Documentation for the program PRT_Conduct.exe
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Overview

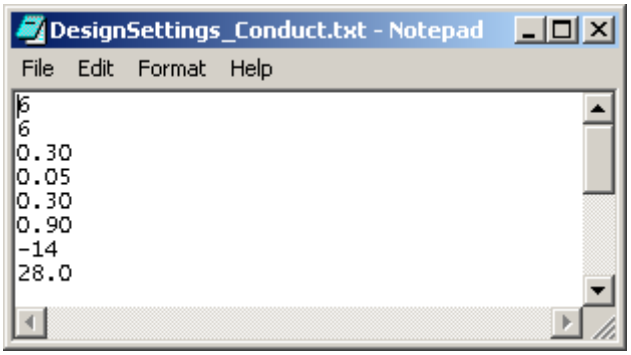
This readme file is intended to explain the inputs and outputs for the program "**PRT_Conduct.exe**" that implements the method described in "Monitoring Late Onset Toxicities in Phase I Trials Using Predicted Risks" by Bekele, Ji, Shen, and Thall. There are 2 input files associated with this program: 1) "**DesignSettings_Conduct.txt**" and 2) "**DataFile_Conduct.txt**." The formats of the **DesignSettings_Conduct.txt** and **DataFile_Conduct.txt** files are vital for proper execution of the program. The input files should be in the same folder as the compiled executable program **PRT_Conduct.exe**.

This program runs on the Microsoft Windows operating system. Please send comments, suggestions and information concerning programming bugs to bbekele@mdanderson.org.

The following program is used to decide whether or not to suspend accrual and, if accrual is not suspended, determine an appropriate dose for the next cohort of patients. These rules should be applied after the last patient of the current cohort has been enrolled. If the rules indicate that accrual should not be suspended, the investigators should enroll the next cohort of patients and treat them at the dose indicated by the rules. If the rules indicate accrual should be suspended, the investigators should re-apply these rules each time a new patients arrives at the clinic or a patient previously not allowed to enroll due to suspended accrual is reconsidered for enrollment. A patient previously not allowed to enroll may be reconsidered anytime the current trial data is updated, which occurs when a toxicity is observed or a currently enrolled patient advances from one interval to the next. From a practical perspective, the investigators may wish to define a maximum waiting time after which a patient would receive an alternative treatment.

1. Description of DesignSettings_Conduct.txt File

The following screenshot is an example of an appropriately formatted **DesignSettings_Conduct.txt** file:

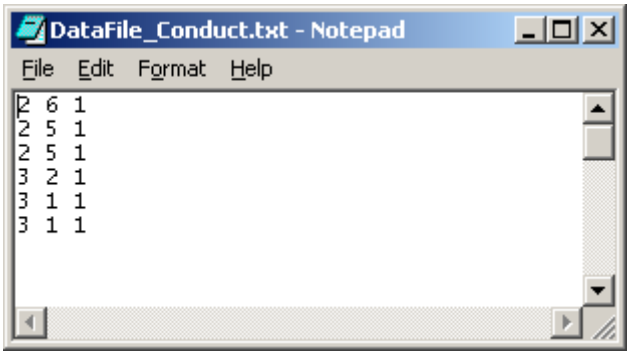


An explanation of the above screenshot is found in the Table below. We employ a color-coding scheme to explain these inputs. Text in red are the actual inputs. Text in black explains the purpose of each input. An example **DesignSettings_Conduct.txt** file is included when the **PRT(Conduct).exe** file is downloaded from the M. D. Anderson software download website.

Line Number(s)	Example Input	General Description of Input
1	**6**	Number of Discrete Time Periods. Denoted as *C* in the paper. Integer Input. Use integer values between 3 and 10.
2	**6**	Number of Doses. Maximum Number of Possible Doses is 10. Integer Input. Use integer values between 2 and 10.
3	**0.30**	π^* Target Toxicity Rate. This input must take on values between 0 and 1. Common values range between 0.20 and 0.35.
4	**0.05**	ε predictive probability cutoff used in decision rules 5 and 6. See paper for recommended values.
5	**0.30**	$\underline{\xi}$ lower posterior probability Cutoff used to define *negligible* toxicity. See paper for recommended values.
6	**0.90**	$\overline{\xi}$ Upper posterior probability Cutoff used to defined *excessive* toxicity.
7	**-14.0**	$\beta_{j,0}$ State-Space Model Prior mean for $\beta_{j,1}$. Assumed to be the same for all j.
8	**28.0**	σ_β^2 Prior variance of $\beta_{j,k} \mid \beta_{j,k-1}$

2. Description of DataFile_Conduct.txt File

The following screenshot provides an example of how to appropriately format the **DataFile_Conduct.txt** file. Each line of input represents data for a given patient including: 1) the dose received by the patient (first column of data in the screen shot); 2) the number of sub-intervals for which a patient has been fully evaluated (second column of data in the screenshot); and 3) whether the patient was censored without toxicity (0 indicates patient was not censored and 1 indicates patient was censored). An example **DataFile_Conduct.txt** file is included when the **PRT_Conduct.exe** file is downloaded from the M. D. Anderson software download website.



The following table explains the status of each patient in the data file

Patient	Dose	Follow-up
1	**2**	Patient has been followed 6 sub-intervals without toxicity
2	**2**	Patient has been followed 5 sub-intervals without toxicity
3	**2**	Patient has been followed 5 sub-intervals without toxicity
4	**3**	Patient has been followed 2 sub-intervals without toxicity
5	**3**	Patient has been followed 1 sub-interval without toxicity
6	**3**	Patient has been followed 1 sub-interval without toxicity

3. Outputs

Output generated by this program is found in found in '**out_Conduct.txt**' and has the following format:

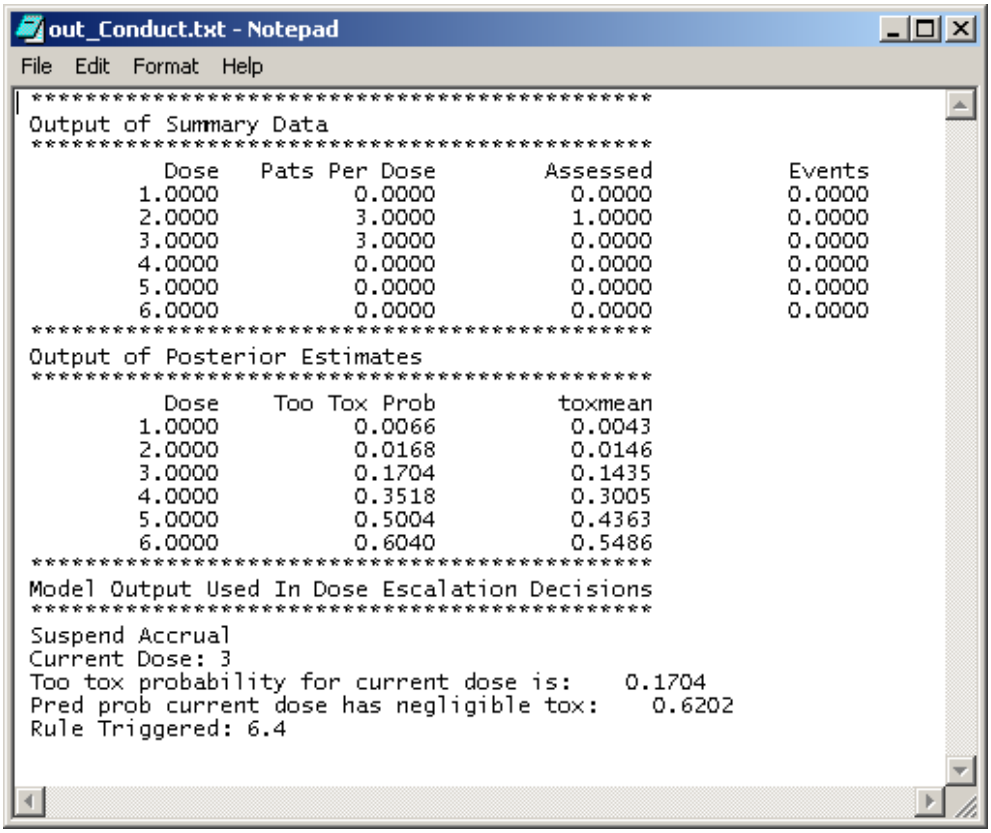
- Decision:

  1) First Dose is too toxic (STOP TRIAL)
  2) Current Dose is too toxic (De-Escalate)
  3) Allow Accrual of patients at current dose
  4) Allow Accrual at Next Highest Dose
  5) Suspend accrual.

- Relevant values for $\xi_k, PN_k(\bullet), PE_k(\bullet), PE_{k+1}(\bullet)$ which triggered Decision Above.

- Rule Triggered (3,4,5.1,5.2,6.1,6.2,6.3,6.4).

An example of the output based on the inputs for the **DesignSettings_Conduct.txt** in section 1 above and **DataFile_Conduct.txt** from section 2 is given in the following screen shot:



The output is organized into 3 sections. The first section, titled "Output of Summary Data", provides summary information regarding the number of patients enrolled by dose (under the heading "Pats Per Dose"), number of patients fully assessed (under the heading "Assessed") and number of patients who have experienced events (under the heading "Events"). The second section, titled "Output of Posterior Estimates", provides information about the posterior probability that a dose is too toxic (under the heading "Too Tox Prob") and the posterior mean probability of toxicity at each dose. The last section "Model Output Used in Dose Escalation Decisions" summarizes the relevant values of values for $\xi_k, PN_k(\bullet), PE_k(\bullet), PE_{k+1}(\bullet)$. In this example, The decision is to suspend accrual because at the current dose, 3, the there is only negligible toxicity since 0.1704 (posterior probability that the 3rd dose is too toxic) is less than 0.30 ($\underline{\xi}$, the lower posterior probability Cutoff used to define *negligible* toxicity). Moreover, because the 3rd dose is deemed to have negligible toxicity we must calculate the predictive probability that the 3rd dose has negligible toxicity. The predictive probability that the 3rd dose has negligible toxicity is 0.6202. Since 0.6202 is less than 0.95=1- ε (where ε is the predictive probability cutoff used in decision rules 5 and 6. See paper for recommended values).