MoDEsT: a user-friendly web tool for designing and evaluating model-based dose escalation trials

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http://www.network-hubs.org.uk/research/network-projects

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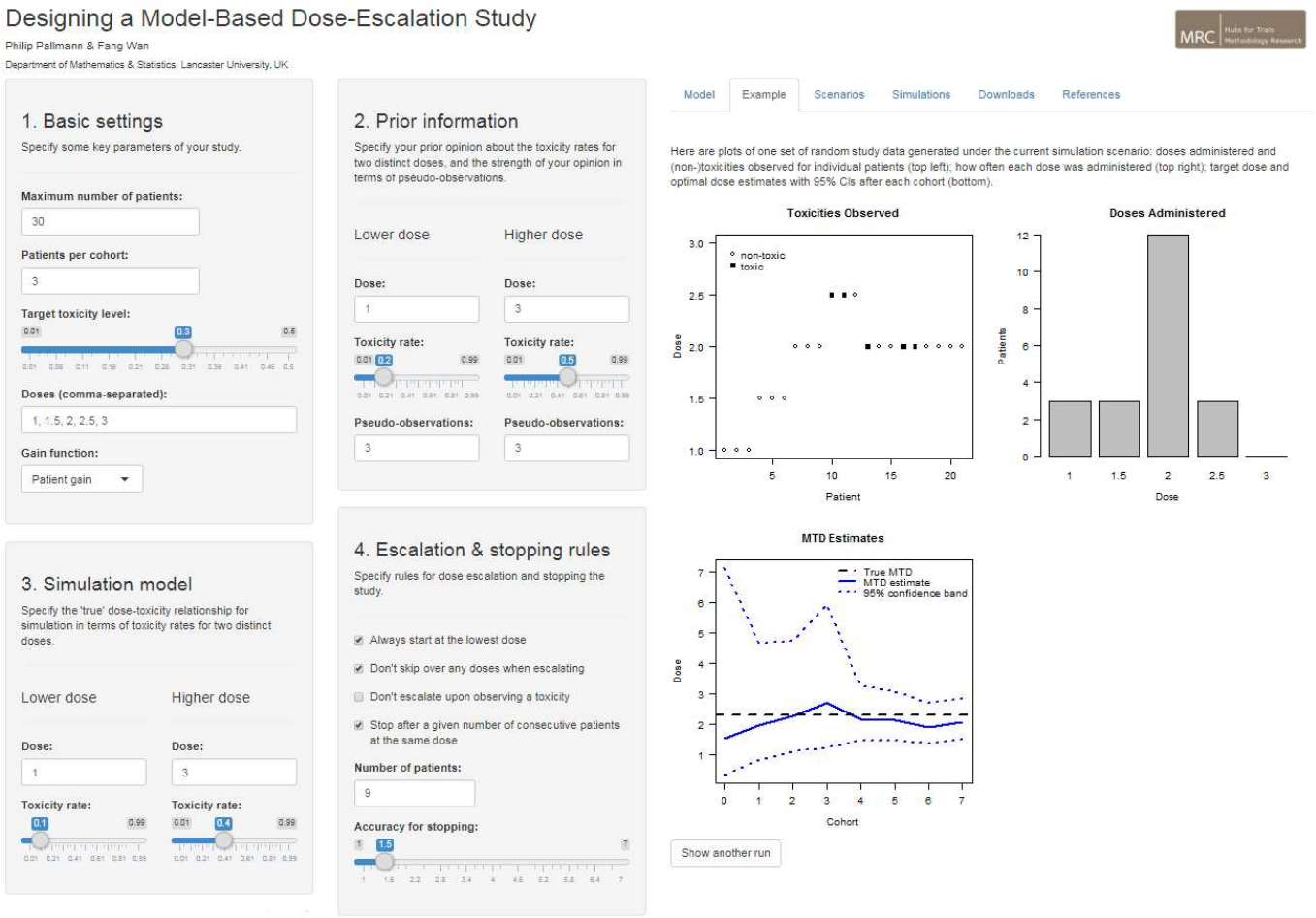
http://modest.lancs.ac.uk

Also available as R package `modest` (Pallmann & Wan 2017)

“Design” module



“Conduct” module

Evaluating a Model-Based Dose-Escalation Study

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MRC Hubs for Trials Methodology Research

1. Upload design file

You can obtain the design file from the design app.

Browse... design.csv

Upload complete

2. Upload data

Enter data manually into a spreadsheet

The dataset must be a CSV file that has (at least) three columns: one for the cohort, one for the dose, and one for the response (0: no toxicity; 1: toxicity).

Browse... Example3.csv

Upload complete

Column headlines in the first row?

Column separator

Comma Semicolon Tab

Decimal separator

Comma Point

Once the dataset has been uploaded, a **cohort**, a **dose**, and a **response** variable must be specified.

Cohort variable

Cohort

Dose variable

Dose

Response variable

Event

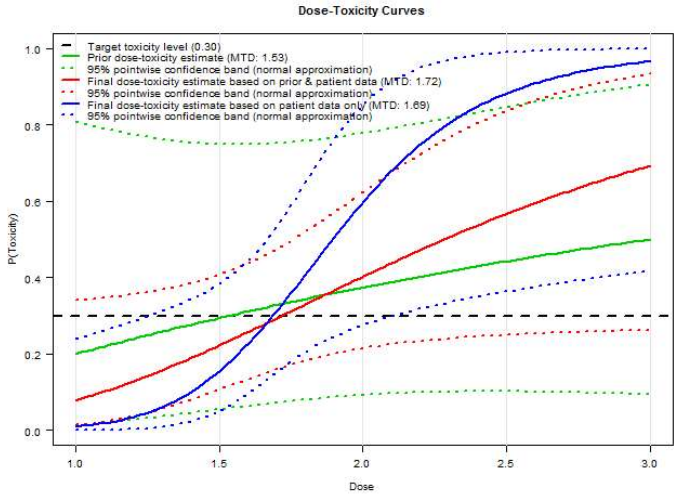
Design Dataset Recommendation Download References

Stop recruitment: the maximum number of patients has been reached.

The logistic model used to describe the dose-toxicity relationship has the form logit(P(toxicity)) = a + b log(dose). The values of the parameters a (intercept) and b (slope) are displayed for the prior and posterior models.

	Intercept	Slope
Prior model	-1.39	1.26
Posterior model (prior & patient data)	-2.46	2.98
Final model (patient data only)	-4.65	7.28

Here is a plot of the dose-toxicity relationship as implied by the prior information and after updating the model with study data, and the target toxicity level.



The study has been stopped, display the final model estimates.

Bayesian decision procedure

1) Logistic model
2) Priors
3) Gain function
4) Escalation and stopping rules

Practical Implementation of Bayesian Dose-Escalation Procedures

This paper reviews Bayesian dose-escalation procedures for phase 1 clinical trials and describes a systematic approach to their implementation. The methodology is constructed for studies in which each subject is administered a single dose of an experimental drug and provides a single binary response, referred to here as toxicity or no toxicity. It is assumed that the probability of toxicity rises with log dose of drug according to a logistic regression model.

It is suggested that the choice of suitable prior distributions be aided via graphical representations of their properties and simulation investigations of their consequences. Possible safety constraints and stopping rules are described. Given this information, the recommended doses for the first cohort of subjects can be computed. Once their responses become available, subjective distributions can be updated, and the recommended doses for the second cohort can be determined. The procedure continues in this way until a stopping rule is reached, or until some maximum number of subjects has been observed. Clinical investigators are free to overrule the doses recommended by the procedure and to substitute those that they feel are more appropriate.

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Journal of Biopharmaceutical Statistics, 8(3), 445–467 (1998)

BAYESIAN DECISION PROCEDURES BASED ON LOGISTIC REGRESSION MODELS FOR DOSE-FINDING STUDIES

John Whitehead[1] and David Williamson[2]

Key words. Clinical trial; Continual reassessment method; Dose escalation; Logistic regression; Maximum tolerated dose; Optimal design

Abstract

Early-phase clinical trials, conducted to determine the appropriate dose of an experimental drug to take forward to later trials, are considered. The objective is to find the dose associated with some low probability of an adverse event. A Bayesian model is presented, and a decision-theoretic procedure for finding the optimal doses for each of a series of cohorts of subjects is derived. The procedure is flexible and can easily be conducted using standard statistical software. The results of simulations investigating the properties of the procedure are presented.

STATISTICS IN MEDICINE, VOL. 14, 885–893 (1995)

BAYESIAN DECISION PROCEDURES FOR DOSE DETERMINING EXPERIMENTS

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SUMMARY

This paper describes the Bayesian decision procedure and illustrates the methodology through an application to dose determination in early phase clinical trials. The situation considered is quite specific: a fixed number of patients are available, to be treated one at a time, with the choice of dose for any patient requiring knowledge of the responses of all previous patients. A continuous range of possible doses is available. The prior beliefs about the dose–response relationship are of a particular form and the gain from investigation is measured in terms of statistical information gathered. How all of these specifications may be varied is discussed. A comparison with the continual reassessment method is made.

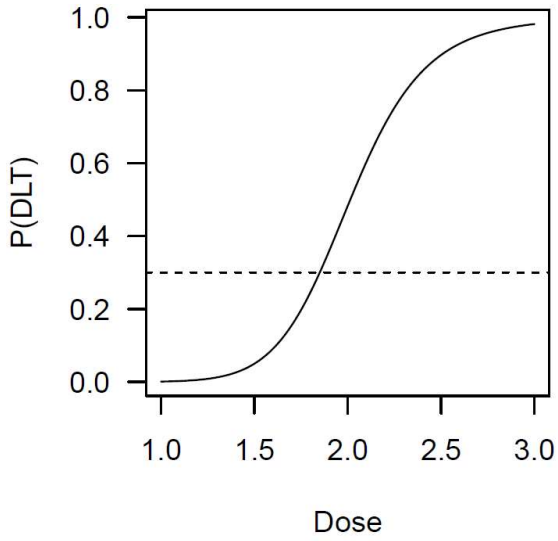
1) Logistic regression model

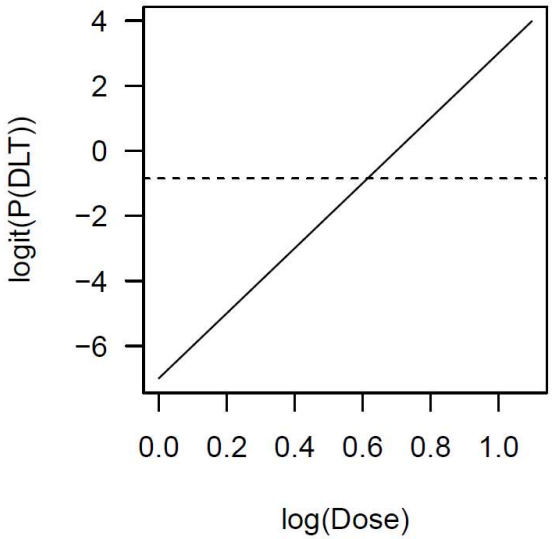
$$\log\left[\frac{P(DLT)}{1-P(DLT)}\right] = \beta_0 + \beta_1 \log(dose)$$

log odds

intercept

slope





2) Priors for dose-toxicity model

Difficult: priors for β_0 and β_1

Less difficult: priors for two doses

1. assume probability P_A of a DLT at dose A, "worth" x_A pseudo-observations
2. assume probability P_B of a DLT at dose B, "worth" x_B pseudo-observations

Example: assume 5% DLTs at 1.5 mg/kg and 50% DLTs at 10 mg/kg, each "worth" 3 observations

3) Gain function

Which dose to recommend for the next cohort?

Patient gain: choose the dose currently thought to be closest to the target toxicity level

→ optimal from a **patient's** perspective

Variance gain: choose the dose that will likely maximise the learning about the dose-toxicity relationship

→ optimal from an **investigator's** perspective

4) Escalation and stopping rules

When escalating:

- always start at the **lowest** dose
- do not **skip over** any doses when escalating
- do not escalate upon **observing a toxicity** in the current cohort

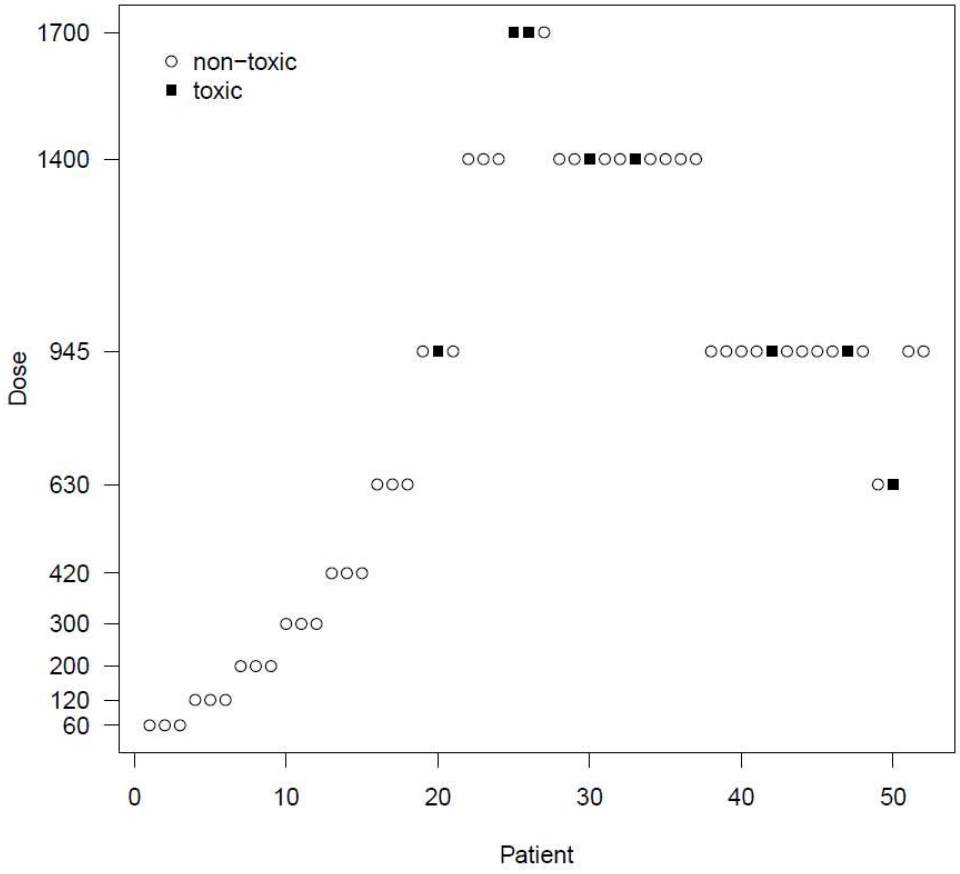
Recommend stopping when:

- the **maximum number** of patients has been reached
- a pre-defined maximum number of **consecutive patients** have received the same dose
- a sufficiently **accurate estimate** of the MTD has been obtained
- no dose among those in the pre-specified set is deemed **safe**

Quercetin data example

Phase I dose-escalation study in cancer patients suffering from a variety of forms of solid tumour no longer amenable to standard therapies (Ferry et al. 1996)

- 9 dose levels
- max. 18 cohorts of size 3
- 20% risk of renal toxicity (WHO grade ≥ 2) acceptable
- aim: find MTD
- 3+3 design (kind of)



Quercetin data example

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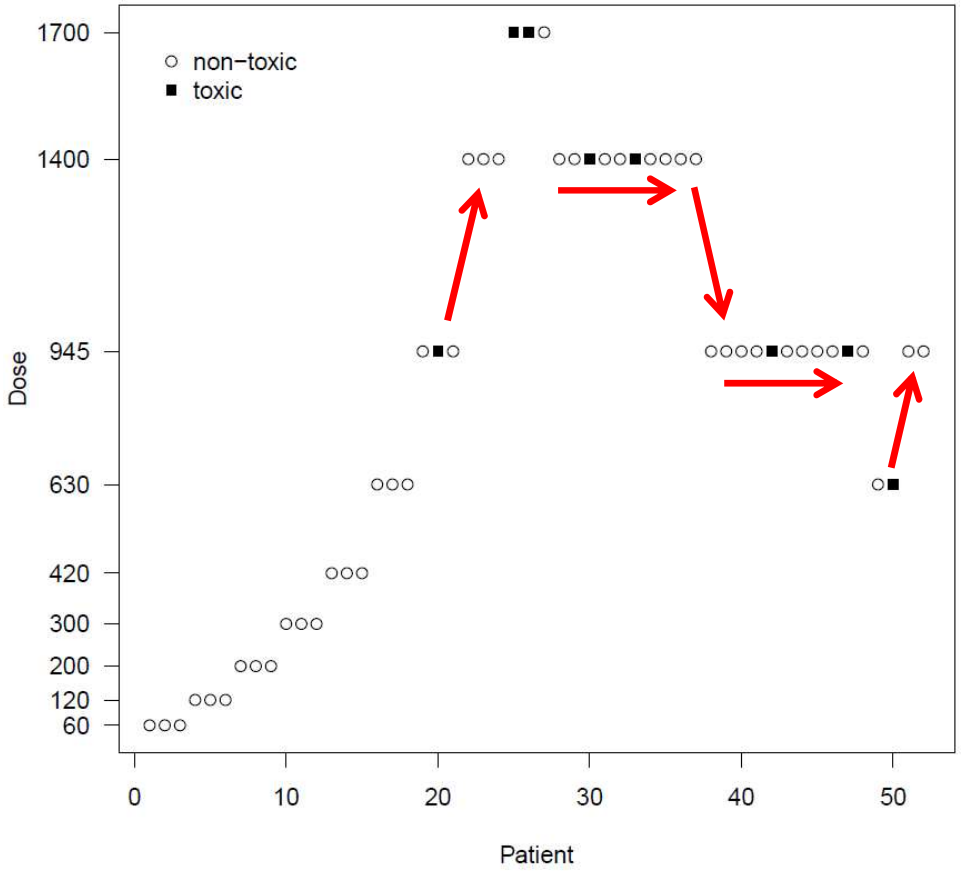

Literature

Ferry DR, Smith A, Malkhandi J, Fyfe DW, deTakats PG, Anderson D, Baker J, Kerr DJ (1996) Phase I clinical trial of the flavonoid quercetin: pharmacokinetics and evidence for *in vivo* tyrosine kinase inhibition. *Clinical Cancer Research*, **2**(4), 659-668.

Pallmann P, Wang F (2017) `modest`: Model-based dose-escalation trials. R package version 0.3-1. http://cran.r-project.org/package=modest

Whitehead J, Brunier H (1995) Bayesian decision procedures for dose determining experiments. *Statistics in Medicine*, **14**(9), 885-893.

Whitehead J, Williamson D (1998) Bayesian decision procedures based on logistic regression models for dose-finding studies. *Journal of Biopharmaceutical Statistics*, **8**(3), 445-467.

Zhou Y, Whitehead J (2003) Practical implementation of Bayesian dose-escalation procedures. *Drug Information Journal*, **37**(1), 45-59.