameter configuration interface under the **Multiple Simulation** tab

Remark: Explanation of the option of **Patient arrival distribution**. When set to `fix`, patients in each cohort arrive simultaneously at a given rate. When set to `unif`, arrivals follow a uniform distribution, and when set to `exp`, they follow an exponential distribution.

1.3.2 Result Analysis

(a) **Single Simulation**

When choosing `CFO`, `aCFO`, or `rCFO`

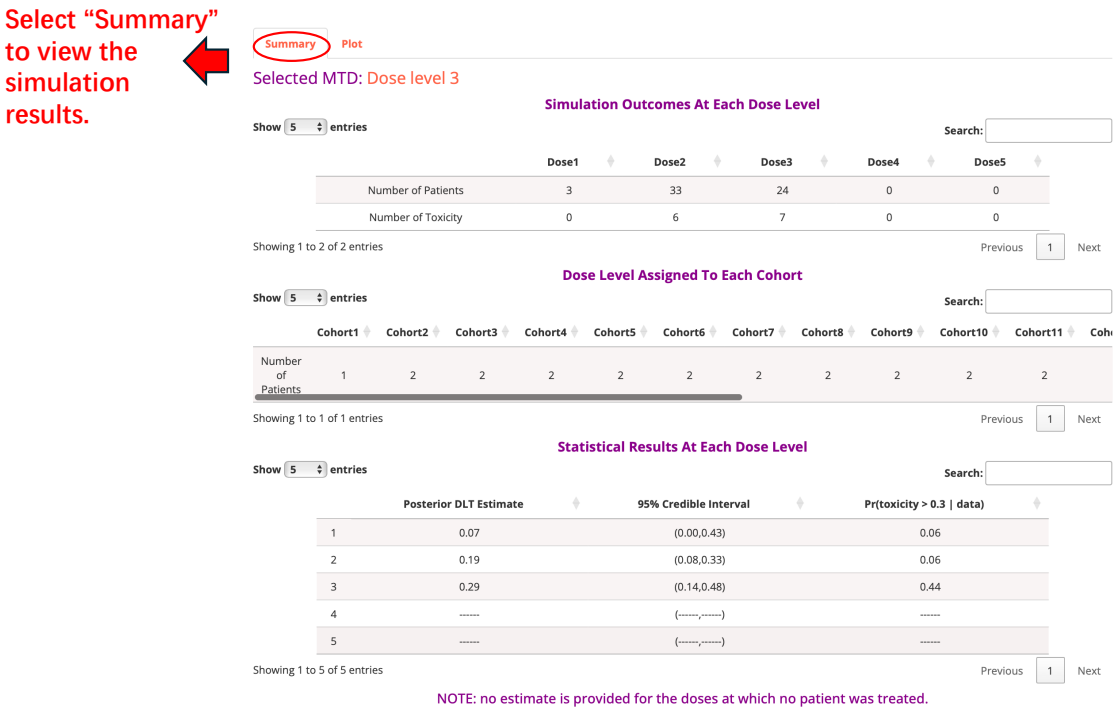

Figure 17: An example of performing a single CFO simulation using the CFO suite

When choosing `TITE-CFO`, `TITE-aCFO`, `fCFO`, or `f-aCFO`

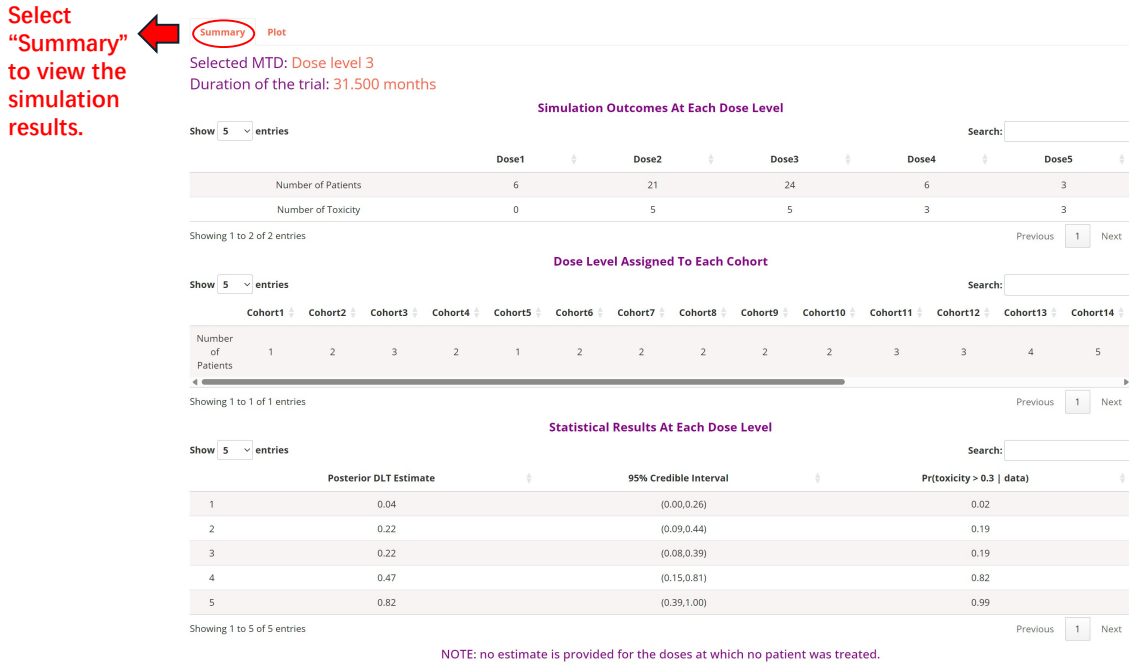

Figure 18: An example of performing a single CFO simulation considering late-onset toxicity using the CFO suite.

(b) **Multiple Simulation**

When choosing `CFO`, `aCFO`, or `rCFO`

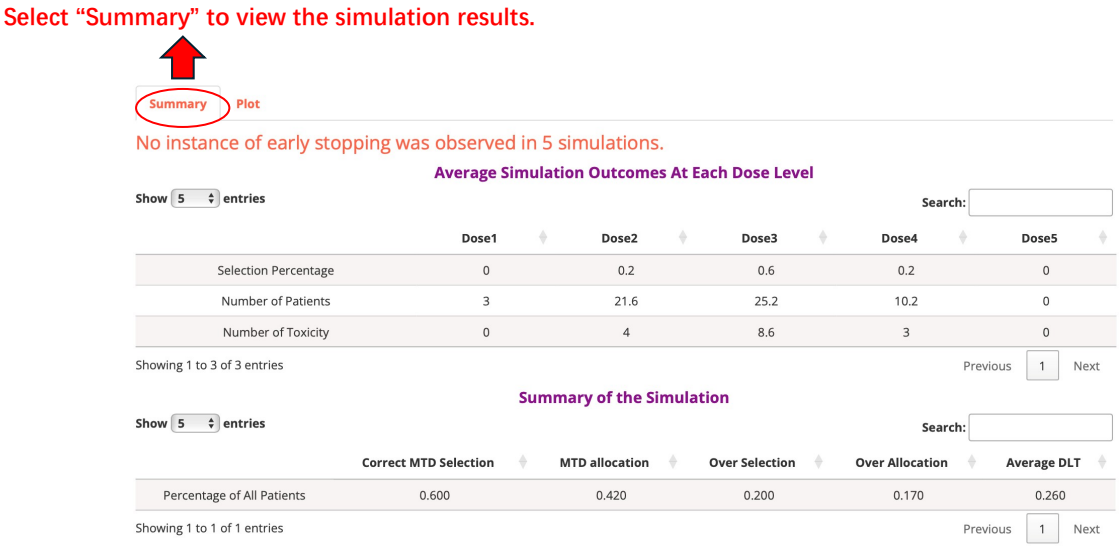

Figure 19: An example of performing multiple CFO simulations using the CFO suite

When choosing `TITE-CFO`, `TITE-aCFO`, `fCFO`, or `f-aCFO`

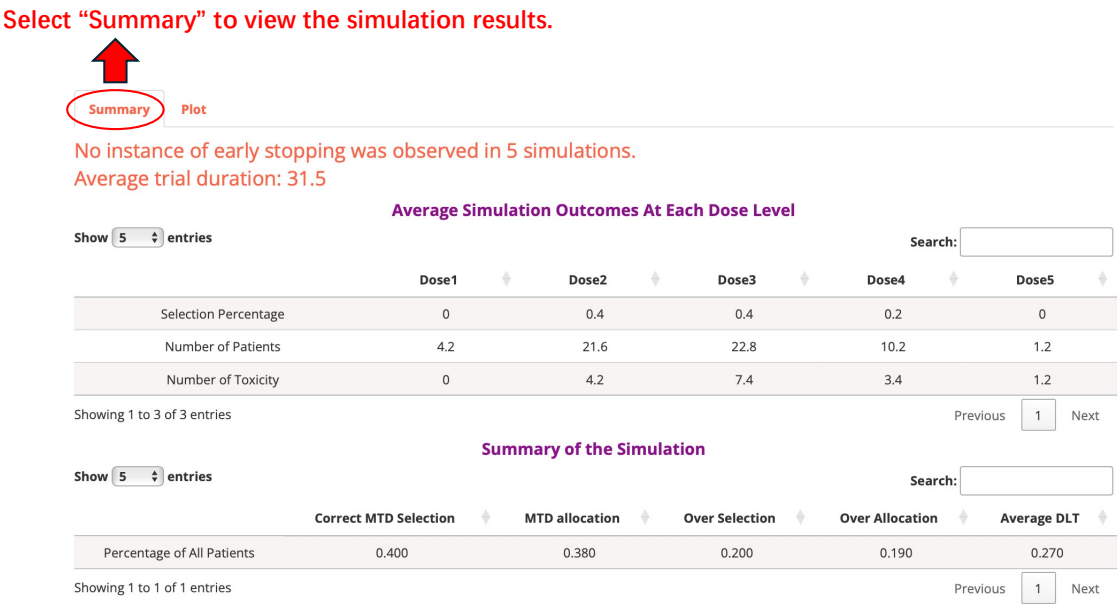

Figure 20: An example of performing multiple CFO simulations using the CFO suite.

2 Other notes regarding the use of the CFO suite

2.1 CFO design for Phase I/II trial

There is little operational difference between using the CFO suite to conduct a phase I/II trial and a phase I trial. You only need to add the additional parameters for the efficacy rate, which can be configured similarly to those for the DLT rate.

2.2 Use CFO2d to conduct a phase I trial

CFO2d is applied in dose-combination trials. Because the DLT rate is a matrix in this case, the process of setting the DLT rate-related parameters and the DLT outcome is slightly different. In **Single Simulation** and **Multiple Simulation**, the matrix is set in **DLT rates configuration**.

In **CFO2d Select MTD** and **Dose For Next Cohort**, the matrix is set in **Observed data configuration**. When configuring the matrix, please ensure that the number of rows is less than or equal to the number of columns.

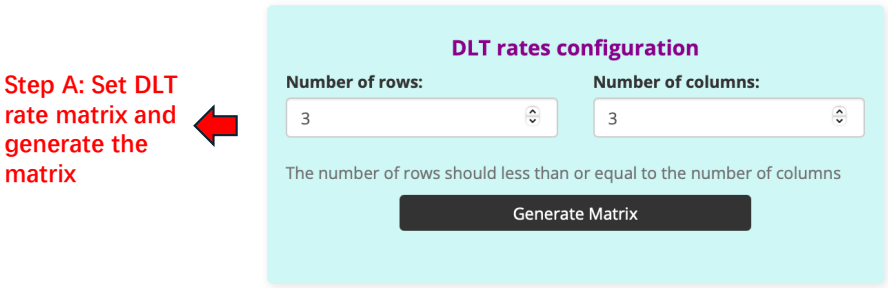

Figure 21: DLT rates matrix configuration interface for the CFO2d.

After setting the shape of the matrix, you can then access the input box for entering the DLT rate. Note that the elements in the DLT rate matrix must increase from left to right and from top to bottom.

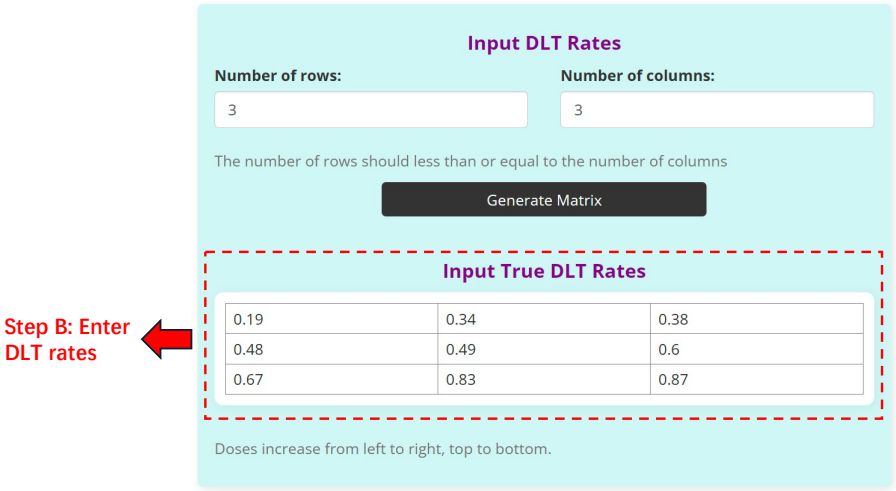

Figure 22: DLT rates matrix configuration interface for the CFO2d.

After defining the DLT rate matrix, the rest of the usage follows a similar approach to that of CFO in Phase I trials. For more details, refer to Section 1.