



MRC
Biostatistics
Unit



UNIVERSITY OF
CAMBRIDGE

Designing Phase I Single Agent Dose-Escalation Studies

Lecture 3: Interactive apps for model-based designs

Pavel Mozgunov & Thomas Jaki

MRC Biostatistics Unit

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Implementation of model-based designs

- Model-based designs require more effort to be implemented;
- Interactive web apps for model-based designs;
- Require **no programming skills**;
- Can be used for both **simulation and implementation**.

Know your enemy: A web app for A+B designs

AplusB: A + B design investigator for phase I dose-escalation studies

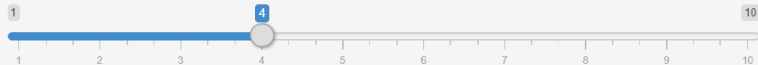
Graham Wheeler

Cancer Research UK & UCL Cancer Trials Centre, University College London, UK; graham.wheeler@ucl.ac.uk

MRC Biostatistics Unit Hub for Trials Methodology Research, Cambridge, UK; graham.wheeler@mrc-bsu.cam.ac.uk

Scenario parameters

Number of dose levels:



App: <https://graham-wheeler.shinyapps.io/AplusB/>

Code: <https://github.com/graham-wheeler/AplusB>

Paper: Wheeler, Sweeting & Mander (2016): PLoS ONE, 11(7)

Bayesian CRM web app

Bayesian Continual Reassessment Method for Phase I Clinical Trials

Simulation

Implementation

Web Application for simulating operating characteristics of the Bayesian CRM

Nolan A. Wages and Gina R. Petroni

Division of Translational Research & Applied Statistics, University of Virginia; nwages@virginia.edu

1. Enter an assumed set of true DLT probabilities, separated by commas. **Note:** The length of this set should be equal to the number of

True DLT probability at each dose level

0.04,0.11,0.25,0.40,0.55

2. Enter the target DLT rate.

Target DLT rate

0.25

App: <https://uvatrapps.shinyapps.io/crmb/>

Paper: Wages, Petroni (2018): BMC Cancer; 18:133.

Designing a Model-Based Dose-Escalation Study

Philip Pallmann & Fang Wan

Department of Mathematics & Statistics, Lancaster University, UK

1. Basic settings

Specify some key parameters of your study.

2. Prior information

Specify your prior opinion about the toxicity rates for two distinct doses, and the strength of your opinion in terms of pseudo-observations.

- aimed at clinical trialists, useful for statistical experts;
- encourages to play around with a variety design options;
- automatically generates PDF reports.

Package: <https://cran.r-project.org/web/packages/modest/>

App: `design()` `conduct()`

Paper: Pallmann et. al (2020). Clinical Trials, 17(2), pp.147-156.

Design: `design()` in R

1. Basic Setting & Allocation Criterion

1. Basic settings

Specify some key parameters of your study.

Maximum number of patients:

Patients per cohort:

Target toxicity level:



Doses (comma-separated):

Gain function:

Patient gain

- Maximum Number of Patients
- Cohort size
- Target Toxicity Level
- Dose levels
- Gain Function
 - ▶ “**Patient Gain**” assigns to the dose currently thought to be closest to the target toxicity level (optimal for the current patient)
 - ▶ “**Variance Gain**” chooses the dose maximising learning about the dose-toxicity relationship (optimal for the investigator)

2. Prior for dose-toxicity model parameters

2. Prior information

Specify your prior opinion about the toxicity rates for two distinct doses, and the strength of your opinion in terms of pseudo-observations.

Lower dose

Dose:

1

Toxicity rate:



Pseudo-observations:

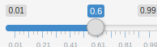
5

Higher dose

Dose:

3

Toxicity rate:



Pseudo-observations:

2

- Defining the prior beliefs for β_0 and β_1 can be difficult.
- Less difficult: prior **beliefs for two distinct doses**.
- Strength of beliefs in terms of **“effective sample sizes”**.

3. Simulation Model

3. Simulation model

Specify the 'true' dose-toxicity relationship for simulation in terms of toxicity rates for two distinct doses.

Lower dose	Higher dose
Dose: <input type="text" value="1"/>	Dose: <input type="text" value="3"/>
Toxicity rate: <input type="range" value="0.1"/> 0.01 0.21 0.41 0.61 0.81 0.99	Toxicity rate: <input type="range" value="0.4"/> 0.01 0.21 0.41 0.61 0.81 0.99

- As we conduct simulation, we need to assume the **true dose-toxicity scenario**.
- In MoDEsT the scenario is defined in terms of the logistic model.
- Similarly to the prior specification, **specify the true (!) toxicities** at the first and last
- The Shiny will fit the logistic model.

4. Escalation and Stopping Rules

4. Escalation & stopping rules

Specify rules for dose escalation and stopping the study.

- ☒ Always start at the lowest dose
- ☒ Don't skip over any doses when escalating
- ☒ Don't escalate upon observing a toxicity
- ☒ Stop after a given number of consecutive patients at the same dose

Number of patients:

9

Accuracy for stopping:

1 1.3 7

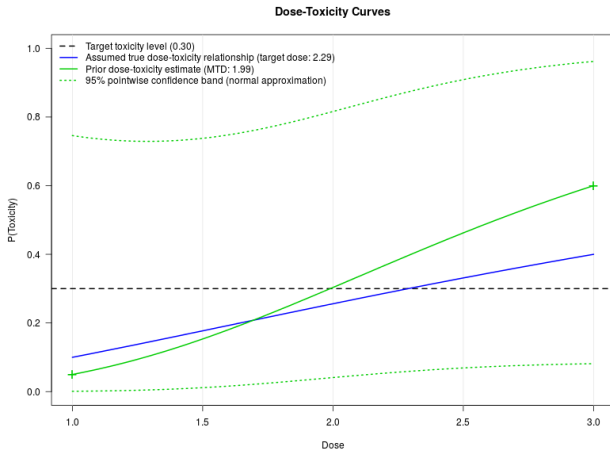
Additional restrictions:

- always start at the **lowest**
- **do not skip** over any doses when escalating
- do not escalate if **toxicity** is observed in current cohort.

Stop recruitment if

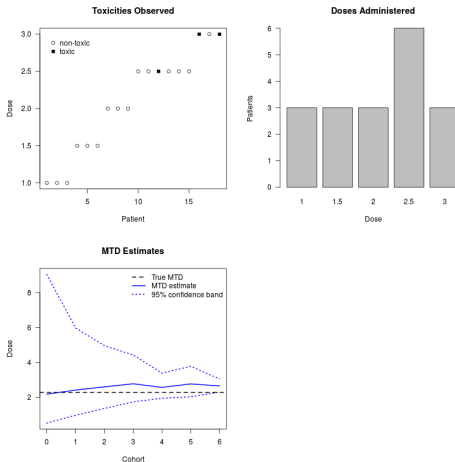
- a pre-defined **number of consecutive patients** receiving the same dose;
- **no safe dose**;
- achieved **sufficiently accurate estimate**.

Output: Model



- Green curve is the **prior** dose-toxicity model
- The blue curve - the **true** dose-toxicity relationship.

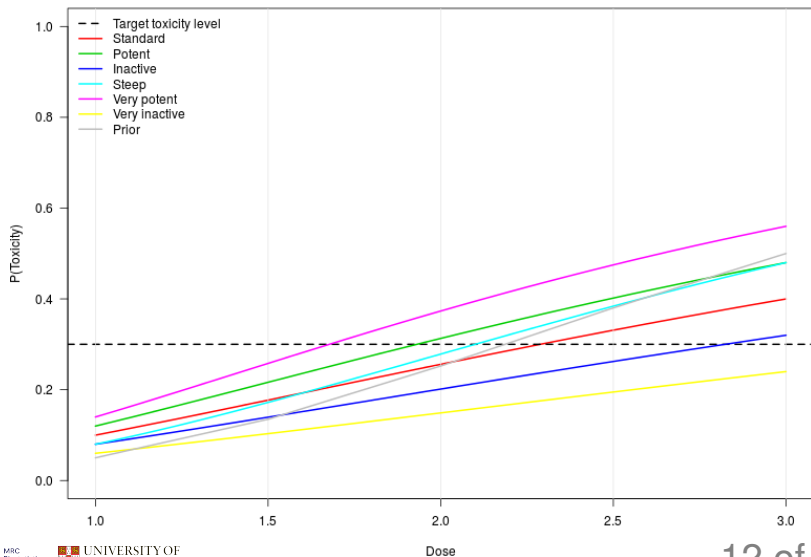
Output: Example



- **One** dose-escalation **study** is simulated.
- The graphs are the **illustrative example**.

Output: Scenarios

Simulation Scenarios



5. Simulations

Specify the simulation settings. The six scenarios are shown under the 'Scenarios' tab.

Scenario:

- ☒ Standard ☐ Potent ☐ Inactive ☐ Steep
☐ Very potent ☐ Very inactive

Repetitions:

Output: Simulations

The first table presents simulation averaged results.

Here are simulation results. Sample size, maximum likelihood estimate (MLE) of the MTD, mean squared error (MSE), bias, and toxicity rate are averaged over all simulation runs.

Scenario	Runs	Sample size	MLE	MSE	Bias	Toxicity rate
Standard	1000	18.39	2.21	0.65	-0.08	0.22

Percentage of simulation runs where the study was stopped for the following reasons:

Scenario	All patients used	Accuracy reached	All doses unsafe	Consecutive patients at a dose reached
Standard	6.7	1.2	1.5	94.5

When multiple simulations are conducted for **different settings**, further rows are added

A number of figures summarising operating characteristics are produced

Output: Downloads

- A CSV design file for the use in the “**Conduct**” app;
- a PDF report summarising the design, prior information, and simulation results;
- A CSV file with detailed results of the simulations run under the current scenario.

Implementation: `conduct()` in R

Conduct

1. **Upload design** file (saved in the DESIGN part of the app)
2. **Upload data** (as a **CSV file**, or entered **manually**).
CSV should contains a row per patient and three columns:
Cohort, Dose, Event

Alternatively, tick the box to enter data **manually**.

2. Upload data

☒ Enter data manually into a spreadsheet

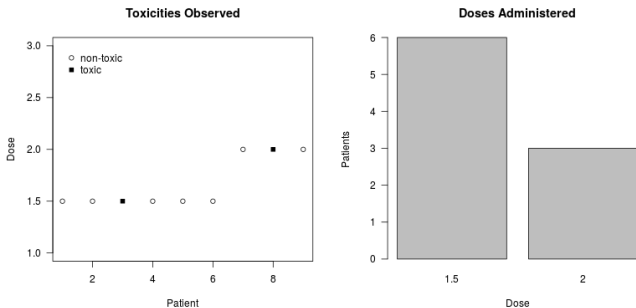
	Cohort	Dose	Event
1	1.00	1.50	<input type="checkbox"/>
2	1.00	1.50	<input type="checkbox"/>
3	1.00	1.50	<input checked="" type="checkbox"/>
4	2.00	1.50	<input type="checkbox"/>
5	2.00	1.50	<input type="checkbox"/>
6	2.00	1.50	<input type="checkbox"/>
7	3.00	2.00	<input type="checkbox"/>
8	3.00	2.00	<input checked="" type="checkbox"/>
9	3.00	2.00	<input type="checkbox"/>

Click on a cell to manipulate its entry.

Right-click anywhere on the table to add or remove rows.

Conduct: Output

1. **Design:** tables give an overview of the design parameters.
2. **Dataset:** a table displays the full dataset and two plots

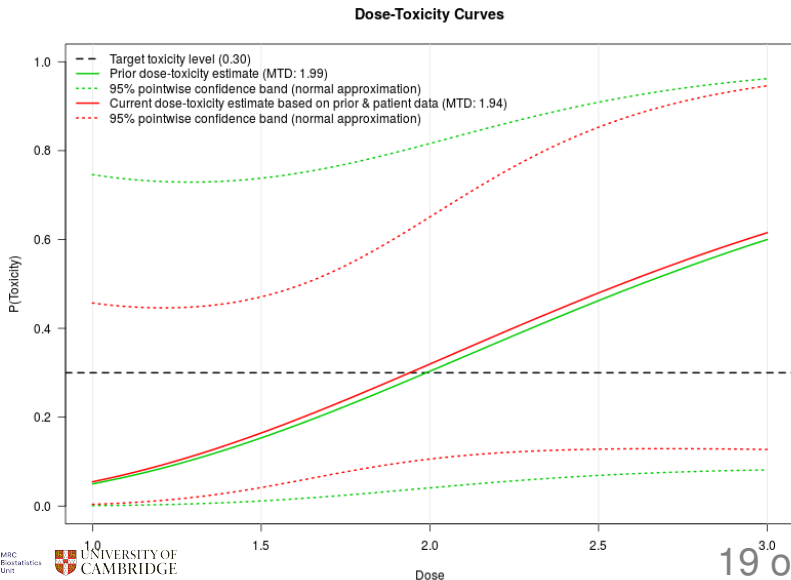


3. **Recommendation** is given for the next cohort:
 - ▶ to repeat/escalate/de-escalate the dose;
 - ▶ to stop recruitment to the study (for particular reasons)

Given the prior information and data from the last 9 patients, the recommended dose for the next cohort of patients is 2.

Conduct: Output

A plot: the estimated **dose-toxicity** & the **MTD**.



A PDF report summarising

- the design,
- prior information,
- study data,
- the recommendation

is available for download.