DELPHI Documentation

Last Updated: February 14, 2021

Phase 1 designs

3+3 Design

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 (**Table 1**). 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.

Table 1: 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.

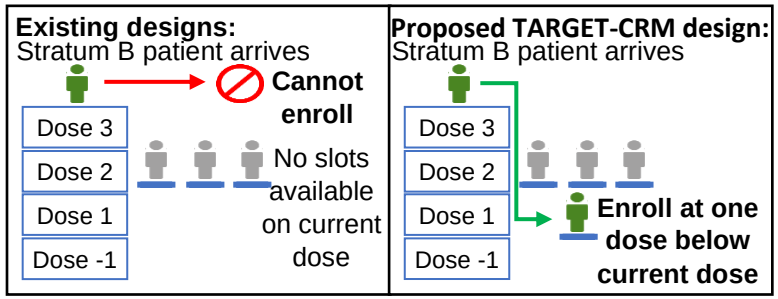
Continual Reassessment Method (CRM)

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 executed. 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.

TARGETed-agent Continual Reassessment Method (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 Cohort A, with unspecified tumor types, or Cohort 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 Cohort 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 Cohort 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 Cohort 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 Cohort B patients with rare tumor subtypes using the TARGET-CRM design.



Design Tab

Input Parameters

Table 2 summarizes the input parameters for the Design tab.

Table 2: Summary of the input parameters for the Design tab.

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	Numeric value from 0 to 1	0.2

	acceptable chance of experiencing a DLT for a patient given the study agent.		
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

Simulated Operating Characteristics

Table 3 summarizes the simulated operating characteristics from the Design tab.

Table 3: Summary of simulated operating characteristics for the Design tab.

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 UPDATED

Frequently Asked Questions (FAQs)

TO BE UPDATED