MRC Biostatistics Unit

UNIVERSITY OF CAMBRIDGE

Designing Phase I Single Agent Dose-Escalation Studies

Lecture 3: Interactive apps for model-based designs

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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**.

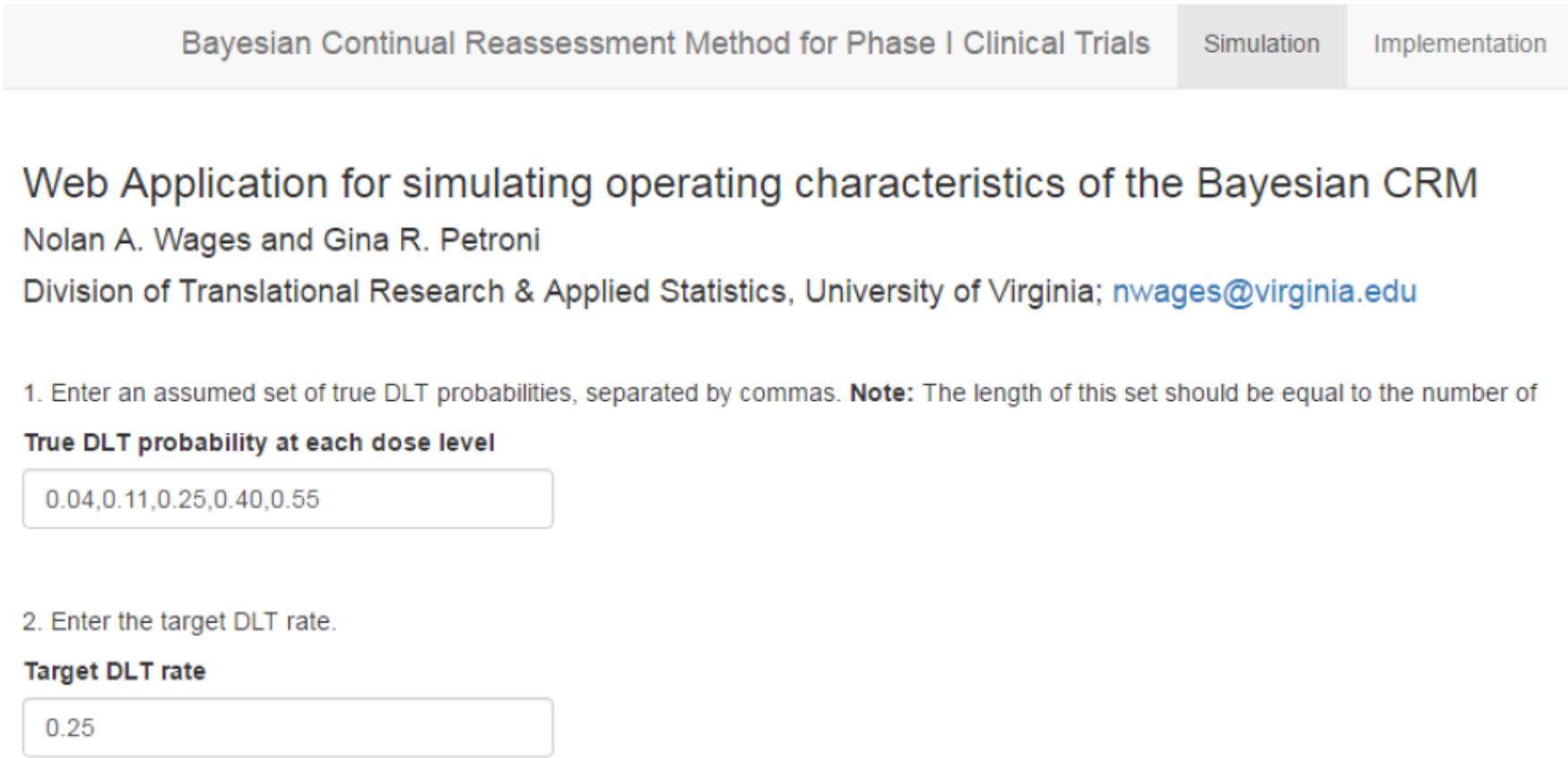
Know your enemy: A web app for A+B designs

App: `https://graham-wheeler.shinyapps.io/AplusB/`

Code: `https://github.com/graham-wheeler/AplusB`

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

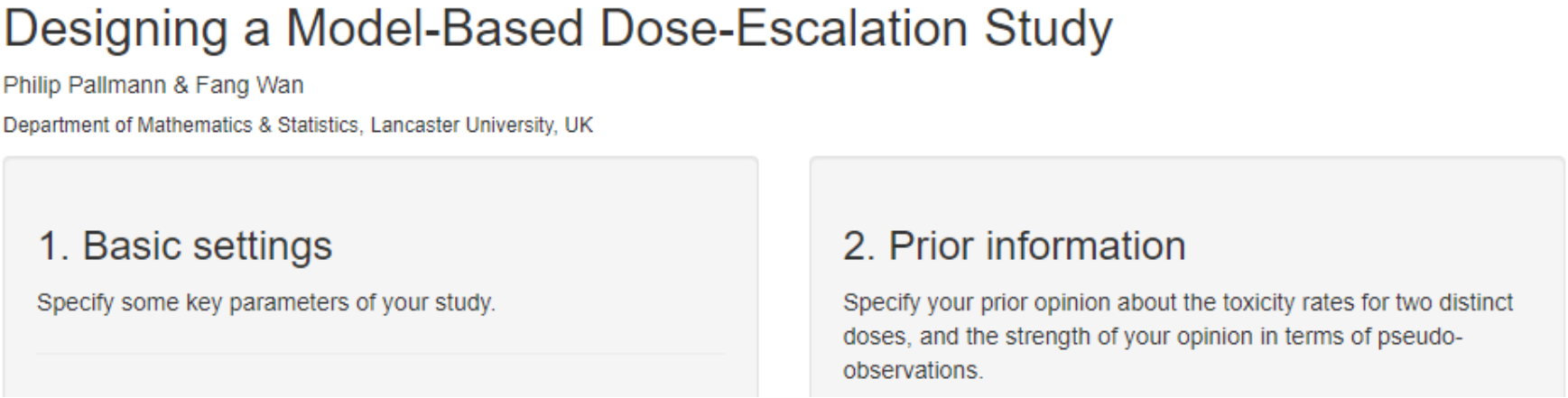
Bayesian CRM web app



App: `https://uvatrapps.shinyapps.io/crmb/`

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

BLRM web app (MoDEsT)



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

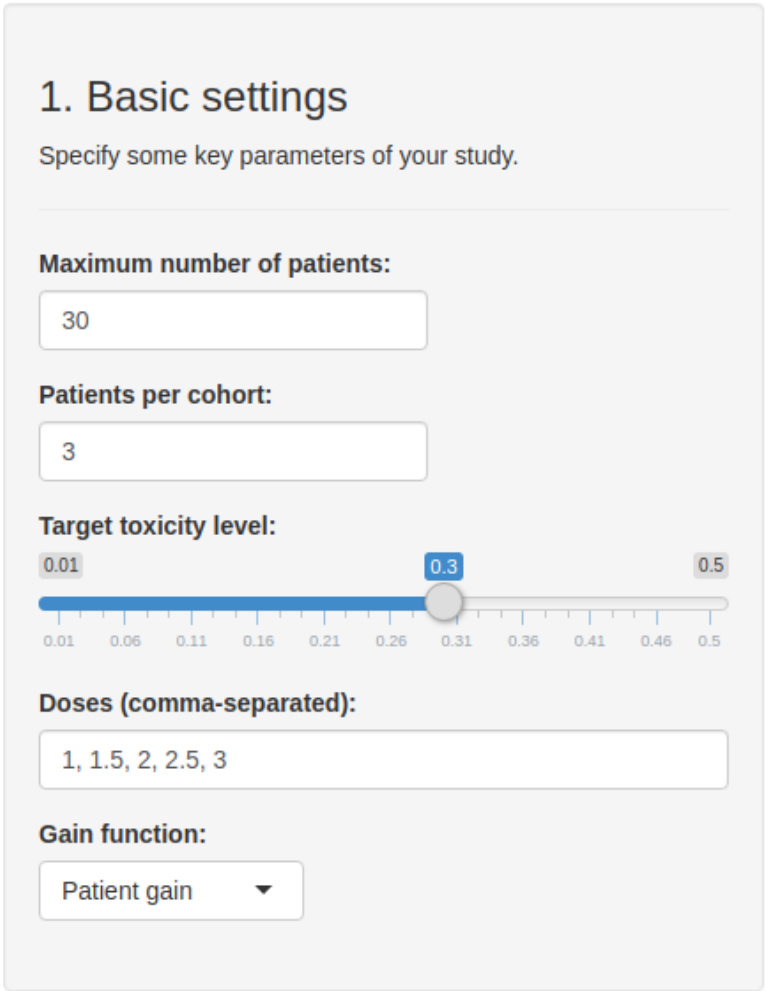
Package: `https://cran.r-project.org/web/packages/modest/`

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

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

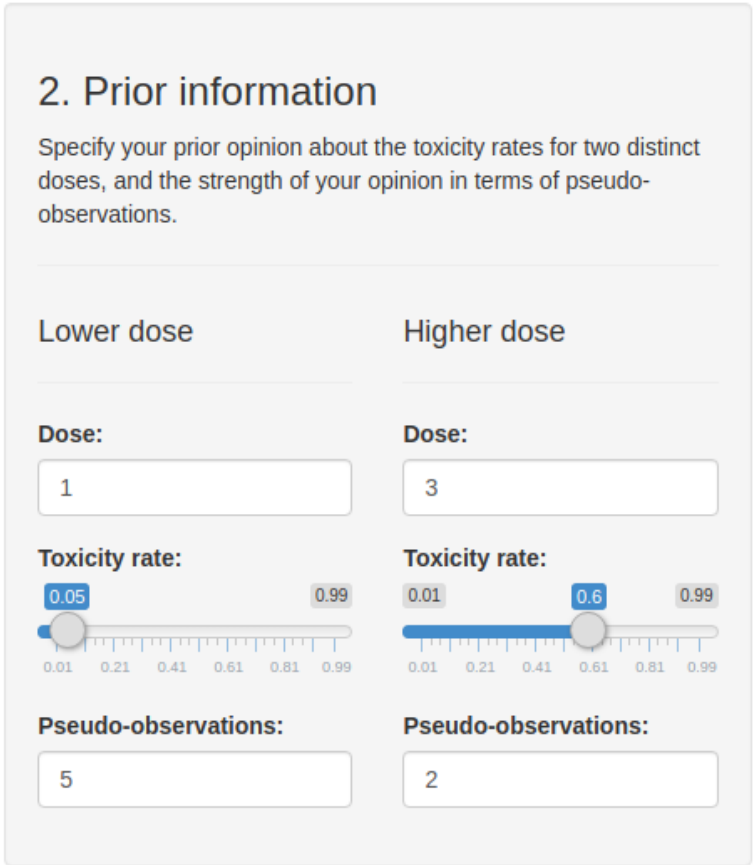
Design: `design()` in R

1. Basic Setting & Allocation Criterion



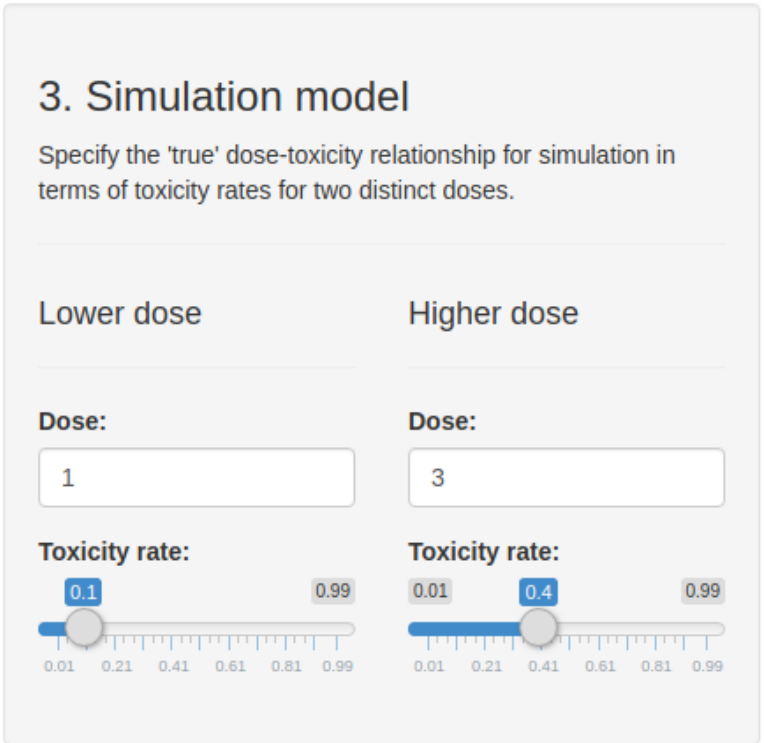
- Maximum Number of Patients
- Cohort size
- Target Toxicity Level
- Dose levels
- Gain Function
  - "**Patient Gain**" assigns to the dose currently thought to be closest to the target toxicity level (optimal for the current patient)
  - "**Variance Gain**" chooses the dose maximising learning about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

2. Prior for dose-toxicity model parameters



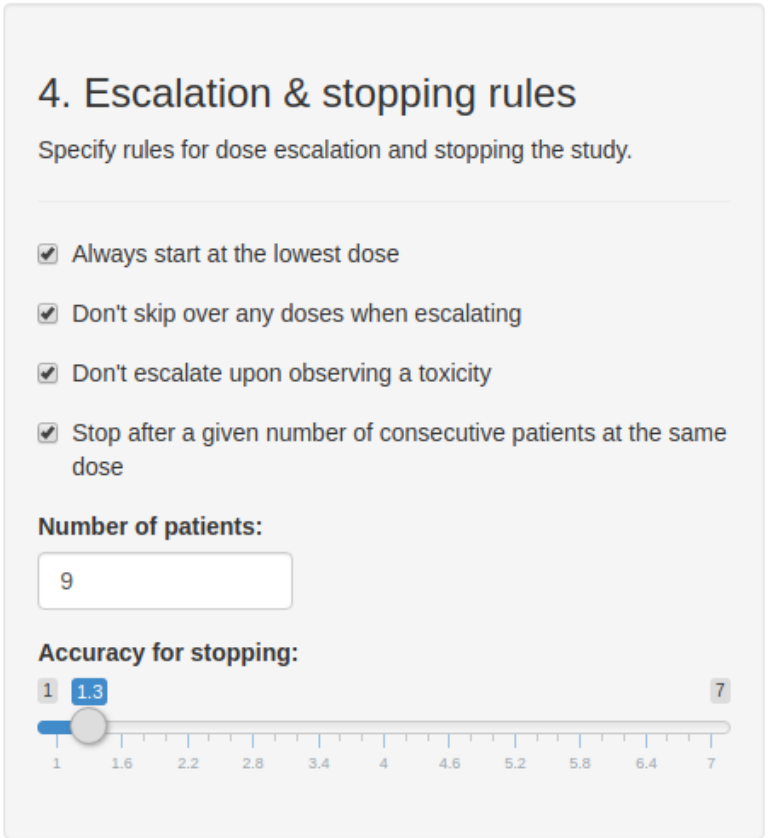
- Defining the prior beliefs for β_0 and β_1 can be difficult.
- Less difficult: prior **beliefs for two distinct doses**.
- Strength of beliefs in terms of "**effective sample sizes**".

3. Simulation Model



- 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



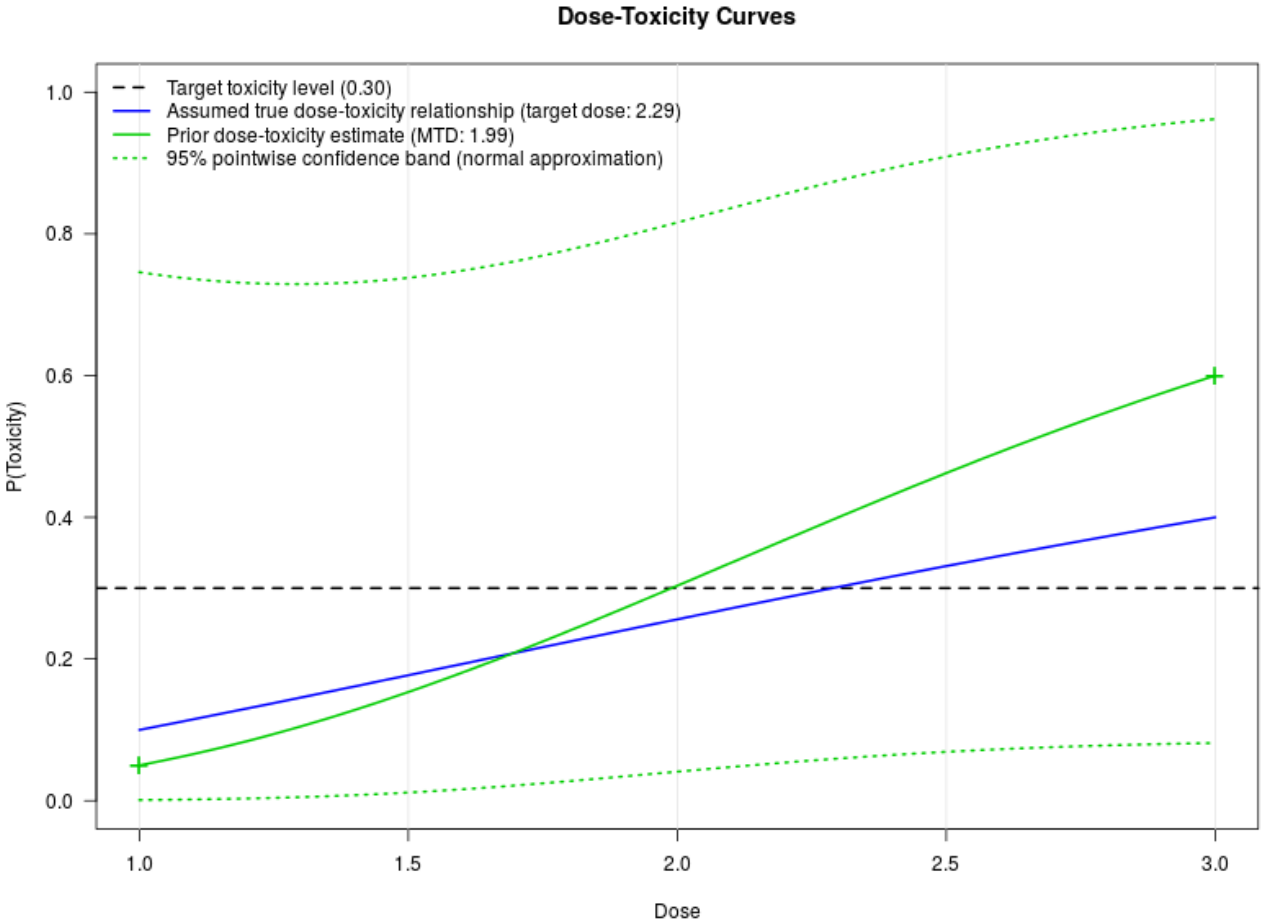
Additional restrictions:

- 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

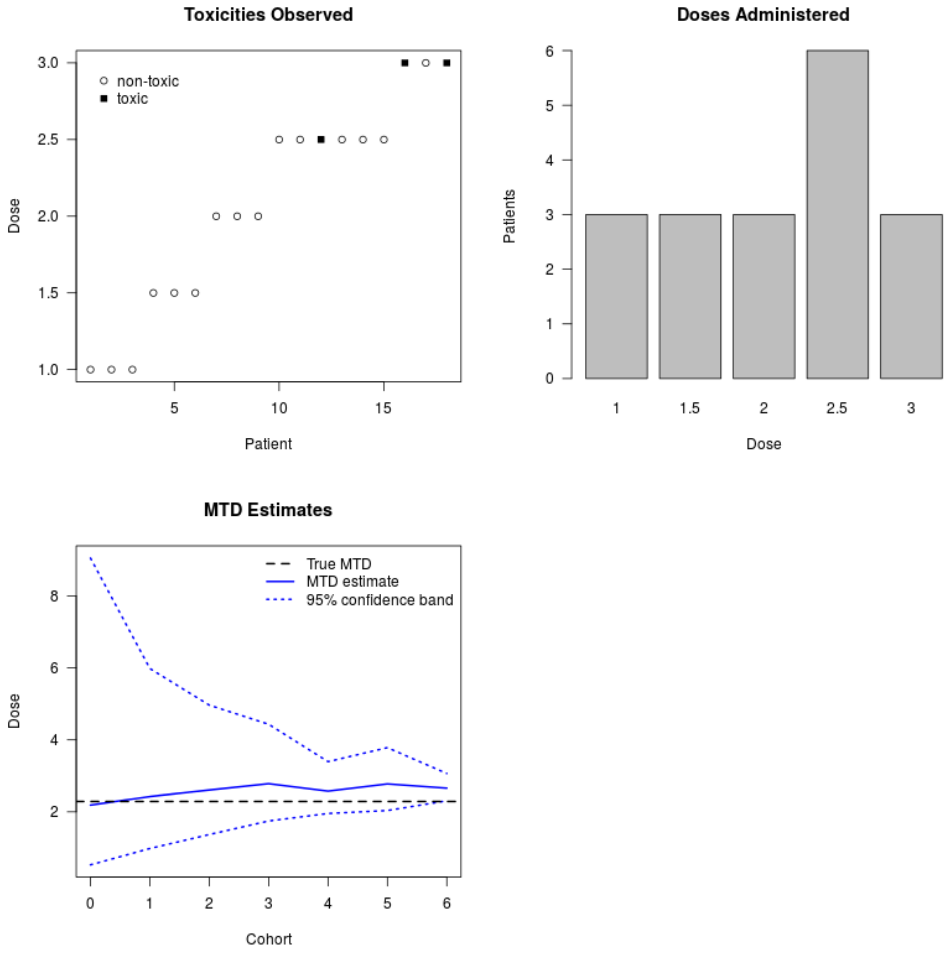
- a pre-defined **number of consecutive patients** receiving the same dose;
- **no safe dose**;
- achieved **sufficiently accurate estimate**.

Output: **Model**



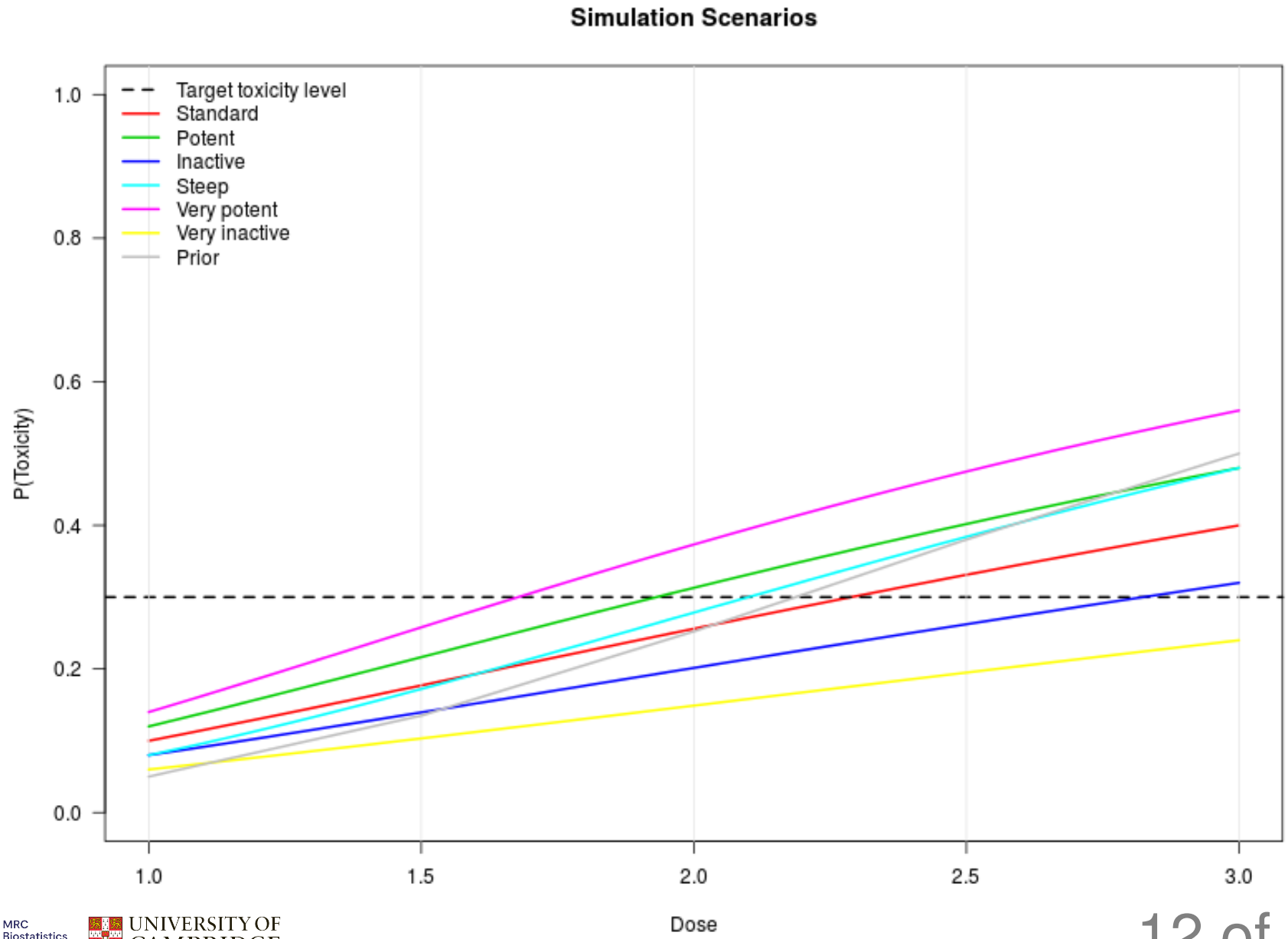
- Green curve is the **prior** dose-toxicity model
- The blue curve - the **true** dose-toxicity relationship.

Output: **Example**

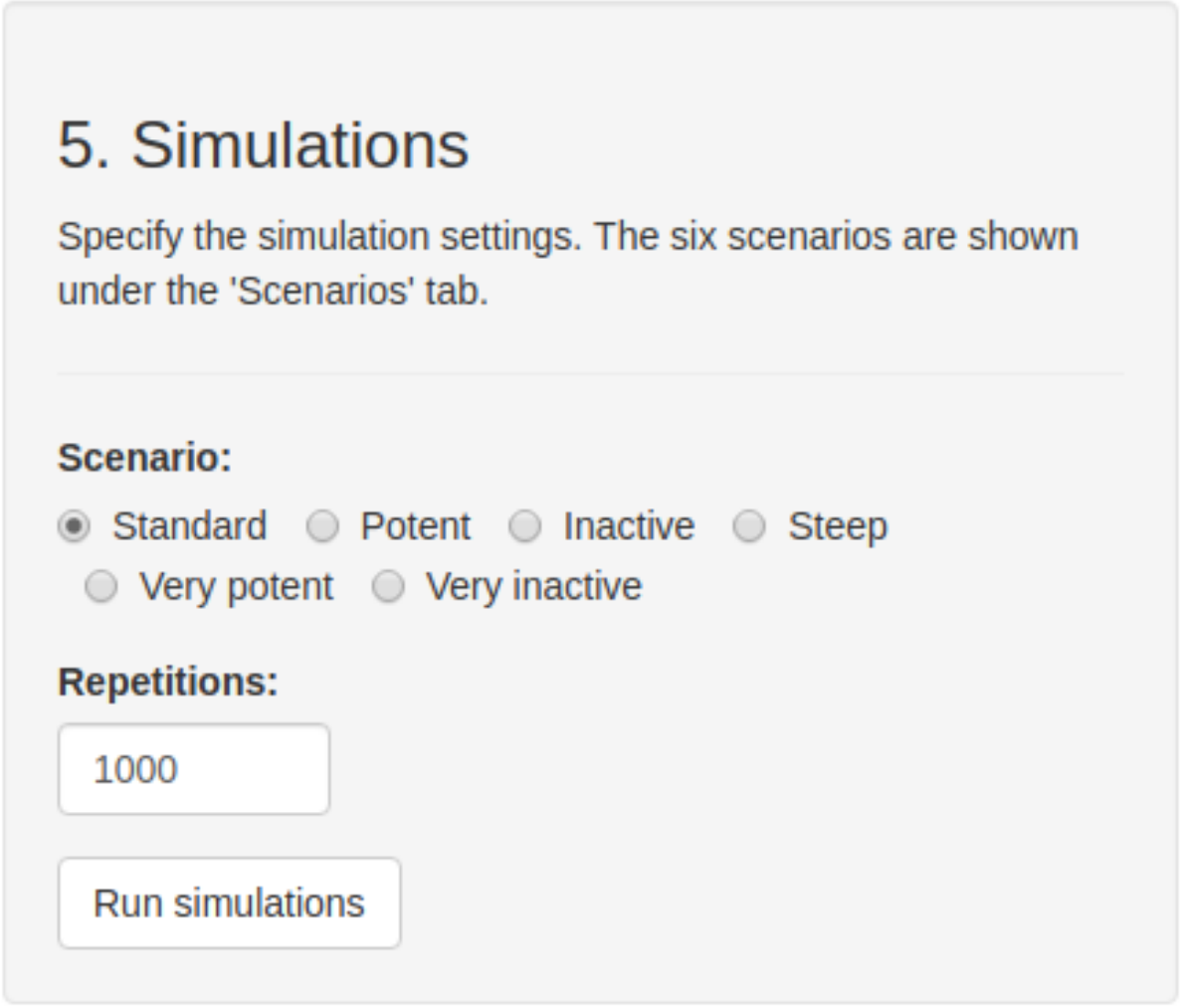


- **One** dose-escalation **study** is simulated.
- The graphs are the **illustrative example**.

Output: **Scenarios**



Run Simulations



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**

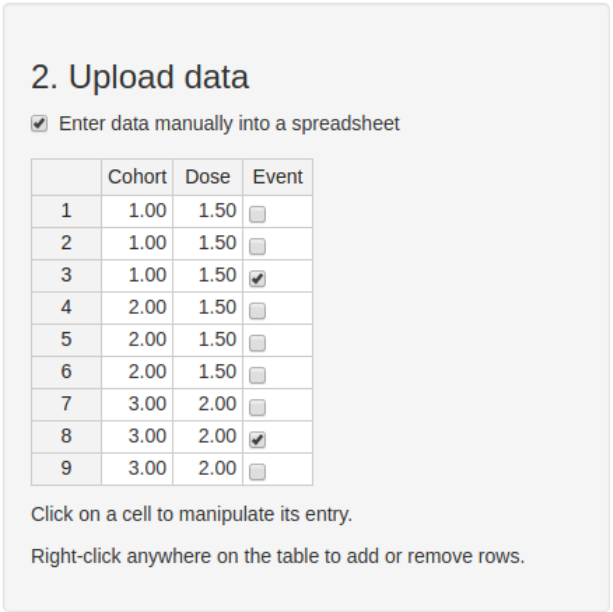
- A CSV design file for the use in the **“Conduct”** app;
- a PDF report summarising the design, prior information, and simulation results;
- A CSV file witht detailed results of the simulations run under the current scenario.

Implementation: `conduct()` in R

Conduct

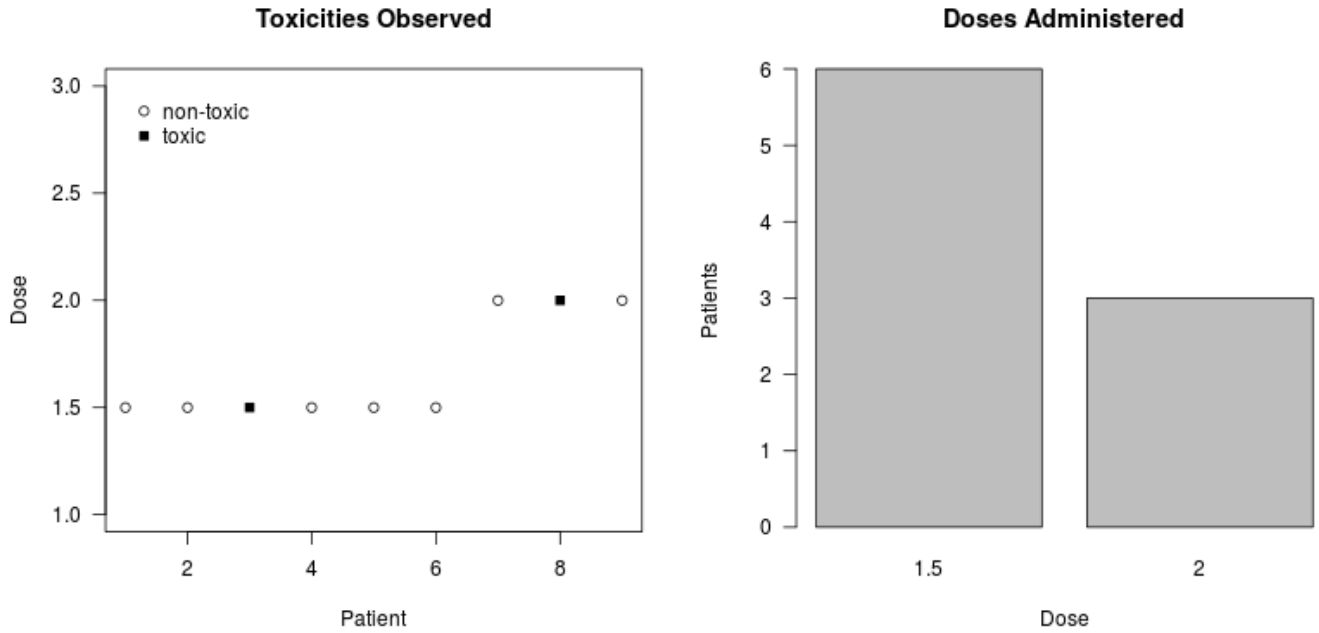
1. **Upload design** file (saved in the DESIGN part of the app)
2. **Upload data** (as a **CSV file**, or entered **manually**).
   CSV should contains a row per patient and three columns:
   Cohort, Dose, Event

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



Conduct: **Output**

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

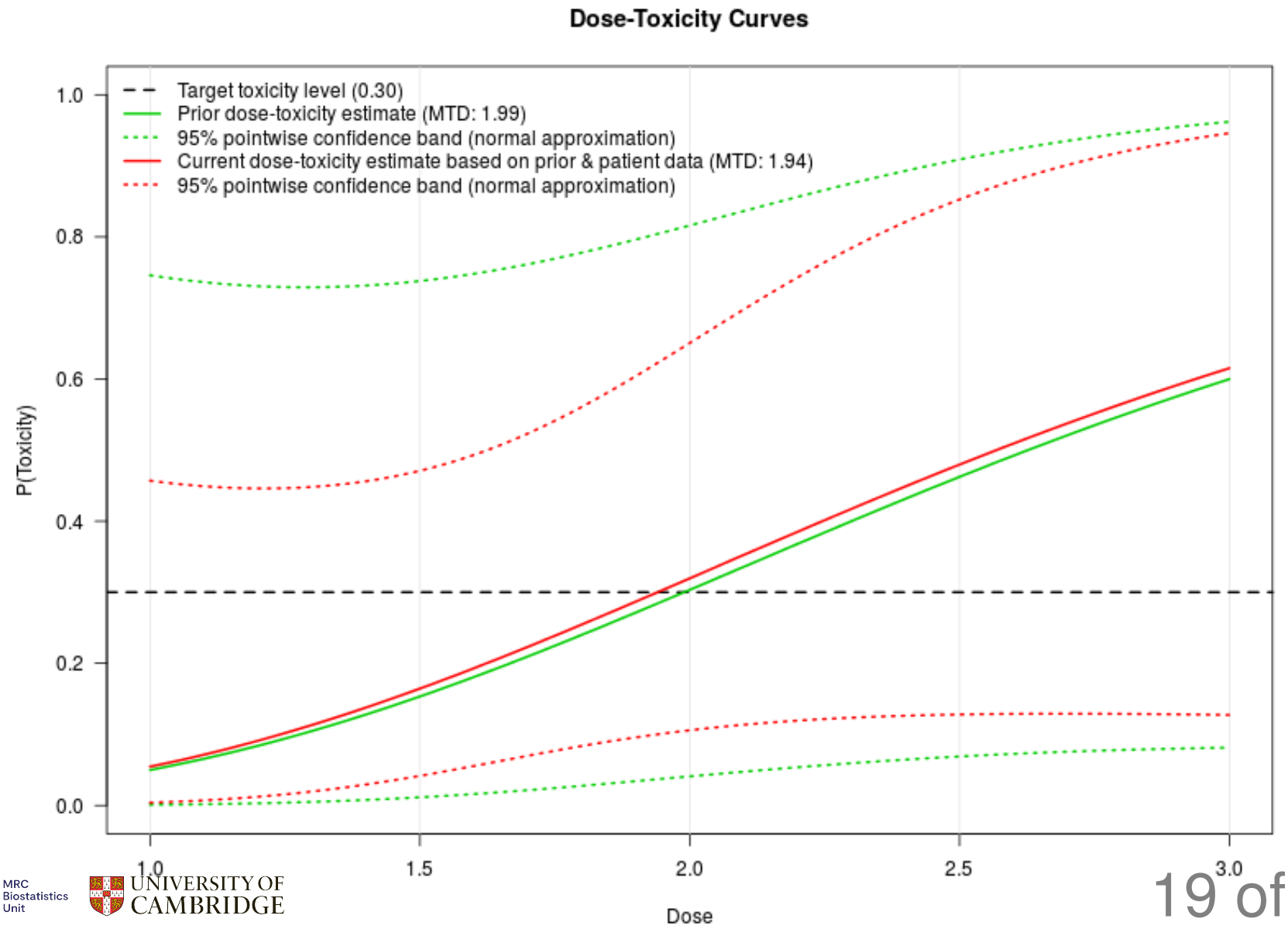


3. **Recommendation** is given for the next cohort:
   - to repeat/escalate/de-escalate the dose;
   - to stop recruitment to the study (for particular reasons)

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**.



Conduct: **Download**

A PDF report summarising

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

is available for download.