# 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 phases: DESIGN, and TRIAL CONDUCT. In the DESIGN phase, 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. After implementing a particular adaptive design, in the TRIAL CONDUCT phase, the user can implement the adaptive trial by calculating 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 additional designs.

## 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(prior, 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** | | |
| 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.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** | | |
| 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 | 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.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) CONDUCT; and (4) HELP.







