

# Designing Phase I Single Agent Dose-Escalation Studies

MRC Biostatistics Unit

## Practical 2: Dose-escalation with `crmPack`

### 1. A model-based dose-escalation study based on safety only

In this practical, we will design a model-based dose-escalation trial that uses DLT/no DLT outcomes only to drive the decision-making. We will use `crmPack` to set up the design and to evaluate it.

The experimental compound is just about to go into humans and the team want to determine the MTD with a target toxicity rate of about 30%. The lowest possible dose is 1 mg, the maximum clinical dose is 150 mg. Doses can be given with 1 mg difference. The starting dose shall be 10 mg.

The file `template1.R` can be used as a starting point for this exercise.

1. There is preclinical evidence that leads to the following prior assumptions: At 10 mg, the expected toxicity is about 10%, and you can assume a 95% credible interval of (5%, 40%). At 100 mg, the expected toxicity is about 40%, and you can assume a 95% credible interval of (15%, 80%). Please use the function `Quantiles2LogisticNormal` to derive from these settings a model with logistic log normal distribution on the parameters. You can use a reference dose of 1 mg and limit the search to 10 seconds. Plot the prior to make sure the required quantiles are approximately kept by the prior.
2. Please use a next best dose recommendation with a target toxicity interval of 20% to 35%, everything above that will be considered overdosing. The design shall limit the overdosing probability below 25% at any point during the trial.
3. The team would like to evaluate the possibility of starting with a cohort size of 1 patient only. As soon as there is 1 DLT, the design would then switch to (at least) 3 patients per cohort. However, at doses above 50 mg, definitely 3 patients should be used. Use `CohortSizeDLT`, `CohortSizeRange` and `maxSize` for the implementation.
4. The maximum number of patients shall be 45 (so the design shall stop when at least 45 patients have been dosed already). For stopping earlier, the target probability should be at least 40% and at least 6 patients shall have been dosed within 10% of the MTD. Also, at least 10 patients should have been dosed in total.
5. The maximum possible increment between doses shall be limited to 100% below a dose of 75 mg, and to 50% above 75 mg.

6. Evaluate the single trial behaviour of the CRM design. Is it reasonable or do you have to change anything? How many cohorts are at least needed to reach 150 mg?
7. Set up three scenario functions: one which resembles the prior assumptions, one which is more toxic, and one which is less toxic. Plot the three dose-DLT rate curves. Then run 20 simulations in each of the scenarios and report summary statistics.
8. Compare with a 3+3 design implemented with the RuleDesign class. First you need to choose a few doses out of the dose range. Be careful that the dose grid respects the maximum increments stated above. Then run 100 simulations for each of the three above scenarios. What do you observe?

## 2. Dual endpoint (toxicity/biomarker) dose escalation

In this exercise, we are going to design a single-agent model-based dose-escalation problem. The clinical team believes that the toxicity might not be a good predictor of efficacy for the experimental agent in question, hence, the decision to consider both toxicity and activity was made. The activity is measured in terms of a biomarker (continuous scale).

A compound is just about to go into humans and the team want to determine the dose which gives the best chance to be in the biomarker target interval of 50 to 70, while controlling the probability of overdosing below 25%. The lowest possible dose is 1 mg, the maximum clinical dose is 150 mg. Doses can be given with 1 mg difference. The starting dose shall be 10 mg.

You can use the file `template2.R` as starting point.

1. Please specify a probit model for the dose-toxicity model which approximately gives 10% DLT rate at a dose of 10 mg and 50% DLT rate at a dose of 150 mg, with considerable uncertainty around it. (No single solution here.)
2. Please specify a joint dose-toxicity/biomarker model using the probit settings from no. 2, and an Emax model for the dose-biomarker relationship with uniform priors for E0 between 0 and 20, for Emax between 20 and 100, for ED50 between 10 and 50. The correlation between toxicity and biomarker should have a uniform prior, and the prior on the biomarker variance should have an inverse-gamma prior with parameters 0.1 and 0.1.
3. Please use a next best dose recommendation with a target biomarker interval of 50 to 70 (absolute scale). The design shall also limit the overdosing probability below 25% at any point during the trial, where any DLT rate above 25% is considered as overdosing.
4. The team will use a constant cohort size of 3 patients.
5. The maximum number of patients shall be 30 (so the design shall stop when at least 30 patients have been dosed already).

For stopping earlier, the target biomarker probability should be at least 40% and at least 6 patients shall have been dosed within 10% of the MTD. Also, at least 10 patients should have been dosed in total.

6. The maximum possible increment between doses shall be limited to 100% below a dose of 75 mg, and to 50% above 75 mg.
7. Set up two scenario biomarker functions: one which never reaches the target biomarker level in the dose range considered, one which reaches it in the middle of the dose range. (For the scenario toxicity functions, use the function in the template file.) Use a biomarker variance of 2, no correlation between toxicity and biomarker, and the prior mean values for the toxicity scenario function.

Then run 20 simulations in each of the two biomarker scenarios and report summary statistics.

8. Depending on your satisfaction with the simulation results, go back to the model prior specifications and see if it helps.