# Designing Phase I Single Agent Dose-Escalation Studies

MRC Biostatistics Unit

## Practical 1: Dose-escalation with MoDesT

In this practical, we are going to design a Phase I dose-escalation trial in patients with late stage pancreatic cancer. The safety outcome of interest is a dose-limiting toxicity (DLT) within the first cycle of the treatment (28 days). The objective of the trial is to study safety and tolerability of the new experimental drug (administered as a monotherapy) and to identify the maximum tolerated dose (MTD), the dose of the new therapy associated with a 25% risk of a DLT. During the trial, patients can be allocated one of 10 doses from the set

$$(0.5mg, 1mg, 2mg, 4mg, 6mg, 8mg, 10mg).$$

Up to 24 patients will be enrolled in the study in the cohort of 3 patients. The escalation will start at the lowest dose level of 0.5mg and no dose-skipping is allowed. The next cohort of patients will be allocated to the dose with the estimated risk of toxicity closet to the target value of 25%. There is currently no further restrictions being discussed. The study will proceed according to the Bayesian Logistic Regression Model as proposed by Whitehead and Williamson (1998).

Eliciting the prior belief on the dose-toxicity relationship from the clinical team, the study statistician has found that prior beliefs for the study can be represented as pseudo-data for five patients, of whom three received dose $d_{-1} = 0.5$ mg and gave $t_{-1} = 0.15$ toxicities and two received dose $d_0 = 10$ mg and gave $t_0 = 0.5$ toxicities.

To start working with the MoDesT Shiny App, run the following code:

```
library("modest")
design()
```

(a) Supply relevant parameter of the prior distribution and the prior setting into the `design` tab of the MoDesT application. What prior beliefs for the dose-toxicity relationship do these pseudo-data imply?

(b) Are the expectation about the safety of the new drug optimistic or pessimistic? What are the advantages and disadvantages to imposing such a prior?

Before recommending the design for the use in the trial, it should be thoroughly evaluated via simulations to ensure that it results in good operating characteristics in various scenarios. Consider the

following simulation scenario: the probability of DLT at 2mg is 1%, and the probability of a DLT at 8mg is 45%.

(c) Supply relevant parameter of the scenario (simulation model). Under this simulation model, what is the true MTD

(d) Run a number of simulations under the assumed simulation model. How many simulations will you choose? Why?

(e) Examine several individual escalation/de-escalation trajectories on the tab "Example". Are these trajectories following intuitive decisions or are there any concerns? If yes, how these could be tackled? Implement your solution and examine the trajectories again.

Now, you need to ensure that the design results in accurate conclusions regardless of the scenario. The tab "Scenarios" creates variations to the "Standard" simulation model specified above.

(f) Under the restricted resources, assume that you need to limit number of scenarios. Which one would you start with?

(g) Run simulations under the selected scenarios and examine the output. Analyse the output. Could you recommend such a design for a use in an actual trial? If not, propose appropriate modifications, implement them and assess the design again.

At the next step of the discussions, the clinical team asks to explore whether the trial could recruit fewer patients. For this, you are asked to explore early stopping rules

(h) Explore "Stop after a given number of consecutive patients at the same dose" rule. Consider several value of the number of patients at the same dose triggering early stopping of the trial. What are the impact on the expected sample size? Are there any disadvantages to this approach?

(i) Once you can recommend a design, download the `csv` design file.

Now, it is time time to conduct the trial using the developed design. Use the developed design to guide the dose recommendation in the trial. Open the "conduct" tab of the MoDesT application using `conduct()` function and upload the design file. Examine the summary of the design and check that the all the parameters of the developed designs are correctly displayed and safe.

Assume that the first cohort of patient was assigned to 0.5mg and no DLTs were observed followed by the cohort of 3 patients at 1mg with no DLTs. Then, a cohort has received 2mg with 2/3 DLTs.

(j) Upload the data into the app. Examine the "Dataset" tab. What is the current recommendation of the model? What is the estimated risk of toxicity at the recommended dose? Why does the model make this recommendation?

(k) Assume that the trial follows the model recommendation, and the next cohort experiences 2/3 DLTs. What is the recommendation now? Examine the output of the model.