

A toxicity-dependent feasibility bound for the Escalation with Overdose Control approach in phase I cancer trials

Graham Wheeler^{1,2} Michael Sweeting³ Adrian Mander²

¹Cancer Research UK & UCL Cancer Trials Centre, University College London, UK

²MRC Biostatistics Unit, Cambridge, UK

³Strangeways Research Laboratory, University of Cambridge, UK

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Goal of a phase I trial is to find the Maximum Tolerated Dose (MTD) of a drug

The Maximum Tolerated Dose (MTD)

“The dose expected to produce some degree of medically unacceptable, dose-limiting toxicity (DLT) in a specified proportion of patients.”

(Babb and Rogatko, 2004)

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The Maximum Tolerated Dose (MTD)

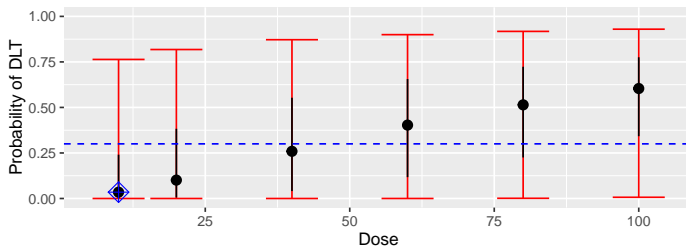
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Traditionally use 3 + 3 dose-escalation design to identify the MTD

- No explicit target DLT rate
- Not all patient data used
- Poor MTD recommendation properties

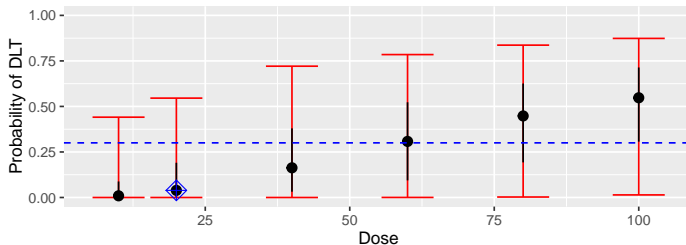
Posterior $p(\text{DLT})$ quantiles: 2.5%, 25%, 50%, 75%, 97.5%
 Diamond shows next recommended dose



Prior belief

Output from R
 package `bcrm`
 (Sweeting et al.,
 2013)

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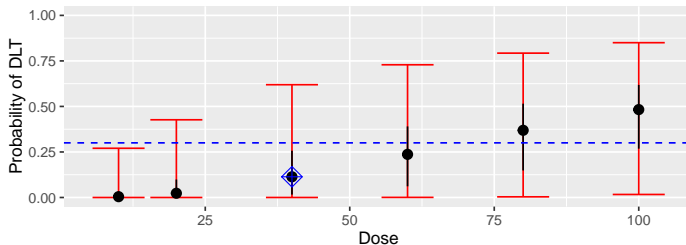


After 2 patients

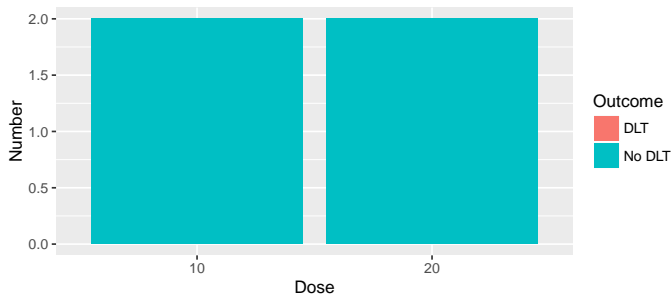


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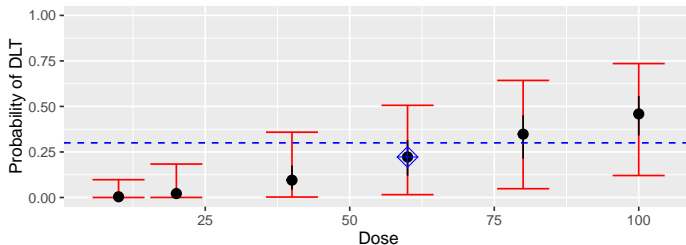


After 4 patients

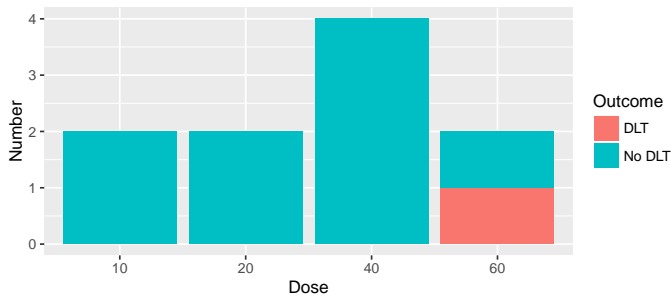


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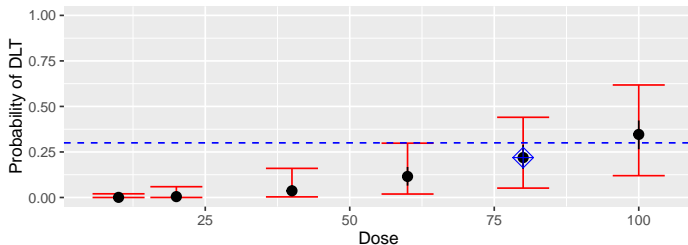


After 10 patients

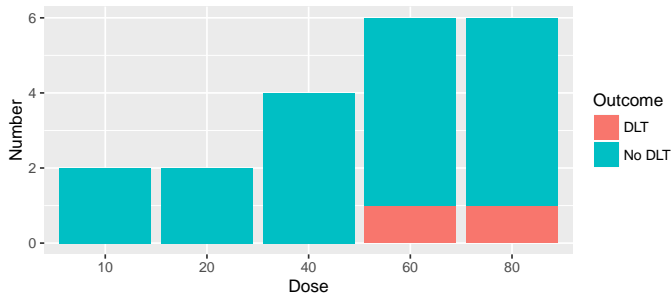


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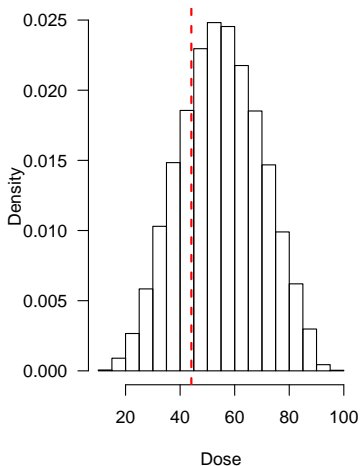
After 20 patients



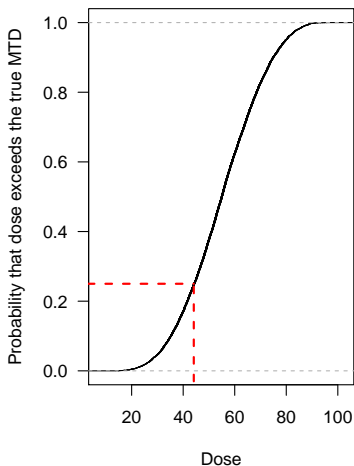
Output from R package *bcrm* (Sweeting et al., 2013)

Dose for next patient is 25th percentile of the MTD distribution (Babb et al., 1998)

Distribution of MTD



Cumulative Distribution of MTD



Dose for next patient is 25th percentile of the MTD distribution (Babb et al., 1998)

- More conservative than choosing mean/median
- The percentile is called the **feasibility bound**

Interpretation of the feasibility bound 1)

The probability that the dose chosen is above the true MTD = 25%

Interpretation of the feasibility bound 2)

Overdosing is $\frac{1-0.25}{0.25} = 3$ times worse than underdosing

Can adapt feasibility bound as more data are collected

- Be less conservative as more information gathered
- Quicker to target the MTD whilst still being cautious
- See Babb and Rogatko (2001); Cheng et al. (2004); Tighiouart and Rogatko (2010)

But we need to think how to change the feasibility bound best

Factors of interest

- What are the chances the correct MTD is chosen?
- How many patients will receive the best dose?
- Will patients be more prone to over/underdoses?
- Is the dose recommendation **coherent**?

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Definition of coherence

*A trial design is **coherent in dose-escalation** if after observing a DLT at dose x , the dose recommendation for the next patient is not bigger than x .*

(Cheung, 2011)

Several proposed approaches can lead to incoherent dose escalation when the feasibility bound is increased after observing a DLT.

Trial of 5-fluorouracil (5-FU) given with leucovorin and topotecan in patients with malignant solid tumours (Babb et al., 1998)

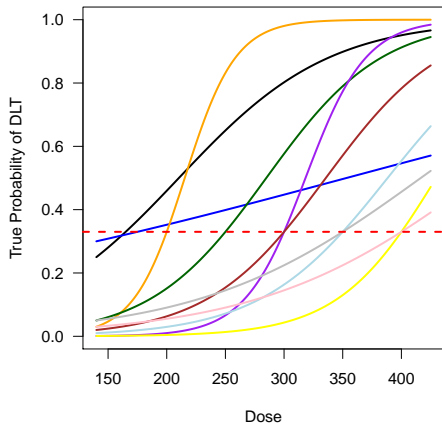
- Aim: Find MTD of 5-FU
- Target DLT rate: 33%
- 40 patients

Use two estimators for MTD at end of trial

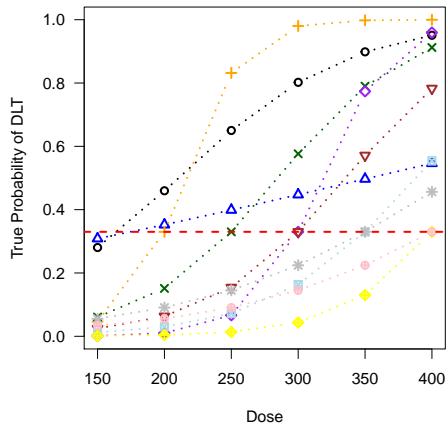
- 1) 50th percentile of posterior MTD distribution
- 2) next recommended dose

<http://tinyurl.com/EWOCguide> - Rogatko and Tighiouart (2013)

Continuous Dose Interval



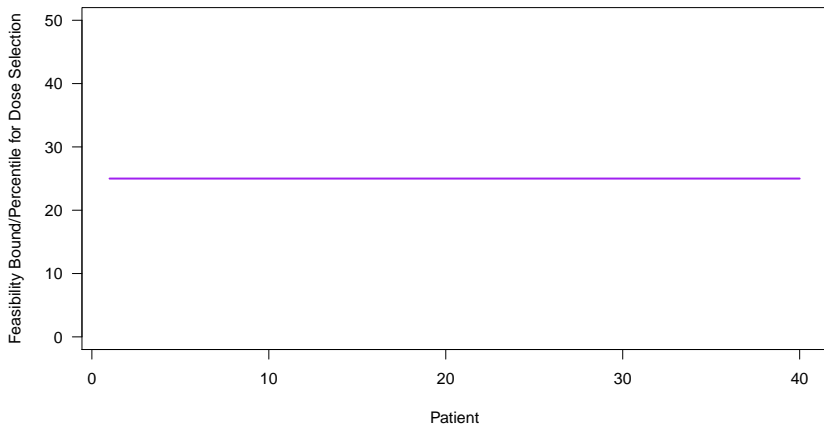
Discrete Dose Set



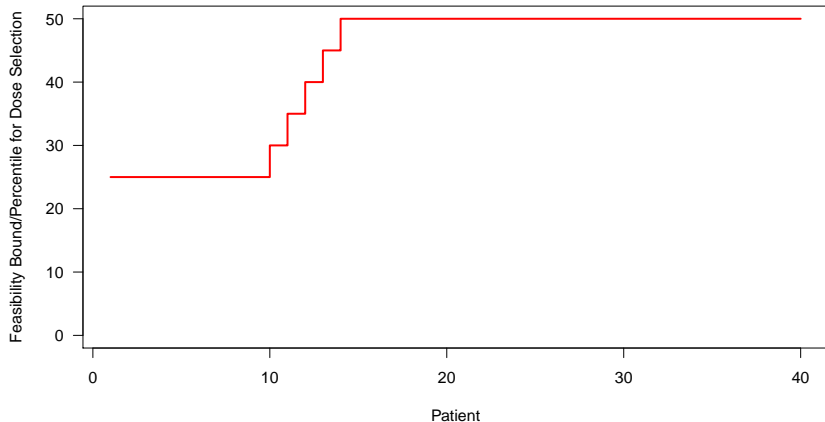
■ Continuous Doses between 140mg/m² and 425mg/m²

■ Discrete Dose: 150, 200, 250, 300, 350, 400 (mg/m²)

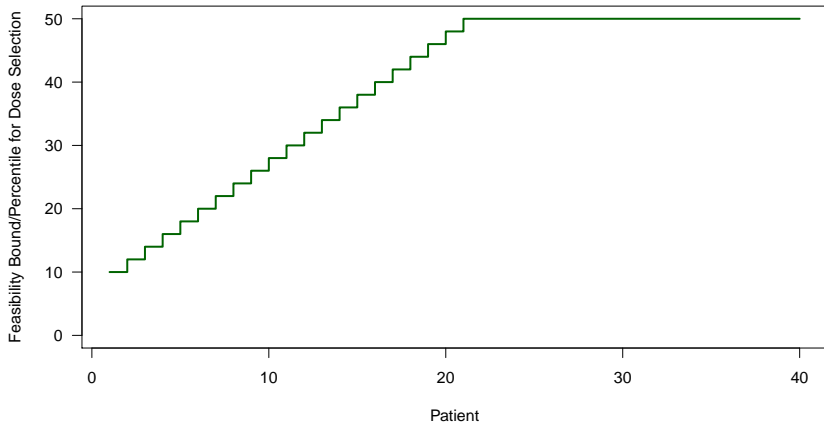
- 1) EWOC — feasibility bound is always 25th percentile;



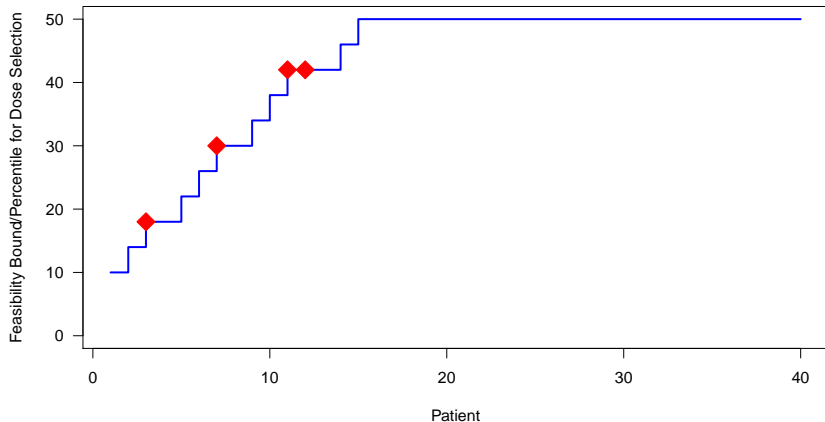
- 2) Feasibility bound is 25th percentile, then increases to 30th, 35th ... 50th percentile for patients 10, 11, ..., 14 (Tighiouart and Rogatko, 2010);



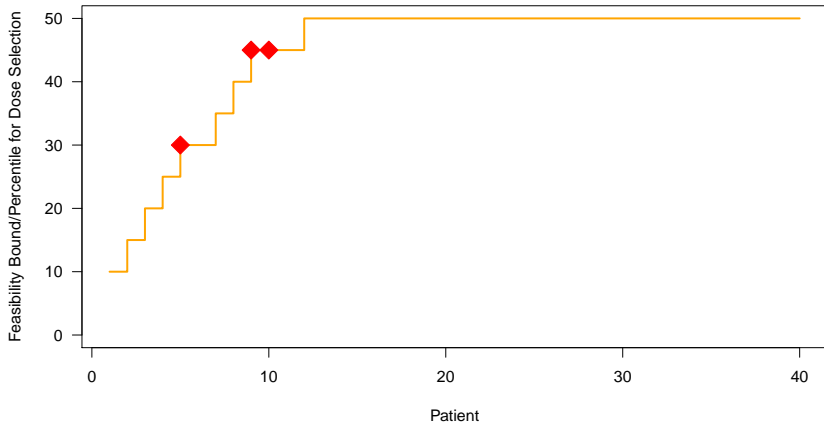
- 3) Feasibility bound begins at lower bound and increases in equal increments such that it is 50th percentile halfway through trial (Chu et al., 2009);



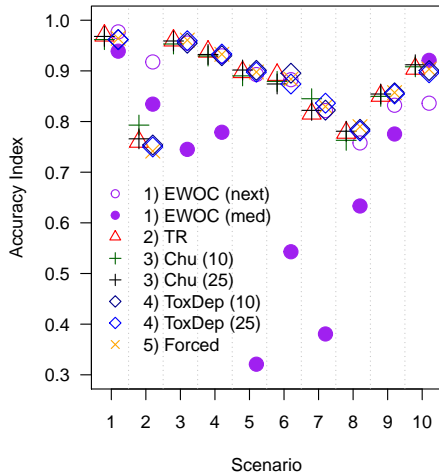
- 4) Same as Design 3, but observing DLTs cause feasibility bound to stay constant;



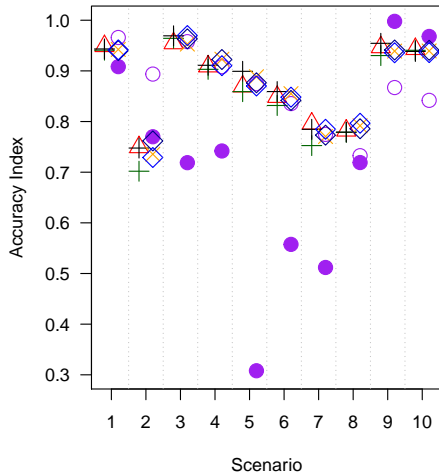
- 5) Increase feasibility bound by 5 percentile points, unless DLT observed, up to 50th percentile.



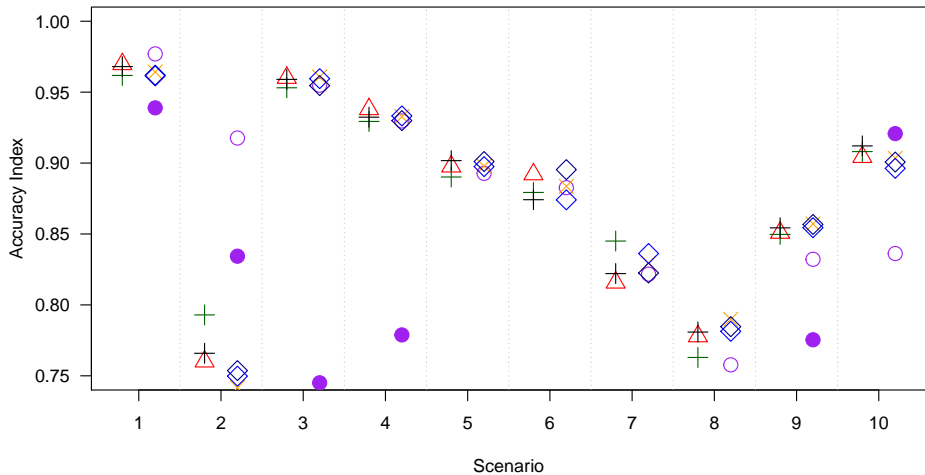
Continuous Dose Scenarios



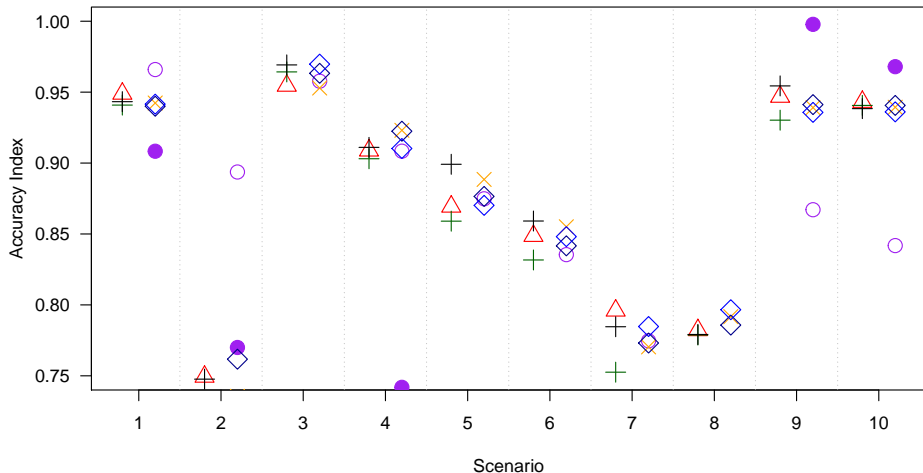
Discrete Dose Scenarios



Continuous Dose Scenarios



Discrete Dose Scenarios



Coherence

- Across simulations for continuous doses scenarios, 2-21 incoherent escalations per scenario observed for designs 2) and 3)
- 1-11mg/m² — Mean 3.5mg/m²
- Incoherence rare for discrete doses (5 instances), but is 50mg/m² jump

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Experimentation

- EWOC most conservative — fewer patients at overdoses and DLTs
- Other approaches perform very similar to each other

A Toxicity-dependent feasibility bound:

- guarantees coherent dose-escalation
- is easy to build into a trial design
- Offers similar MTD recommendation accuracy to other approaches

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- Paper submitted to Statistics in Medicine (under revision)

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- Cancer Research UK and UCL Cancer Trials Centre

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