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

$$\{0.5, 1, 2, 4, 6, 8, 10\} \text{ mg}.$$

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.

(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?
These prior beliefs are optimistic as the last dose is thought to be the prior MTD.

(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?

Without any further escalation constraints such an optimistic prior can lead to overly aggressive escalation decisions and lead to assign many patients to overly toxic doses. At the same time, if the drug indeed has a flat dose-toxicity relationship, such prior beliefs will allow to reach the higher (target) doses earlier.

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
The true MTD is 6mg.

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

Given a relative quick computation time, 1000 simulation could be run very quickly. For the actual real simulation study, one should use more to have a more reliable estimates of the operating characteristics of the design.

(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.

Given such an optimistic prior, one can discover that under some trajectories after a DLT outcome is observed, a dose-escalation is still recommended. This could be unintutive and undesirable feature of the design (as we need to align the design as close as possible with what will happen in the actual trial to optimise its performance. One solution is to add the restriction of not escalating after observing a DLT. An alternative is to revise the prior distribution as it is the reason for such a behaviour.

Now, when trajectories are satisfactory, 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?

Under the restricted resources, one ought to focus on the "base" simulation scenario and on more extreme ones, i.e. the steepest scenario (very potent) and the flattest scenario (very inactive).

(g) Run simulation 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.

If the solution above was to disable escalation after a DLT outcome, then one can still notice that under such an optimistic prior the design tends to select overly toxic doses with high probability. To tackle this further, one can revise the toxicity rate at the highest dose. One of the solution

is to increase it to 0.5-0.6 (0.6 is chosen in this solution). The cost of this is that under flatter scenarios one can decrease the proportion of correct dose selections.

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?

After examining the early stopping rule, one can find the decrease in the expected sample size. At the same time, for a very low number of patients (e.g. 6 patients, which is a common number in trials [not endorsed]), this can result in severely decreased proportion of correct selection, especially in flatter scenarios where it is harder to reach the highest doses.

(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 study is already in progress. 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 and 2/3 DLTs were observed.

(j) Upload the data into the app. Examine the "Dataset" tab and see whether you find it useful to communicate the trial state to the team. What is the current recommendation of the model? Is it intuitive? What is the estimated risk of toxicity at the recommended dose? Why does the model make this recommendation?

The recommendation now is to stay at 2mg. Given no DLT outcomes on lower doses and limited prior information, this is an intuitive solution and aligned with the estimates of the model (rather than triggered by the escalation restriction).

(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.

The recommendation now is to de-escalate to 1mg. Given 4/6 DLT outcomes on current dose, the current dose is estimated to be too toxic and the lower 1mg is recommended.