# DEDUCE: DEsign and conDUCt of dose Escalation trials Trial Conduct tab

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## Objective

To describe the technical specifications of the Trial Conduct tab of the DEDUCE app.

## Methods

The function call to execute the CRM design is given below. This function calls the “*crm*” function from the *dfcrm* package.

|  |
| --- |
| conduct.crm <- function(prior, target.tox, tox, level, n=length(level), dose.labels=NULL, include=1:n, pid=1:n, cohort.size, num.slots.remain, current.dose) |

The function call to execute the TARGET-CRM design is given below. This function calls the “*crm*” function from the *dfcrm* package.

|  |
| --- |
| conduct.target.crm <- function(prior, target, tox, level, n=length(level), dose.labels=NULL, include=1:n, pid=1:n, cohort.size, num.slots.remain, current.dose) |

## Input parameters

Table 1 presents trial-related input parameters.

Table : Trial input parameters

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Input Parameter** | **Label** | **Tooltip** | **Interface** | **Default value** | **Range** |
| design | 1. Dose-escalation design | Please select the dose escalation design of interest. | Radio button (select one) | CRM: selected | Options:   * CRM * TARGET-CRM |
| num.doses | 1. How many doses will there be? | Please enter the number of doses that will be used | Slider | 4 | 3 to 10 doses |
| dose.labels | 1. Dose level labels | Please enter the dose level labels (separated by commas) for each dose level evaluated in the trial. | Textbox | -1, 1, 2, 3 | Each label is an alphanumeric string. Number of labels must match num.doses |
| target.tox | 1. Target toxicity probability | Please enter the target toxicity probability of the study agent. | Slider | 0.2 | 0 to 1; hundredths 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 | 0.05,0.12,0.20,0.30 | Each numeric value ranges from 0 to 1. Prior must increase monotonically. Number of values must match num.doses |
| 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. | Slider | 3 | Options:  1, 2, 3, 4, 5, 6, 7, 8, 9 |
| num.slots.remain | 1. Number of slots remaining | Please enter the number of slots remaining to be enrolled for the current cohort of patients. | Slider | (no default) | 0 to  (cohort.size – 1) |
| current.dose | 1. Current dose level | Please enter the dose level of the current cohort of patients being enrolled. | Radio button (select one) | (no default) | Options:  (Use doselabels vector) |

Table 2 presents an example of the patient-level trial data to date. This table needs to have a dynamic number of rows, one per patient enrolled in the trial. The number of columns is fixed.

Table : Example patient-level data observed to date

|  |  |  |  |
| --- | --- | --- | --- |
| **Patient ID** *<PID>* | **Dose administered** *<level>*  *[The level should correspond to the dose labels provided in <doselabels>]* | **DLT observed** *<tox>* | **Include patient in model** *<include>* |
| C1 | 1 | 0 | 1 |
| C2 | 1 | 0 | 1 |
| C3 | 1 | 0 | 0 |
| C4 | 1 | 1 | 1 |
| … | … | … | … |

Each column from the patient-level data translates to a vector of values that is entered into the R function. Table 3 presents a detailed description of each input vector.

Table : Description of input vectors for patient-level data

|  |  |  |  |
| --- | --- | --- | --- |
| **Input Parameter** | **Description** | **Algorithm / Limits** | **Example values** |
| pid | Vector of patient IDs, one ID per patient. | Take vector of PID’s from Table 2. PIDs can be any alphanumeric string. No duplicate values are allowed. | pid <- c(“C1”,”C2”,”C3”,”C4”) |
| level | Vector of the dose level administered to each patient, one per patient | User enter dose levels using dose labels. Dose levels much match one of the provided dose labels <doselabels>.  In backend, convert vector of dose labels to the original ordered sequence of doses (1, 2, 3, …) | User entered:  (1, 1, 1, 1)  After conversion to sequential dose numbers:  level <- (2, 2, 2, 2) |
| tox | Vector of indicators whether a dose limiting toxicity (DLT) was observed for each patient, one per patient | Take vector of observed toxicities from Table 2:   * 0 = No DLT observed * 1 = DLT observed | tox <- (0, 0, 0, 1) |
| include | Vector of indicators whether to include that patient in the dose escalation model, one per patient. | User enters indicator whether to include patient in the dose escalation model.   * 0 = Do not include in the model * 1 = Include in the model   In backend, select subset of PIDs to be included in the model | User entered:  user.include <- c(1,1,0,1)  Subset vector and find vector indicies for values equal to 1:  *include <- which(as.logical(user.include)])*  include = c(1,2,4) |

### Input option: import patient-level data as CSV file.

Users can upload a CSV file with the patient-level data in Table 2 (same format). The 4 input vectors are generated from the uploaded data.

## Output

After executing the *conduct.crm* or *conduct.target.crm* function, the print function is called to generate the output.

|  |
| --- |
| print.target.crm(*<conduct.target.crm object>*) |

|  |
| --- |
| print.crm(*<conduct.crm object>*) |

The formatted report is automatically generated. An example output is presented below:

|  |
| --- |
| > test <- conduct.target.crm(prior=c(0.05,0.10,0.2,0.30), target.tox=0.2, tox=c(0,0,0,0), dose.labels=c("100mg","200mg","300mg","400mg"),  + level=c(2,2,2,3), pid=c("C1","C2","C3","C4"), include=c(1,2,3,4), cohort.size=3, num.slots.remain=2, current.dose=3)  >  > print.target.crm(test)  DOSE ESCALATION RECOMMENDATIONS  Trial design: TARGET-CRM  Software: DEDUCE app version 1.0  URL: https://bengarski.shinyapps.io/DELPHI/  Today: Tue Mar 02 14:12:11 2021  DATA SUMMARY (CRM)  PID Level Toxicity Included  C1 2 0 1  C2 2 0 1  C3 2 0 1  C4 3 0 1  Toxicity probability update (with 90 percent probability interval):  Dose Level Prior n total.wts total.tox Ptox LoLmt UpLmt  100mg 1 0.05 0 0 0 0.002 0 0.201  200mg 2 0.1 3 3 0 0.008 0 0.291  300mg 3 0.2 1 1 0 0.033 0 0.422  400mg 4 0.3 0 0 0 0.078 0 0.524  Next recommended dose level: 300mg  Recommendation is based on a target toxicity probability of 0.2  Estimation details:  Empiric dose-toxicity model: p = dose^{exp(beta)}  dose = 0.05 0.1 0.2 0.3  Normal prior on beta with mean 0 and variance 1.34  Posterior mean of beta: 0.75  Posterior variance of beta: 0.698  Additional details:  Current dose level: 300mg  Cohort size: 3  Number of slots remaining at current dose level: 2  Dose escalation rules:  - No dose skipping upon dose escalation.  - Intra-cohort dose de-escalation is allowed.  - Intra-cohort dose escalation is not allowed. |

### Output option: print report to PDF.

Users can print the formatted report to PDF format.

## Output (Details)

The variables used to regenerate the desired output is provided below. The following code assumes that conduct.target.crm() has been executed and the output object is stored in ***test***. The blue-colored output in on the left column corresponds to the variable names on the right column.

|  |  |
| --- | --- |
| **Desired Output** | **Variable name** |
| DOSE ESCALATION RECOMMENDATIONS  Trial design: TARGET-CRM  Software: DEDUCE app version 1.0  URL: https://bengarski.shinyapps.io/DELPHI/ | Fixed text |
| Today: Tue Mar 02 14:12:11 2021 | Display current date and time |
| DATA SUMMARY (CRM)  PID Level Toxicity Included  C1 2 0 1  C2 2 0 1  C3 2 0 1  C4 3 0 1 | Display table from user-inputted patient data:  <test$crm.out$pid>  <test$crm.out$level>  <test$crm.out$tox>  <test$crm.out$include> |
| Toxicity probability update (with 90 percent probability interval): | Fixed text |
| Dose Level Prior n total.wts total.tox Ptox LoLmt UpLmt  100mg 1 0.05 0 0 0 0.002 0 0.201  200mg 2 0.1 3 3 0 0.008 0 0.291  300mg 3 0.2 1 1 0 0.033 0 0.422  400mg 4 0.3 0 0 0 0.078 0 0.524 | **Regenerate table using following variables:**  **\*\*Subset data for only PID’s with include==1\*\***  **Dose** = Each user-specified dose level label <test$crm.out$dosename>  **Level** = sequential numbering of doses starting with 1  **Prior** = <test$crm.out$prior>  **n** = tabulation of how many patients were given each dose. Need to calculate based on user-inputted data  **total.wts** = vector of zeros  **total.tox** = tabulation of how many patients had a DLT at each dose. Need to calculate based on user-inputted data.  **Ptox =** <test$crm.out$ptox>  **LoLmt** = <test$crm.out$ptoxL>  **UpLmt** = <test$crm.out$ptoxU> |
| Next recommended dose level: 300mg | The recommended dose is: <test$crm.out$mtd> |
| Recommendation is based on a target toxicity probability of 0.2 | The target toxicity probability is: <test$crm.out$target> |
| Estimation details:  Empiric dose-toxicity model: p = dose^{exp(beta)} | Fixed text |
| dose = 0.05 0.1 0.2 0.3 | List the prior toxicity probabilities again: <test$crm.out$prior> |
| Normal prior on beta with mean 0 and variance 1.34 | List the variance: <test$crm.out$prior.var> |
| Posterior mean of beta: 0.75 | List the posterior mean: <test$crm.out$estimate> |
| Posterior variance of beta: 0.698 | List the posterior variance: <test$crm.out$post.var> |
| Additional details: | Fixed text |
| Current dose level: 300mg | Use user-inputted current dose level (converted to user-inputted labels):  <crm.out$crm.out$dosename[crm.out$current.dose]> |
| Cohort size: 3 | List user-inputted cohort size:  <crm.out$cohort.size> |
| Number of slots remaining at current dose level: 2 | List number of slots remaining:  <crm.out$num.slots.remain> |
| Dose escalation rules:  - No dose skipping upon dose escalation.  - Intra-cohort dose de-escalation is allowed.  - Intra-cohort dose escalation is not allowed. | Fixed text |