# DELPHI app: technical specifications

## Objective:

To develop the DELPHI (DEsign and simuLate PHase I) simulation platform and DELPHI online app for the design and conduct phase 1 trials with rule-based and adaptive designs.

## Overview:

DELPHI consists of two parts: DESIGN, and TRIAL CONDUCT. In DESIGN, a user can evaluate and compare the operating characteristics for potential phase 1 designs through trial simulations, and select the optimal design for the disease/biology/patient needs of the trial. In TRIAL CONDUCT, a particular adaptive design is implemented during the ongoing conduct of the trial. The user implements the adaptive trial, including determining the recommended dose for the next patient. DELPHI will feature modular programming with standardized input and output parameters across designs, so that new designs can be rapidly added to the modular framework by our lab or external investigators.

For the pilot DELPHI online app, we will focus on implementing two designs using R Shiny: (1) TARGET-CRM; and (3) 3+3. The framework needs to be scalable to include up to 6 additional designs to be simultaneously compared.

## Methods

### TARGET-CRM specifications

The TARGET-CRM modifies the *dfcrm* package to conduct the trial simulations. The function call is presented below.

target.crm <- function(prior, target.tox, number.trials, true.tox, arrival.rate, prop.B, target.crm, min.cohortB=0, cycle.length, cohort.size, max.N, start.level)

### 3+3 specifications

The function call for the 3+3 design is presented below.

three.plus.three <- function(target.tox, number.trials, true.tox, arrival.rate, prop.B, cycle.length, start.level)

The detailed description of the input parameters is presented in Table 1. A detailed description of the function output is presented in Table 2. Some input parameters and output parameters only pertain to the TARGET-CRM design.

Table 1: Input parameters for TARGET-CRM and 3+3 functions

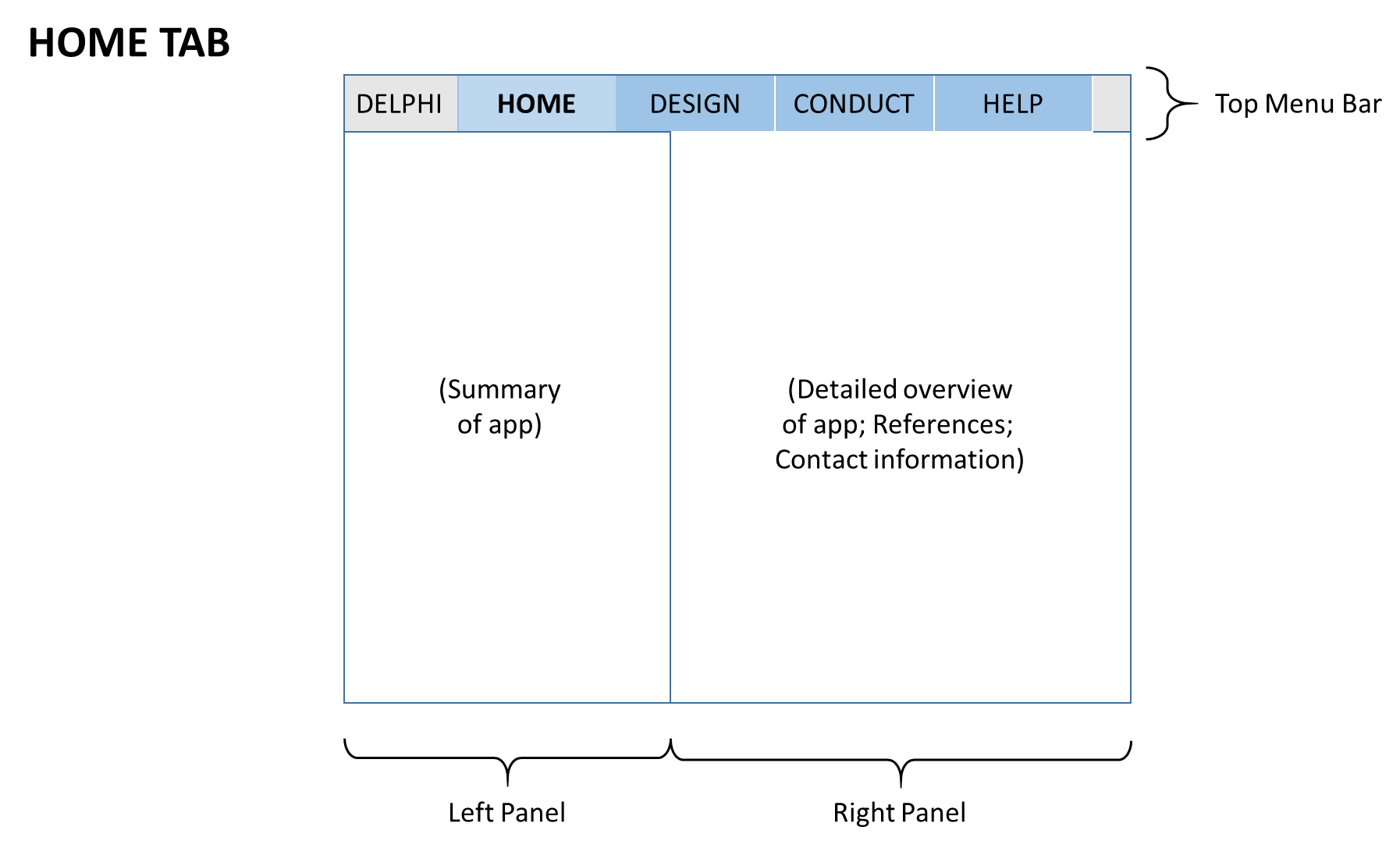
|  |  |  |
| --- | --- | --- |
| **Parameter** | **Description** | **Example** |
| **GENERAL INPUT PARAMETERS** | | |
| target.tox | Target toxicity probability of study agent | Probabilities range from 0 to 1.  target.tox=0.2 |
| number.trials | Number of mock trials to simulate | Number of trials >= 1  number.trials=1000 |
| true.tox | Vector of true toxicity probabilities for each dose level evaluated in the trial | Toxicity probabilities must increase monotonically with each subsequent dose level. Probabilities range from 0 to 1.  Example of a trial with 4 dose levels:  true.tox=c(0.05,0.12,**0.20**,0.30)  Here, the TRUE MTD is dose level 3 because its true toxicity probability is closest to the target toxicity probability (target.tox) of 20%. |
| start.level | Starting dose level | Starting dose level must be an integer ranging from 1 to total number of doses evaluated.  Example of a trial starting on dose level 2:  start.level=2 |
| arrival.rate | Mean inter-arrival time for enrolling patients (in days) | Arrival rate is greater than 0  arrival.rate=15 |
| prop.B | Proportion of enrolling patients belonging to Cohort B. We wish to enrich for these Cohort B patients with specific tumor subtypes / genomic alterations. | Proportion ranges from 0 to 1.  prop.B=0.1 |
| cycle.length | Duration of DLT observation period in days | DLT observation period is greater or equal to 1.  cycle.length=28 |
| **TARGET-CRM SPECIFIC INPUT PARAMETERS** | | |
| prior | Vector of prior toxicity probabilities for each dose level evaluated in the trial. | Toxicity probabilities must increase monotonically with each subsequent dose level. Probabilities range from 0 to 1.  Example of a trial with 4 dose levels:  prior=c(0.05,0.1,0.2,0.3) |
| target.crm  [TARGET-CRM design ONLY] | Option for different variations of the TARGET-CRM design: | target.crm=0: NO enrollment of patients at one dose below  target.crm=1: Enrollment of patients at one dose below  target.crm=2: Enrollment of patients at current best dose based on available information, cannot be higher than current dose |
| min.cohortB  [TARGET-CRM design ONLY] | Option to require a minimum number of Cohort B patients to be enrolled in the trial | Minimum number of Cohort B patients ranges from 0 to the maximum sample size (max.N)  min.cohortB=2 |
| cohort.size  [TARGET-CRM design ONLY] | Number of patients to be treated at the current dose before a dose escalation decision is made. | Cohort size must be an integer greater or equal to 1.  cohort.size=3 |
| max.N  [TARGET-CRM design ONLY] | Maximum number of patients to be enrolled | Maximum sample size must be an integer greater or equal to 1  max.N=20 |

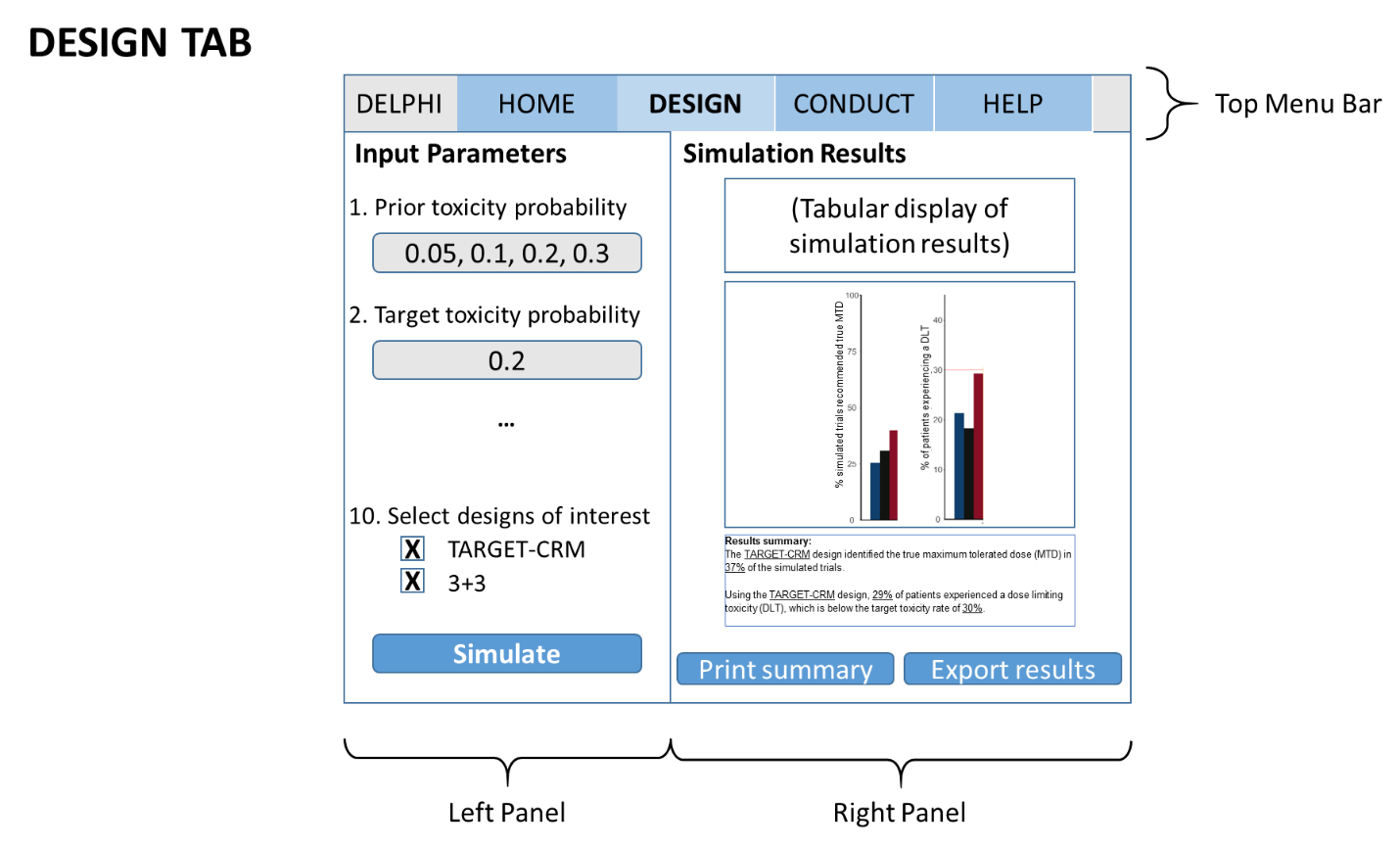
Table 2: TARGET-CRM and 3+3 function outputs

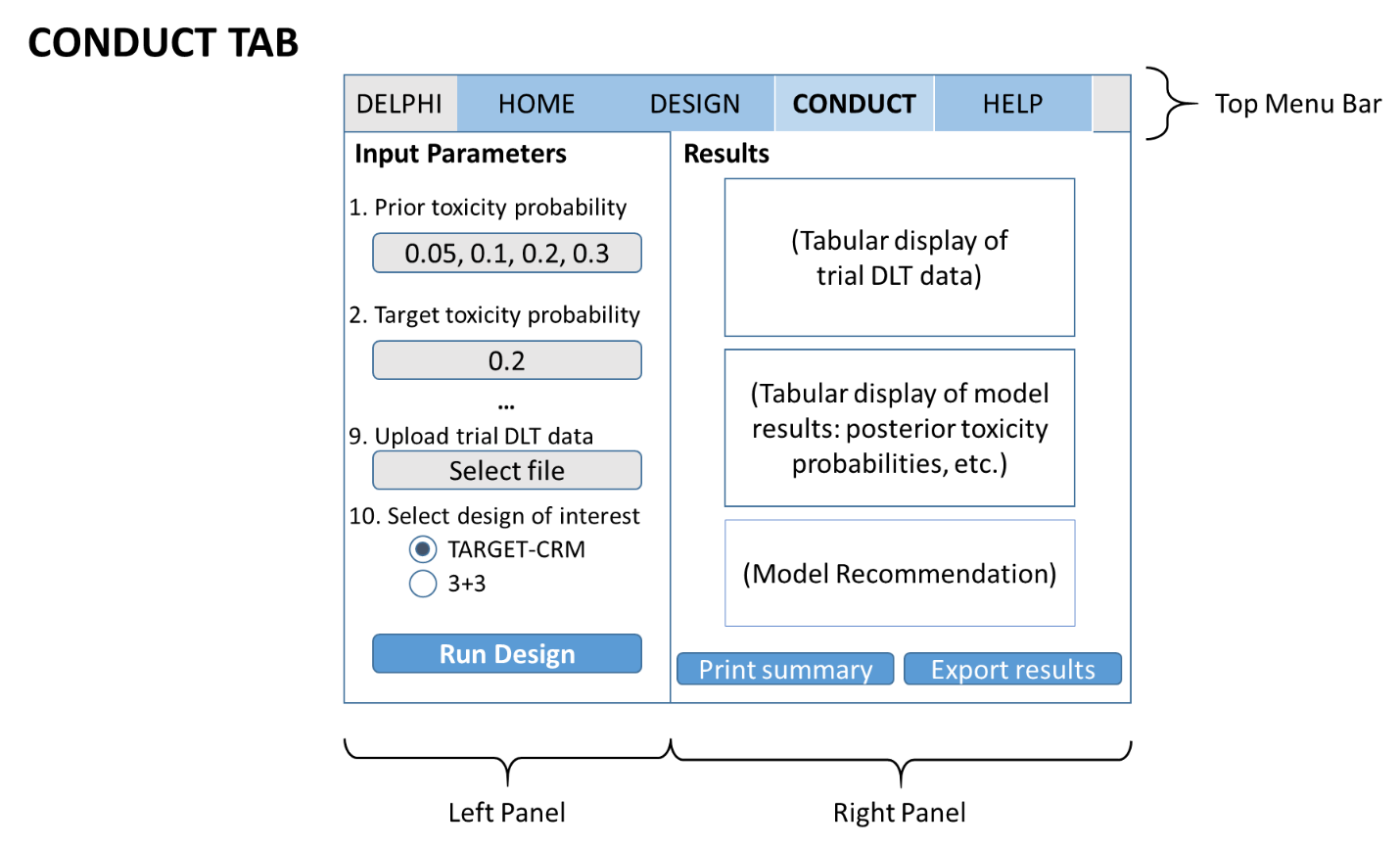
|  |  |  |
| --- | --- | --- |
| **Output** | **Description** | **Example** |
| MTD.selection | Vector with the proportion of simulated trials that selected each dose level as the maximum tolerated dose (MTD) | Proportion ranges from 0 to 1. The sum of proportions across all doses must sum to 1.  Example for a trial with 4 dose levels:  1 2 3 4  0.0445 0.2735 0.3880 0.2940 |
| PCS | Proportion of simulated trials that selected the TRUE maximum tolerated dose. The true MTD is the dose level with the true toxicity probability (true.tox) closest to the target toxicity probability (target.tox). | Proportion ranges from 0 to 1.  Example for a trial with 4 dose levels where dose level 3 is the TRUE MTD:  0.3880 |
| patient.allocation | Vector with the proportion of patients treated at each dose level | Proportion ranges from 0 to 1. The sum of proportions across all doses must sum to 1.  Example for a trial with 4 dose levels:  0.1528 0.3448 0.2993 0.2029 |
| obs.tox.overall | Overall proportion of patients experiencing a DLT | Proportion ranges from 0 to 1.  Example: 0.137 |
| obs.tox.table | Vector with the proportion of patients experiencing a DLT at each dose level | Proportion ranges from 0 to 1. The sum of proportions across all doses must sum to 1.  Example for a trial with 4 dose levels:  0.0470 0.1196 0.1974 0.3006 |
| mean.obs.N | Mean total sample size in simulated trials | Mean number ranges from 0 to max.N. |
| min.obs.N | Minimum total sample size in simulated trials | Minimum number ranges from 0 to max.N. |
| max.obs.N | Maximum total sample size in simulated trials | Maximum number ranges from 0 to max.N. |
| mean.cohortB | Mean number of cohort B patients treated at one dose below the current dose level (as per the TARGET-CRM design).  For the 3+3 design, mean.cohortB = 0 by default because no patient can enroll at one dose below the current dose. | Mean number ranges from 0 to max.N.  Example:  0.4965 |
| sd.cohortB | Standard deviation (SD) of number of cohort B patients treated at one dose below the current dose level (as per the TARGET-CRM design)  For the 3+3 design, sd.cohortB = 0 by default because no patient can enroll at one dose below the current dose. | Standard deviation is greater than 0.  Example:  0.6922 |
| mean.duration | Mean study duration in days | Mean study duration is greater than 0.  Example:  355.1 |
| sd.duration | Standard deviation of study duration in days | Standard deviation is greater than 0.  Example:  22.9 |

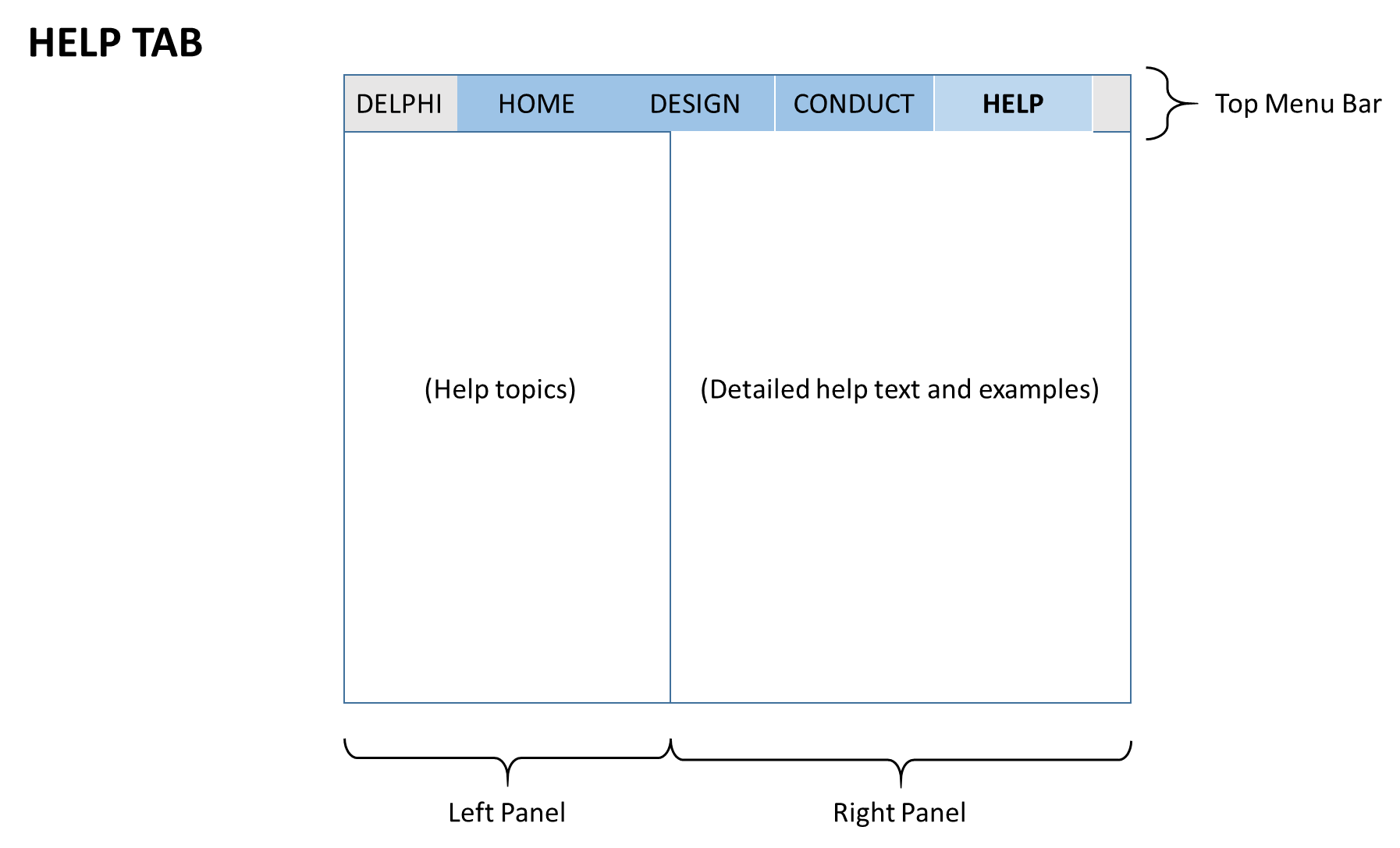
## Proposed R Shiny Interface

The proposed R Shiny interface will include 4 main “tabs”: (1) HOME; (2) DESIGN; (3) TRIAL CONDUCT; and (4) HELP.









## DESIGN Tab: Detailed Specifications

Table 3 presents a detailed description of the input parameters for the DESIGN tab.

Table 3: Description of input parameters for DESIGN tab

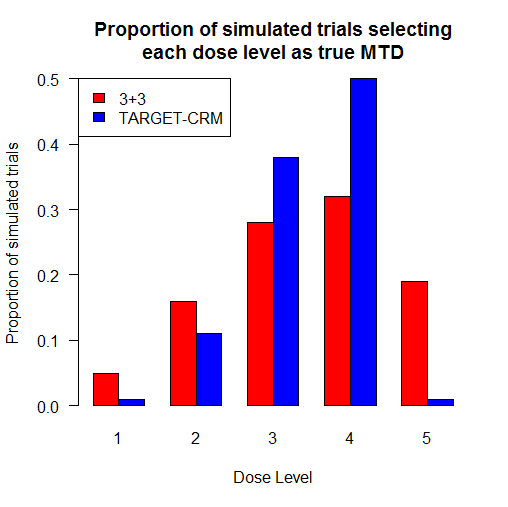
|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Input Parameter** | **Label** | **Tooltip** | **Interface** | **Default Value** | **Range** |
| **General simulation parameters** | | | | | |
| design | 1. Dose-escalation designs | Please select the dose escalation design(s) of interest. | Checkbox | 3+3: checked  TARGET-CRM: unchecked | Options:   * 3+3 * TARGET-CRM |
| dose.labels | 1. Dose level labels | Please enter the dose level labels for each dose level evaluated in the trial. | Text box | “-1”, “**1”**, “2”, “3” | Each label is an alphanumeric string |
| true.tox | 1. True toxicity probability vector | Please enter the estimated true toxicity probabilities for each dose level evaluated in the trial. Toxicity probabilities must increase with each subsequent dose level. | Text box | **0.05,0.12,0.20,0.30** | Each numeric value ranges from 0 to 1 |
| start.level | 1. Starting dose level | Please enter the starting dose level using the dose level labels above | Text box | “1” | An alphanumeric string matching one of the labels from *dose.labels* |
| target.tox | 1. Target toxicity probability | Please enter the target toxicity probability of the study agent. | Slider | 0.2 | 0 to 1; hundredths only |
| arrival.rate | 1. Patient enrollment rate | Please enter the estimated average time between enrolling patients (in days). | Slider | 15 | 0 to 180; whole numbers only |
| cycle.length | 1. Duration of DLT observation period | Please enter the duration of the DLT observation period (in days). | Slider | 28 | 0 to 365; whole numbers only |
| prop.B | 1. Proportion of patients from Cohort B | Please enter the proportion of enrolled patients belonging to the “enrichment” Cohort B. | Slider | 0.1 | 0 to 1; hundredths only |
| number.trials | 1. Number of simulated trials | Please enter the number of simulated trials. A larger number of simulations increases the precision of simulation results and computation time. | Text box | 100 | 1 to 10,000; whole numbers only |
| **TARGET-CRM simulation parameters (ONLY)** | | | | | |
| prior | 1. Prior toxicity probability vector | Please enter the estimated prior toxicity probabilities for each dose level evaluated in the trial. Toxicity probabilities must increase with each subsequent dose level. | Text box | c(0.05,0.12,0.20,0.30) | Each numeric value ranges from 0 to 1 |
| cohort.size | 1. Cohort size | Please enter the cohort size. The cohort size is the number of patients to be treated at the current dose level before a dose escalation decision is made. | Text box | 3 | Options:  1, 2, 3, 4, 5, 6, 7, 8, 9 |
| max.N | 1. Maximum sample size | Please enter the maximum number of patients to be enrolled per trial. | Slider | 18 | 1 to 200; whole numbers only |
| target.crm | 1. TARGET-CRM option | Please enter the desired variation of the TARGET-CRM design | Drop-down menu | 1 | Option 0: NO enrollment of Cohort B patients at one dose below  Option 1: Enrollment of Cohort B patients at one dose below  Option 2: Enrollment of Cohort B patients at current dose |
| min.cohortB | 1. (Optional) Minimum enrollment of Cohort B patients | Please enter the minimum number of Cohort B patients to be enrolled in the trial. | Slider | 0 | 0 to maximum sample size (max.N) |

### Output figures and tables

For **Figure 1**, plot a histogram the proportion of simulated trials selecting each dose level as the true MTD for each design.

* Y-variable: *MTD.selection.table / number.trials*
* *X-variable: dose level*

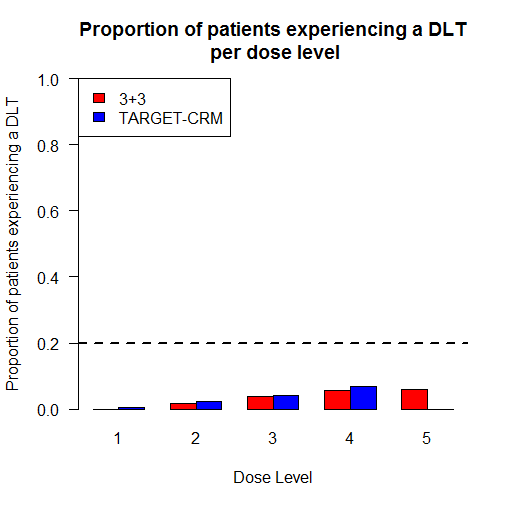
Figure 1: Proportion of simulated trials selecting each dose level as the true MTD



For **Figure 2**, plot a histogram the proportion of patients experiencing a DLT per dose level for each design.

* Y-variable: *obs.tox.table*
* *X-variable: dose level*
* Horizontal dashed line at height = *target.tox*
* *Y-axis dynamically scaled to show all bars and the horizontal dashed line.*

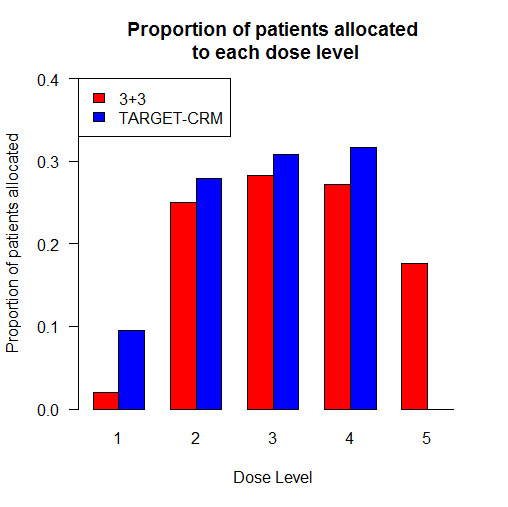
Figure 2: Proportion of patients experiencing a DLT per dose level



For **Figure 3**, plot a histogram the proportion of patients allocated to each dose level for each design.

* Y-variable: *patient.allocation.table*
* *X-variable: dose level*

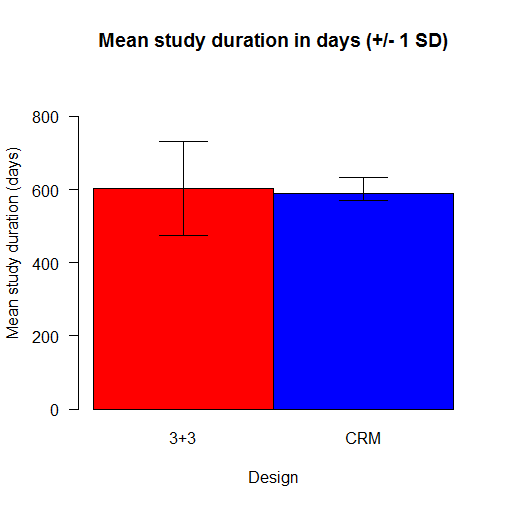
Figure 3: Proportion of patients allocated to each dose level



For **Figure 4**, plot a histogram with the mean study duration in days for each design (+/- 1 SD).

* Y-variable: *mean.duration*
* Error bars:
  + Lower limit = *mean.duration – sd.duration*
  + Upper limit = *mean.duration + sd.duration*

Figure 4: Mean study duration in days (+/- 1 SD)



For **Table 1**, output the simulation results in tabular format by dose escalation design.

Table 1: Summary of simulation results

|  |  |  |  |
| --- | --- | --- | --- |
| **Operating characteristic** | **3+3 design** | **TARGET-CRM design** | **Output variable name  (do not display)** |
| Proportion of Correct Selection (PCS) | 0.318 | 0.5 | *PCS* |
| True MTD | Dose 4 | Dose 4 | *true.MTD* |
| Proportion of trials selecting dose X as true MTD: |  |  | *MTD.selection.table / number.trials* |
| Dose 1 | 0.12 | 0.01 |  |
| Dose 2 | 0.25 | 0.11 |  |
| Dose 3 | 0.312 | 0.38 |  |
| Dose 4 (… (to maximum number of doses) | 0.318 | 0.50 |  |
| Proportion of patients experiencing a DLT overall | 0.173 | 0.138 | *obs.tox.overall* |
| Proportion of patients experiencing a DLT per dose level |  |  | *obs.tox.table* |
| Dose 1 | 0.01 | 0.02 |  |
| Dose 2 | 0.03 | 0.04 |  |
| Dose 3 | 0.05 | 0.07 |  |
| Dose 4 (… (to maximum number of doses) | 0.08 | 0.09 |  |
| Mean total sample size | 15.36 | 18 | *mean.obs.N* |
| Minimum total sample size | 9 | 18 | *min.obs.N* |
| Maximum total sample size | 21 | 18 | *max.obs.N* |
| Proportion of patients enrolled per dose level |  |  | *patient.allocation.table* |
| Dose 1 | 0.02 | 0.05 |  |
| Dose 2 | 0.18 | 0.15 |  |
| Dose 3 | 0.35 | 0.30 |  |
| Dose 4 (… (to maximum number of doses) | 0.45 | 0.50 |  |
| Mean study duration in days | 608.54 | 588.89 | *mean.duration* |
| Standard deviation of study duration in days | 31.21 | 135.85 | *sd.duration* |
| Mean number of cohort B patients enrolled during DLT observation period (TARGET-CRM only) | N/A | 0.3 | *mean.cohortB* |
| Standard deviation of number of cohort B patients enrolled during DLT observation period (TARGET-CRM only) | N/A | 0.54 | *sd.cohortB* |

Start here

### Dynamically created report text

The following report template is dynamically created using the simulation results. The data items in **BOLD** are dynamically populated using the R object in brackets <*R object*>.

**Simulated Operating Characteristics of Phase 1 Dose Escalation Design(s)**

**Report date:** <*date*> November 3, 2020

**Objective:**

To evaluate the operating characteristics of the following dose escalation designs: <*design*> **3+3 and TARGET-CRM.**

**Methods:**

Trial operating characteristics are averaged over *<number.trials>* **100** simulated trials. Simulated trials have *<length(true.tox)>* **4** dose levels starting on dose level *<start.level>* **1**, assuming true toxicity probabilities of <*true.tox*> (**0.05,0.12,0.20,0.30**). The target toxicity probability is <*target.tox*> **0.2**. One patient arrives every <*arrival.rate*> **15** days on average. The DLT observation period is <*cycle.length*> **28** days.

<*include the following text only if TARGET-CRM is selected*>

For the TARGET-CRM design, the prior toxicity probabilities per dose level are <*prior*> (**0.05,0.12,0.20,0.30**). The cohort size is <*cohort.size*> **3** and the maximum sample size <*max.N*> is **18**. Cohort B patients are [define]. The TARGET-CRM design <display text based on selected *target.crm* option>:

(0) does not allow enrollment of Cohort B patients at one dose level below the current dose during the DLT observation period of the current cohort of patients. This design is equivalent to the standard CRM design.

(1) allows enrollment of Cohort B patients at one dose level below the current dose during the DLT observation period of the current cohort of patients. This is the more conservative TARGET-CRM design.

(2) allows enrollment of Cohort B patients at the current dose during the DLT observation period of the current cohort of patients. This is the more aggressive TARGET-CRM design.

Simulated TARGET-CRM trials are required to have a minimum enrollment of <*min.cohortB*> **0** Cohort B patients.

Simulations were conducted using the *DELPHI* R Shiny app available at <*URL*>.

**Results:**

*[Template for TWO OR MORE designs]*

***Accuracy:***The <*select design with highest PCS*> **TARGET-CRM** design has greatest probability of selecting the true MTD (dose level <*true.MTD*> **4**). The proportion of correct selection (PCS) of the MTD for the TARGET-CRM design is <*PCS*> **0.5**. The PCS for the 3+3 design is <*PCS*> **0.318**. For each dose level, Figure 1 presents the proportion of simulated trials that a given dose level was selected as the true MTD.

***Safety:*** The proportion of patients experiencing a DLT for the 3+3 design is <*obs.tox.overall*> **0.173**, which is **lower / greater** than the target toxicity probability of <target.tox> **0.2**. The proportion of patients experiencing a DLT for the TARGET-CRM design is <*obs.tox.overall*> **0.138**, which is **lower / greater** than the target toxicity probability of <target.tox> **0.2**. Figure 2 presents the proportion of patients experiencing a DLT for each dose level.

**Patient allocation:** The <*select design with the highest patient allocation for the true.MTD in patient.allocation.table*> **TARGET-CRM** design has the greatest probability of assigning patients at the true MTD (dose level <*true.tox*> **4**). The proportion of patients assigned to the true MTD for the TARGET-CRM design is <*patient.allocation.table*> **0.50**. The proportion of patients assigned to the true MTD for the 3+3 design is <*patient.allocation.table*> **0.45**. Figure 3 presents the proportion of patients assigned to each dose level.

**Study duration:** The <*select design with shortest mean.duration*> **TARGET-CRM** design has the shortest mean study duration. The mean study duration for the 3+3 design is <*mean.duration*> **608.54** days (standard deviation [SD] <*sd.duration*> = **31.21**). The mean study duration for the TARGET-CRM design is <*mean.duration*> **588.89** days (<*sd.duration*> SD=**135.85**).

**Sample size:** The mean total sample size for the 3+3 design is <*mean.obs.N*> **15.36** <*min.obs.N; max.obs.N*> (range=**9-21**).The mean total sample size for the TARGET-CRM design is <*mean.obs.N*> **18** <*min.obs.N; max.obs.N*>(range=**18-18**).

**Enrollment of Cohort B patients (TARGET-CRM only):** The proportion of patients in the population belonging to Cohort B is <*prop.B*> **0.2**. The mean number of Cohort B patients enrolled during the DLT observation period is <*mean.cohortB*> **0.3** (<*sd.cohortB*> SD=**0.541**)

*[Template for ONE design]*

***Accuracy:***The proportion of correct selection (PCS) of the MTD for the <design> **TARGET-CRM** design is <*PCS*> **0.5**. For each dose level, Figure 1 presents the proportion of simulated trials that a given dose level was selected as the true MTD.

***Safety:*** The proportion of patients experiencing a DLT for the <*design*> **TARGET-CRM** design is <*obs.tox.overall*> **0.138**, which is **lower / greater** than the target toxicity probability of <*target.tox*> **0.2**. Figure 2 presents the proportion of patients experiencing a DLT for each dose level.

**Patient allocation:** The proportion of patients assigned to the true MTD (dose level <*true.tox*> **4**) for the <design> **TARGET-CRM** design is <*patient.allocation.table*> **0.50**. Figure 3 presents the proportion of patients assigned to each dose level.

**Study duration:** The mean study duration for the <*design*> **TARGET-CRM** design is 608.54 days (standard deviation [SD] = 31.21).

**Sample size:** The mean total sample size for the <*design*> **TARGET-CRM** design is <*mean.obs.N*> **18** <*min.obs.N; max.obs.N*> (range=**18-18**).

<*Include only if TARGET-CRM design is selected*> **Enrollment of Cohort B patients:** The proportion of patients in the population belonging to Cohort B is <*prop.B*> **0.2**. The mean number of Cohort B patients enrolled during the DLT observation period is <*mean.cohortB*> **0.3** (<*sd.cohortB*> SD=**0.541**)

## Exporting results

1. Print / generate PDF of all figures, tables, and report text in a single document.
2. Export Table 1 to Excel / CSV format.

# DELPHI Home Tab

* Title: “DEsign and simuLate PHase I (DELPHI)”
* Overview
  + DEsign and simuLate PHase I (DELPHI) is an interactive, web-based platform to design and conduct phase 1 clinical trials using rule-based and adaptive designs.
  + DELPHI consists of two parts: DESIGN, and TRIAL CONDUCT.
    - DESIGN: Users can evaluate and compare the operating characteristics for potential phase 1 designs through trial simulations, and select the optimal design for the disease/biology/patient needs of the trial.
* TRIAL CONDUCT: A particular adaptive design is implemented during the ongoing conduct of the trial. The user implements the adaptive trial, including determining the recommended dose for the next patient. Introduction to Phase 1 Trials
  + The primary objective of a phase 1 trial is to identify the maximum tolerated dose (MTD) of the study agent. During the trial, individual or cohorts of patients enroll sequentially on assigned dose levels of the study agent. Clinicians observe enrolled patients for the occurrence of dose limiting toxicities (DLTs) during the DLT observation period (typically one cycle of therapy [3-4 weeks]). Based on the observed DLT data to date, the trial’s design recommends the dose level for the next cohort of patients. The trial proceeds until a pre-defined maximum sample size is attained or a stopping rule is triggered.
* Features
  + Implemented designs:
    - Adaptive designs
      * Continual Reassessment Method (CRM)
      * TARGETed-agent Continual Reassessment Method (TARGET-CRM)
    - Rule-based designs
      * 3+3
  + DESIGN phase:
    - Users can directly compare operating characteristics across multiple designs for the same set of simulation parameters.
    - DELPHI dynamically generates a written report summarizing the simulation results.
  + TRIAL CONDUCT phase:
    - Users can upload trial parameters and dose limiting toxicity data to DELPHI to conduct trial using the desired trial design.
      * DELPHI dynamically generates a report summarizing the recommendations for the selected trial design.
    - Modular programming
    - DELPHI will feature modular programming with standardized input and output parameters across designs, so that new designs can be rapidly added to the modular framework by the DELPHI development team or external investigators. (see additional details in the HELP tab)
* Authors
  + Principal Investigators:
    - Clement Ma, PhD
    - Wendy B. London, PhD
  + Development Team: Northwestern Mutual Life Insurance Company
    - Ben Garski
    - Danielle Pankey
    - Judy Berdan
    - Stan Crane
    - Lori Kiraly
    - Susan Stegman
    - Audra Brennan
  + Test Users
    - TBD
* Acknowledgement
  + We would like to thank the Northwestern Mutual “Tech for Good” team for their year-long pro-bono software development and project management support for the DELPHI platform. [NM to insert / revise text]

# DELPHI Help Tab

* PDF documentation (link to PDF file)
  + (link: https://pubmed.ncbi.nlm.nih.gov/2790129/)
  + (link: https://pubmed.ncbi.nlm.nih.gov/2350571/)

[See separate formatted PDF documentation.]

* Phase 1 designs
  + 3+3
    - The rule-based 3+3 design (Storer, 1989) is one of the most common designs used in phase 1 trials. The 3+3 design proceeds as follows. Cohorts of three patients will be enrolled on the current dose level. If 0 out of 3 patients experience a DLT, the next cohort of 3 patients will be enrolled at the next dose level. If ≥2 out of 3 patients experience a DLT, dose escalation will be stopped. This dose level will be declared the maximally administered dose. Three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose. If 1 out of 3 patients experience a DLT, 3 additional patients will be enrolled at the current dose level. If 0 out of these 3 additional patients experience a DLT, the next cohort of 3 patients will be enrolled at the next dose level. If ≥1 out of these 3 additional patients experience a DLT, dose escalation will be stopped. This dose level will be declared the maximally administered dose. Three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose.
    - **Dose Escalation Schema for 3+3 design**

|  |  |
| --- | --- |
| **Number of Participants with DLT at a Given Dose Level** | **Escalation Decision Rule** |
| 0 out of 3 | Enter 3 participants at the next dose level. |
| >2 out of 3 | Dose escalation will be stopped. This dose level will be declared the maximally administered dose. Three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose. |
| 1 out of 3 | Enter 3 more participants at this dose level.   * If 0 of these 3 participants experience DLT proceed to the next dose level. * If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose. |
| ≤1 out of 6 at highest dose level at or below the maximally administered dose | This will be the maximum tolerated dose. |

* + - CRM
      * The Bayesian adaptive continual reassessment method (O’Quigley, 1990) uses the observed DLT data to date and prior information for the toxicity to model the dose-toxicity relationship of the study agent. The CRM proceeds as follows. A cohort of X patients will be enrolled at the current dose level (the cohort size is pre-specified by the investigator). When the DLT observation period is complete for the current cohort of patients, the CRM model will be excuted. The posterior toxicity probabilities will be computed using the prior toxicity probabilities and observed DLT data. The recommended dose for the next cohort of patients will the dose level with the posterior toxicity probability closest to the target toxicity probability. For dose escalation, the recommended dose level can never be more than one sequential dose level above the current dose level; for dose de-escalation, the recommended dose may be one or two dose levels below the current dose level. The trial proceeds until the maximum sample size is attained. The MTD is the dose level with posterior toxicity probability closest to the target toxicity probability.
    - TARGET-CRM
      * The TARGET-CRM design is a variation of the standard CRM design. Consider a phase 1 trial of a targeted agent, whereby patients belong to either Stratum A, with unspecified tumor types, or Stratum B, with specific rare tumor aberrations who are anticipated to better respond to the targeted agent. The commonly-used 3+3 design requires patients to enter a waitlist and suspends enrollment while the current cohort of patients are being observed for DLTs. Rare Stratum B patients may be unable to enroll due to a long waitlist or arriving during the DLT observation period (**Figure 1**). The TARGET-CRM design allows Stratum B patients to enroll at one dose level below the currently-evaluated dose level of the cohort of 3 patients under observation. All patients, including Stratum B patients enrolled at one dose level below the current dose, will inform the dose escalation decisions. We applied this design to an ongoing phase 1 trial of a novel targeted therapy, ALRN-6924, in children with relapsed/refractory cancers (NCT03654716).
      * **Figure 1:** Continuous enrollment of Stratum B patients with rare tumor subtypes using the TARGET-CRM design.



**Existing designs:**

Dose 3

Dose 2

Dose 1

Dose -1



No slots available on current dose



**Cannot enroll**



**Proposed TARGET-CRM design:**

Dose 3

Dose 2

Dose 1

Dose -1



**Enroll at one dose below current dose**



Stratum B patient arrives

Stratum B patient arrives

* Design tab
  + Input Parameters

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| --- | --- | --- | --- |
| **Input Parameter** | **Description** | **Range / Limitations** | **Example** |
| **GENERAL INPUT PARAMETERS** | | | |
| Number of dose levels | The total number of dose levels to be evaluated in the phase 1 trial | Whole numbers from 2 to 10 | 4 |
| Dose escalation designs | Select one or more dose escalation designs of interest | Options:   * 3+3 * TARGET-CRM |  |
| Dose level labels (Optional) | A list of optional labels for each dose level evaluated.  If user-specified labels are not provided, dose levels will be numbered sequentially from dose level “1” as the lowest dose level. | Each label is an alphanumeric string.  Labels are separated by commas. | “-1”, “1”, “2”, “3” |
| True toxicity probability | A list of the true toxicity probabilities for each dose level evaluated in the trial. | Numeric value from 0 to 1.  Toxicity probabilities must increase with each subsequent dose level. Probabilities are separated by commas. | 0.05, 0.12, 0.20, 0.30 |
| Starting dose level | The starting dose level for the trial | If user-specified labels are provided: an alphanumeric string matching one of the user-specified labels above  If user-specified labels are not provided: the numeric dose level starting with dose level “1” as the lowest dose level | “1” |
| Target toxicity probability | The target toxicity probability of the study agent. This is typically the maximum acceptable chance of experiencing a DLT for a patient given the study agent. | Numeric value from 0 to 1 | 0.2 |
| Patient enrollment rate | The average time between enrolling patients (in days). Patients will enroll following a Poisson distribution with this mean. | Whole numbers from 0 to 180 | 15 |
| Duration of DLT observation period | The duration of the DLT observation period (in days). This is typically the length of one cycle of therapy (~28 days) | Whole numbers between 0 to 365 | 28 |
| Proportion of patients from Cohort B | The proportion of enrolled patients belonging to the “enrichment” Cohort B. | Numeric value from 0 to 1 | 0.1 |
| Number of simulated trials | The total number of simulated trials. A larger number of simulations increases the precision of simulations and computation time. | Numeric value from 1 to 10,000 | 100 |
| **TARGET-CRM SPECIFIC INPUT PARAMETERS** | | | |
| Prior toxicity probability vector | A list of prior toxicity probabilities for each dose level evaluated in the trial. | Numeric value from 0 to 1.  Toxicity probabilities must increase with each subsequent dose level. Probabilities are separated by commas. | 0.05, 0.12, 0.20, 0.30 |
| Cohort size | The number of patients to be treated at the current dose level before a dose escalation decision is made.  Cohort sizes of 1, 2, or 3 patients are commonly used. | Whole numbers from 1 to 9 | 3 |
| Maximum sample size | The maximum number of patients to be enrolled per simulated trial. The trial ends when the maximum number of patients have been enrolled. | Whole numbers from 1 to 200 | 18 |
| Target-CRM option | [TARGET-CRM design ONLY]  The desired variation of the TARGET-CRM design | Option=0: NO enrollment of patients at one dose below. Defaults to standard CRM design.  Option=1: Enrollment of patients at one dose below  Option=2: Enrollment of patients at current best dose based on available information, cannot be higher than current dose | 1 |
| Minimum number of Cohort B patients (Optional) | [TARGET-CRM design ONLY]  The minimum number of Cohort B patients to be enrolled per trial.  If this parameter is greater than zero, the trial will continue until the minimum number of Cohort B patients have been enrolled. Accrual of Cohort A patients will be suspended once the maximum sample size has been reached; only Cohort B patients will be enrolled. | Whole numbers from 0 to the maximum sample size | 0 |

* + Outputs

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| --- | --- |
| **Operating characteristic** | **Description** |
| Proportion of Correct Selection (PCS) | The proportion of simulated trials where the selected MTD is the true MTD. A design with a higher PCS has greater accuracy. |
| True MTD | The dose level which has the true toxicity probability closest to the target toxicity probability. |
| Proportion of trials selecting dose X as true MTD: | The proportion of simulated trials recommending dose X as the true MTD. |
| Proportion of patients experiencing a DLT overall | The overall proportion of all simulated patients across all simulated trials who experience a DLT. This metric is an indicator of patient safety. |
| Proportion of patients experiencing a DLT per dose level | The proportion of all simulated patients across all simulated trials who experience a DLT per dose level. |
| Mean total sample size | The average total sample size per simulated trial. |
| Minimum total sample size | The minimum sample size across all simulated trials. |
| Maximum total sample size | The maximum sample size across all simulated trials. |
| Proportion of patients enrolled per dose level | The proportion of all simulated patients across all simulated trials enrolled at each dose level. A good design will enroll a higher proportion of patients at or near the true MTD. |
| Mean study duration in days | The average duration of a trial. A shorter study duration is usually preferable. |
| Standard deviation of study duration in days | The standard deviation of the trial duration. |
| Mean number of cohort B patients enrolled during DLT observation period (TARGET-CRM only) | The average number of patients from Cohort B enrolled during the DLT observation period. This metric applies to the TARGET-CRM design only. |
| Standard deviation of number of cohort B patients enrolled during DLT observation period (TARGET-CRM only) | The standard deviation of the number of patients from Cohort B enrolled during the DLT observation period. This metric applies to the TARGET-CRM design only. |

* + Conduct tab **(To be completed; Leave placeholder)**
    - Inputs
    - Outputs
    - Example
  + Frequently Asked Questions
    - **(To be completed; Leave placeholder)**