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

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Background

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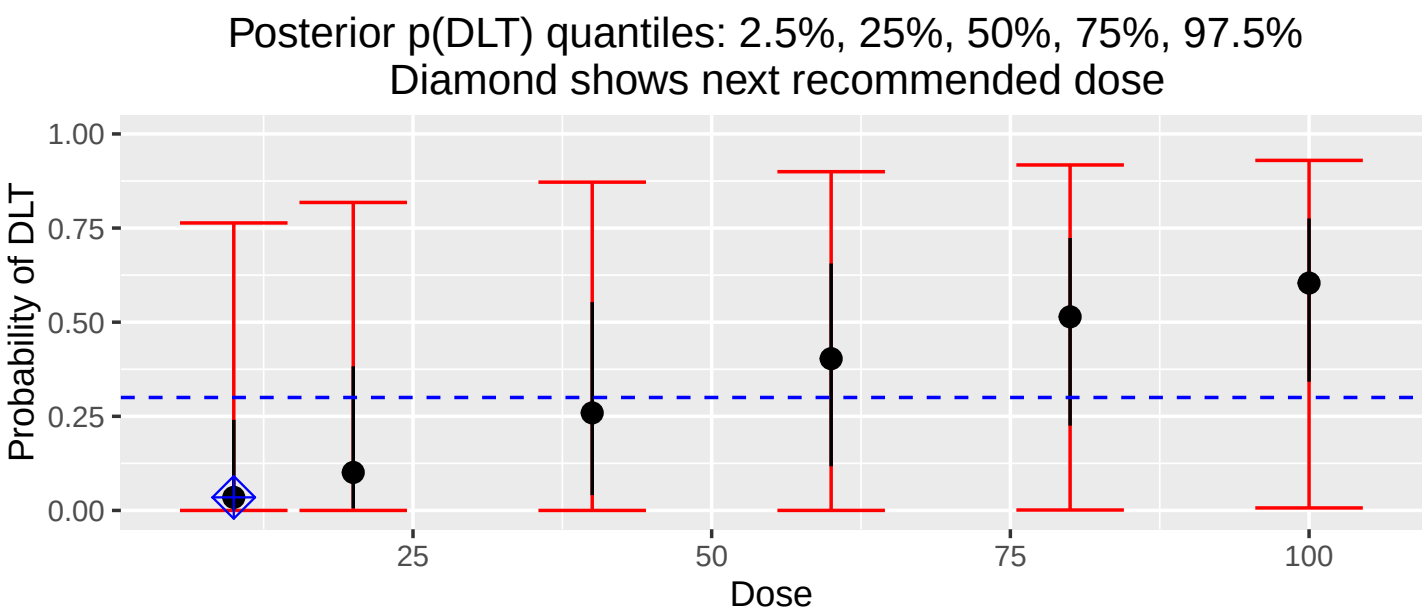
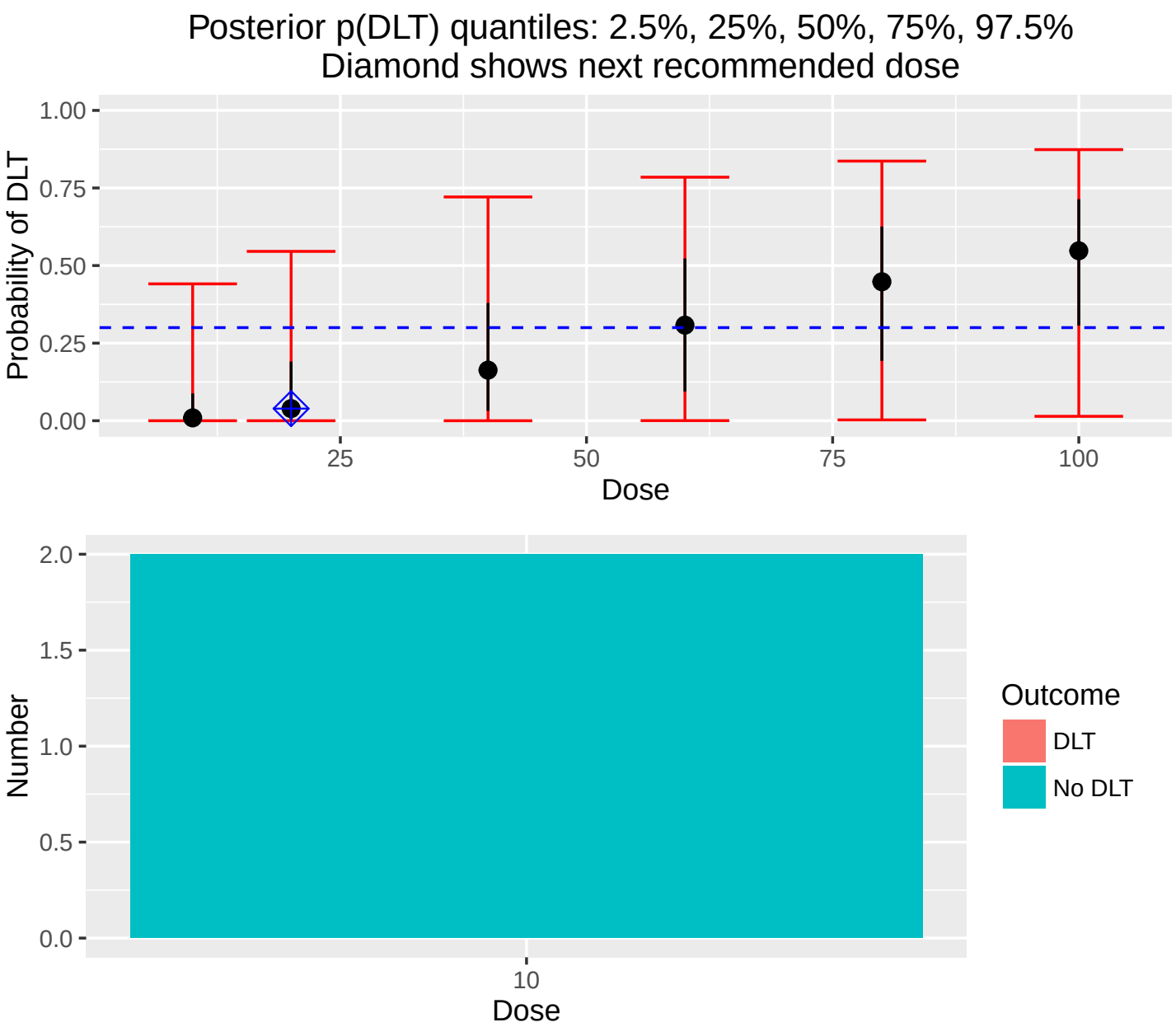
Traditionally use $3 + 3$ dose-escalation design to identify the MTD

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



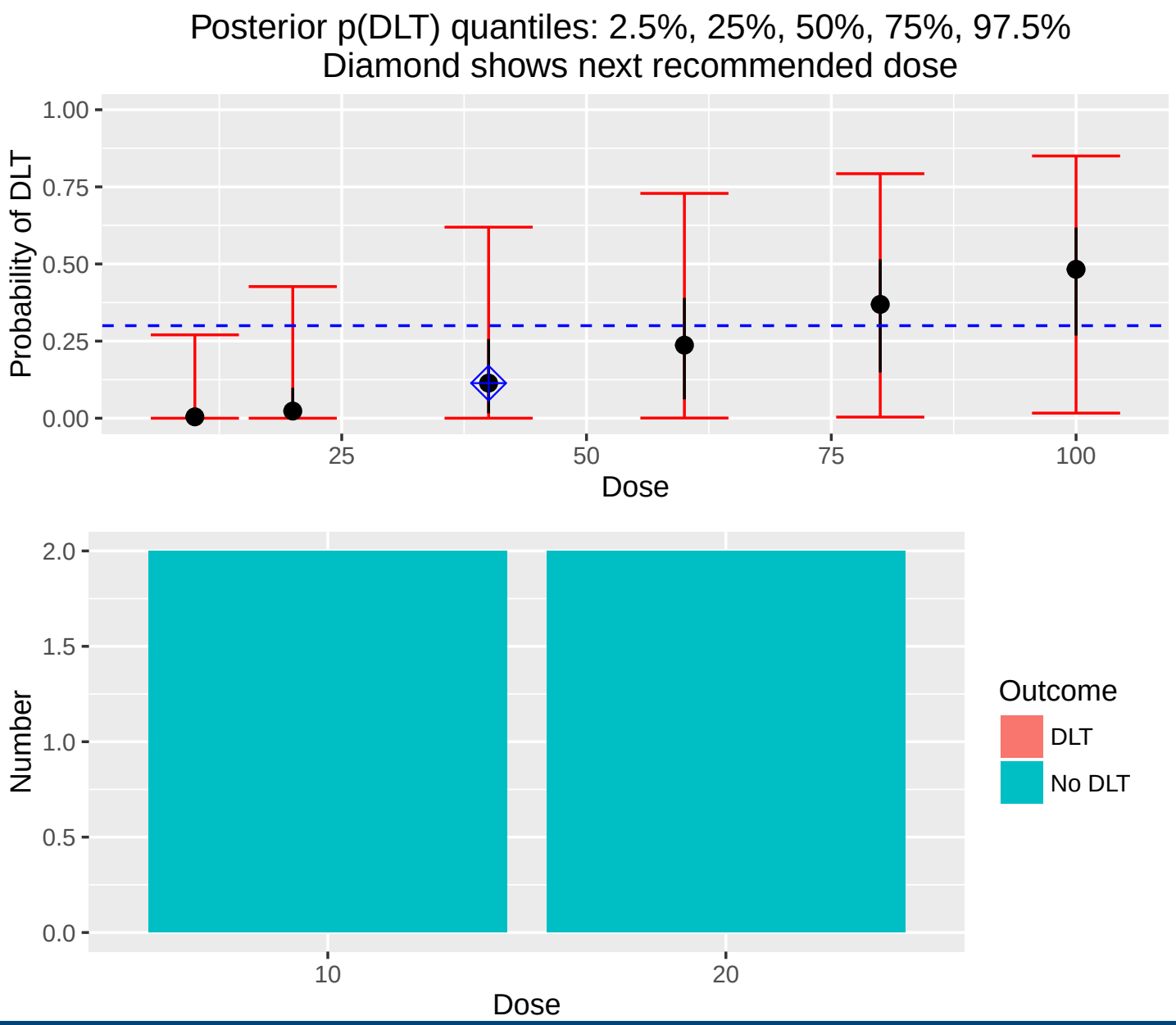
Prior belief

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



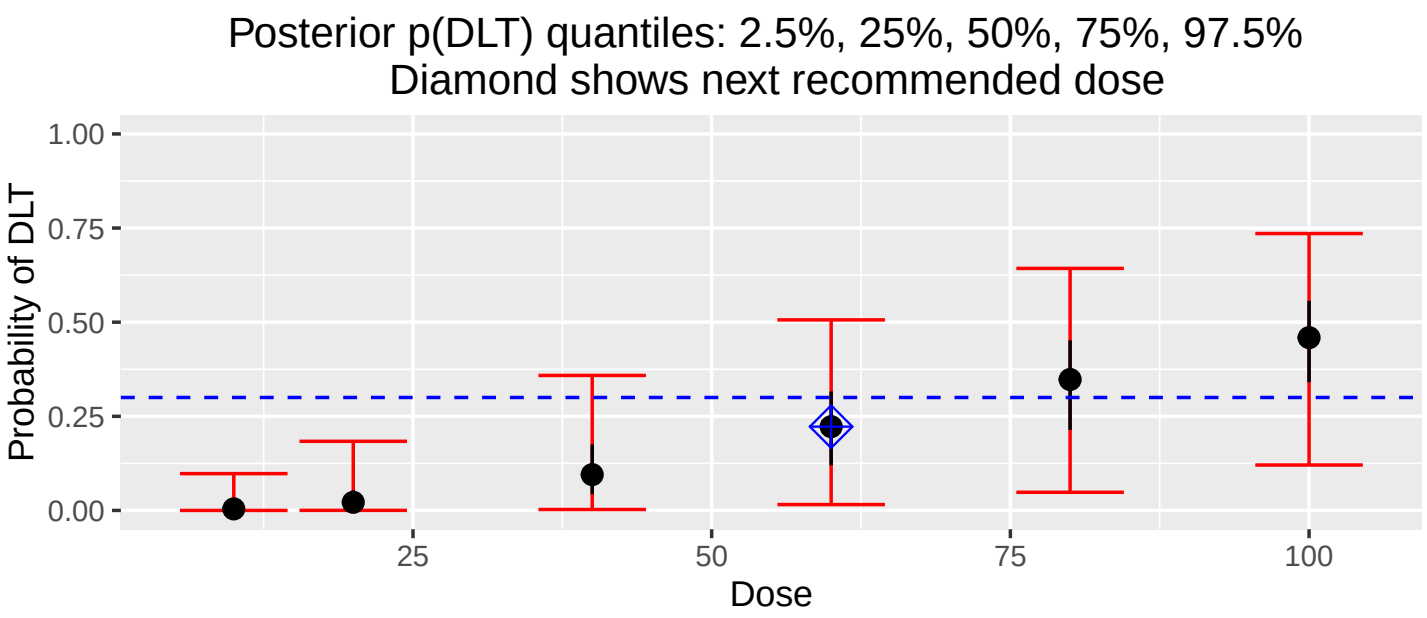
After 2 patients

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

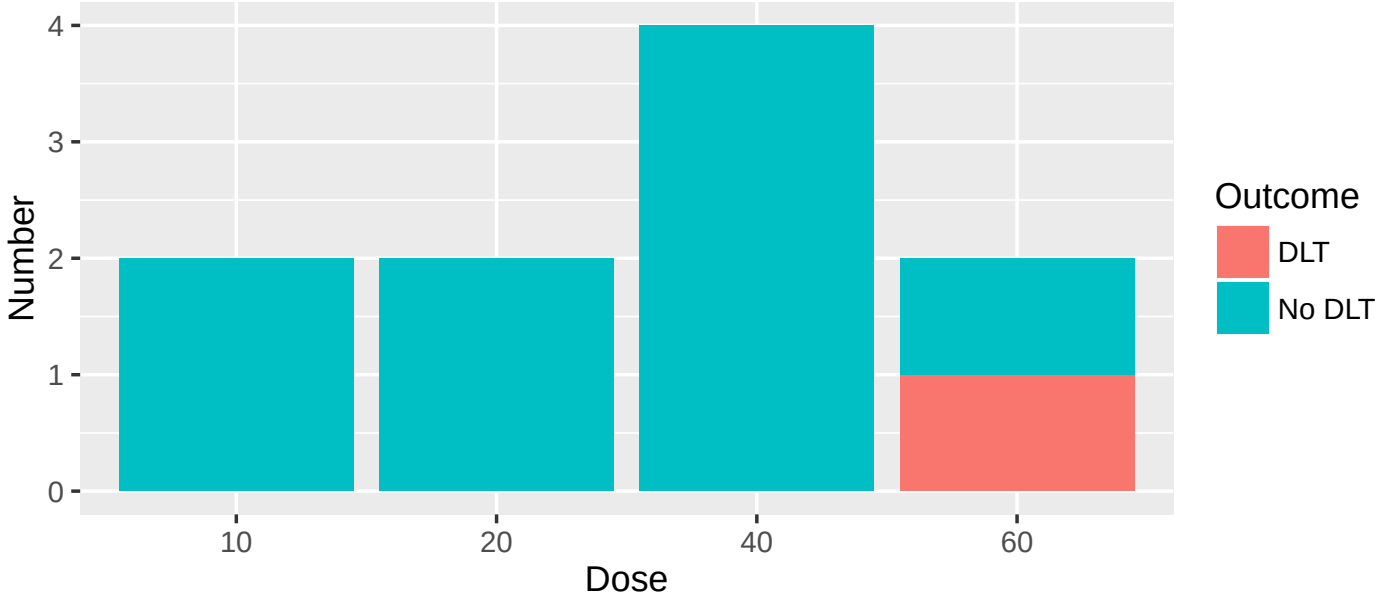


After 4 patients

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



After 10 patients



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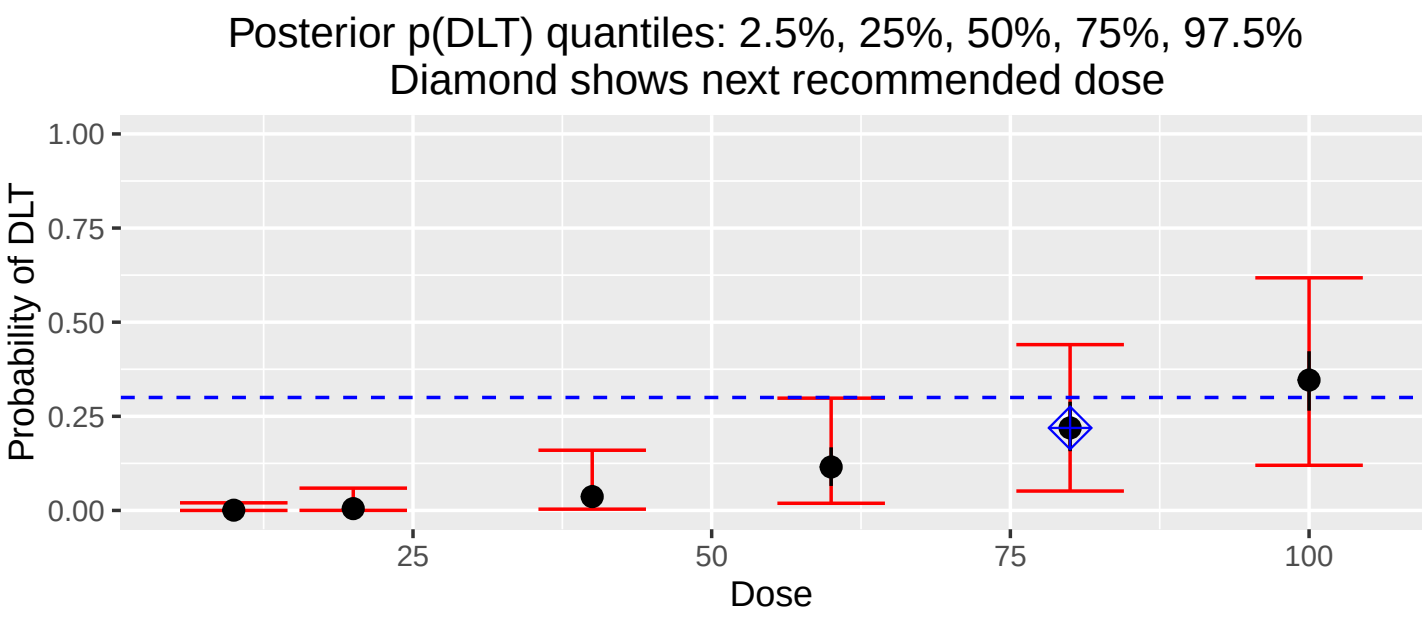
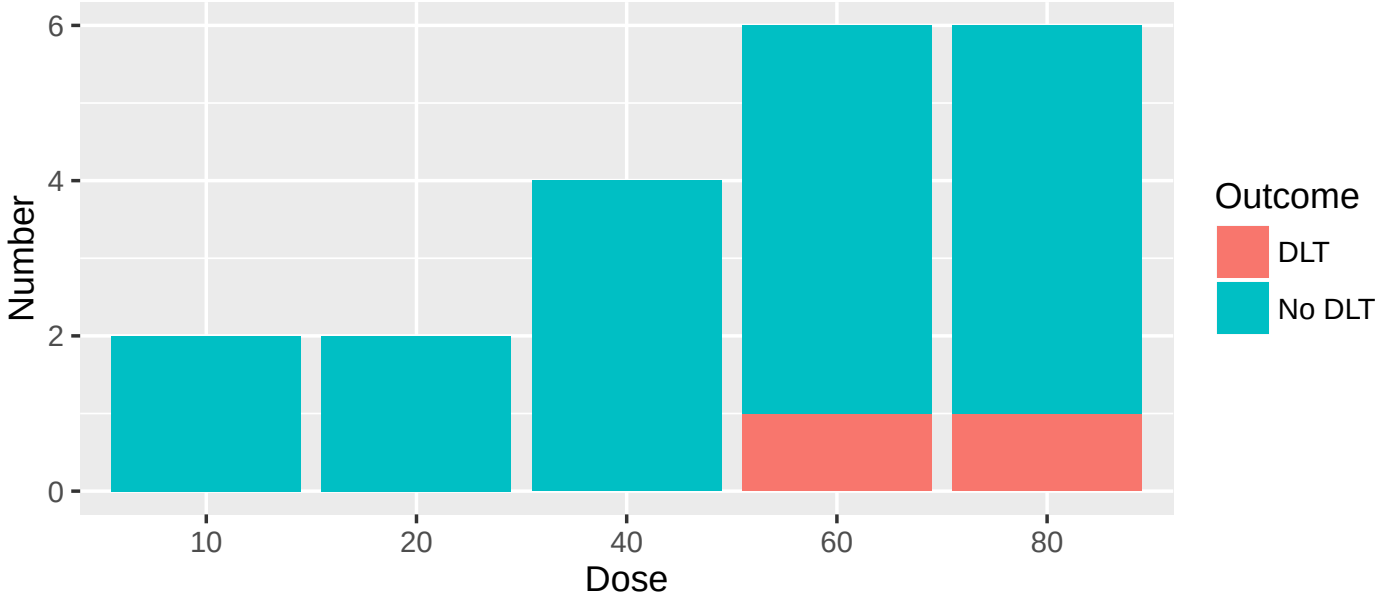


After 20 patients



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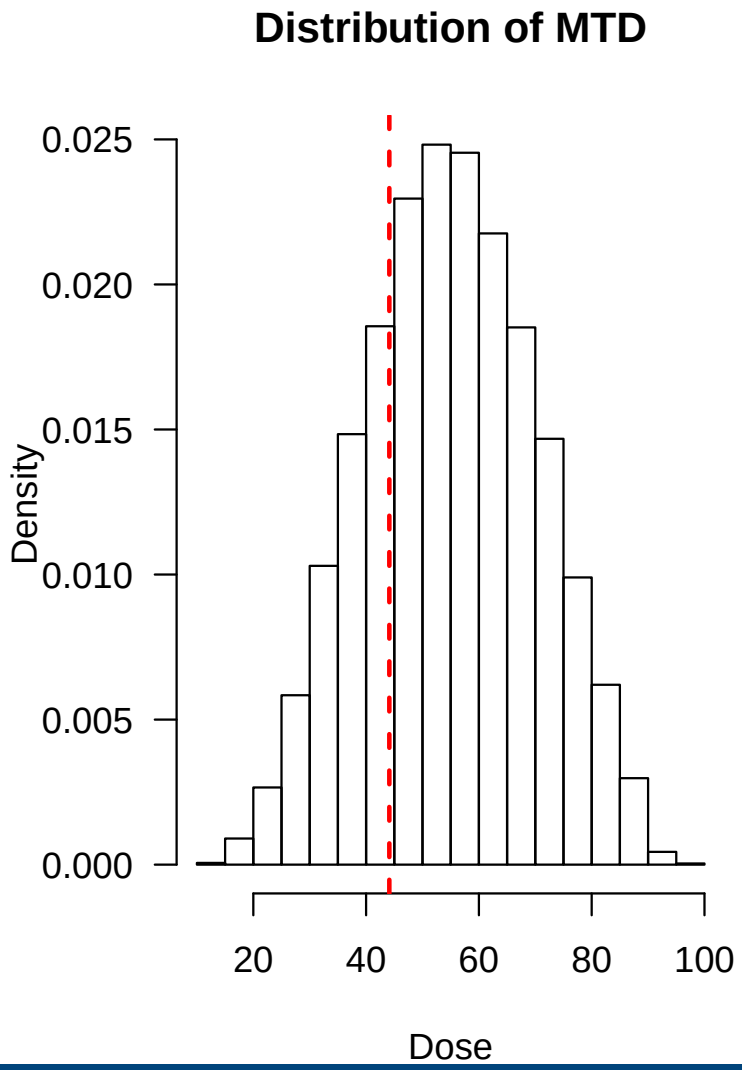
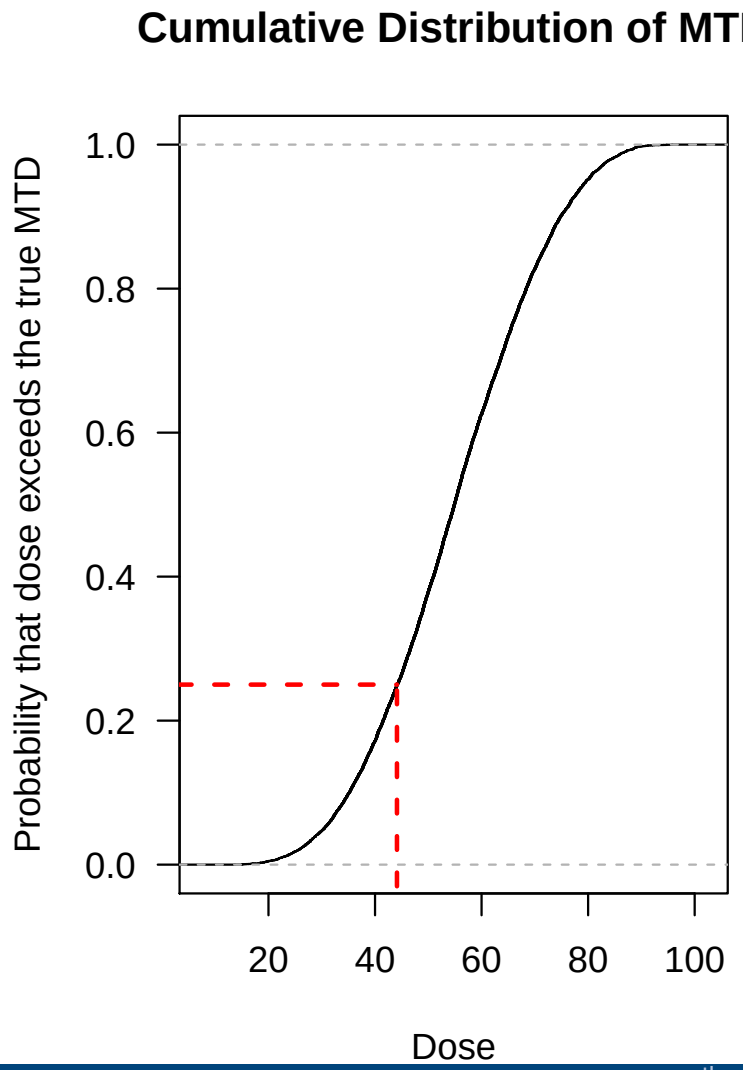
Escalation With Overdose Control (EWOC)

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





Escalation With Overdose Control (EWOC)

Dose for next patient is 25^{th} 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

Varying the feasibility bound

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.

A Simulation Study

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

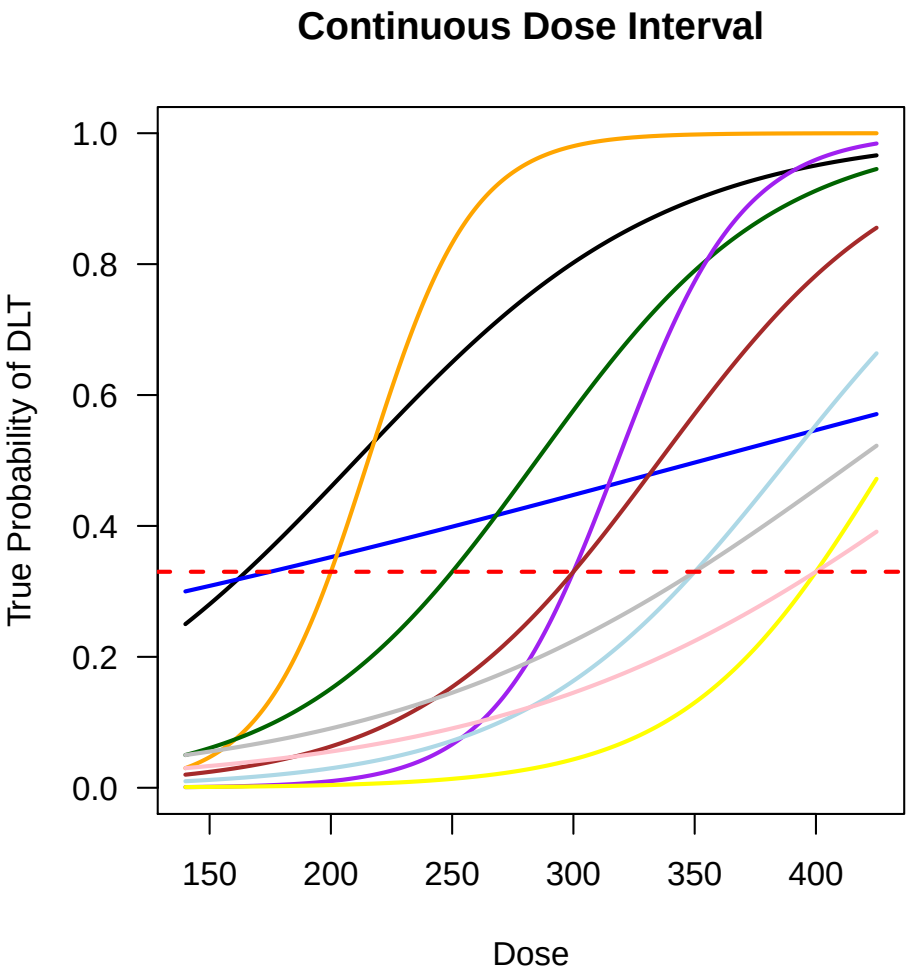
- Aim: Find MTD of 5-FU
- Target DLT rate: 33%
- 40 patients

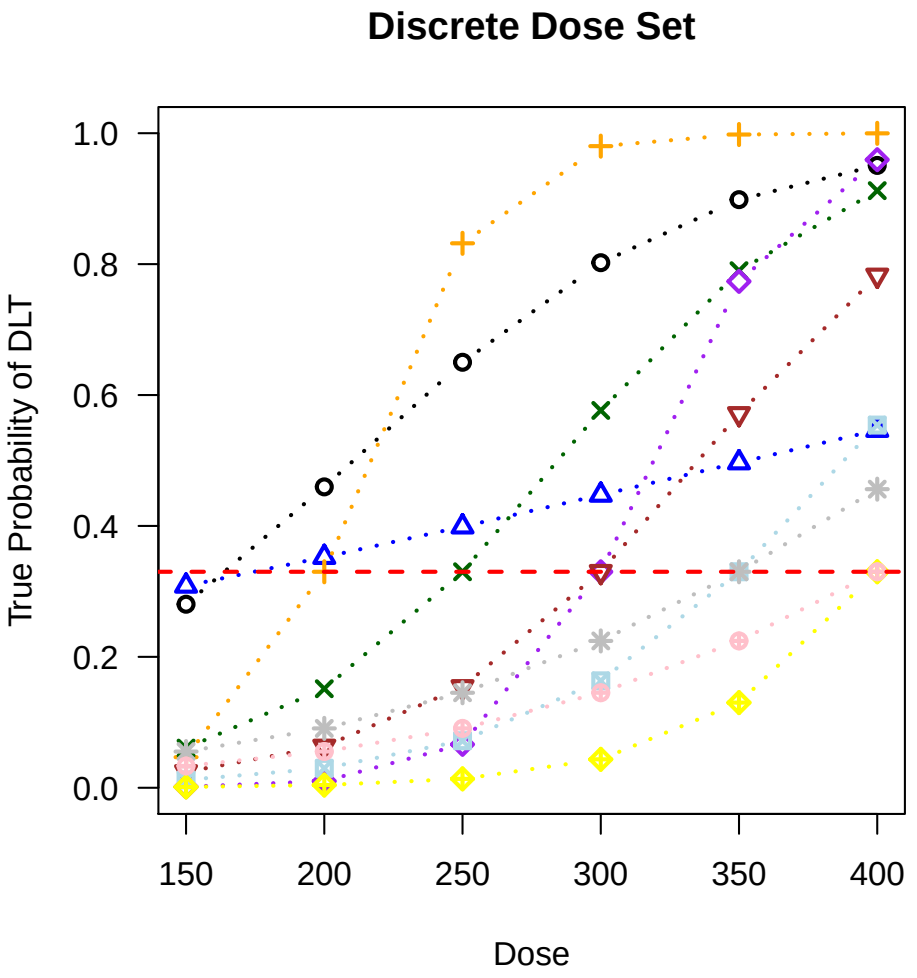
Use two estimators for MTD at end of trial

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

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

Scenarios

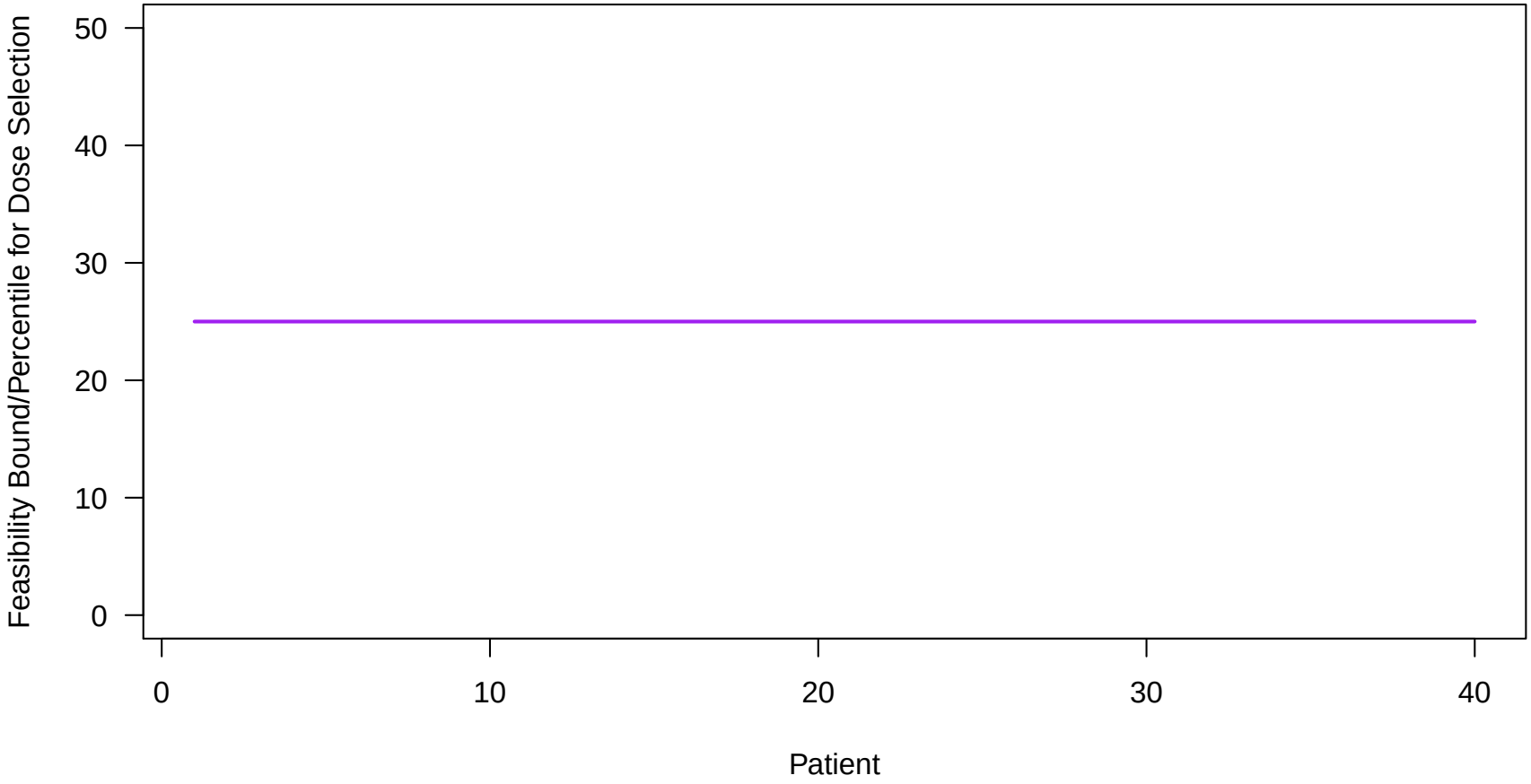




- Continuous Doses between 140mg/m^2 and 425mg/m^2
- Discrete Dose: 150, 200, 250, 300, 350, 400 (mg/m^2)

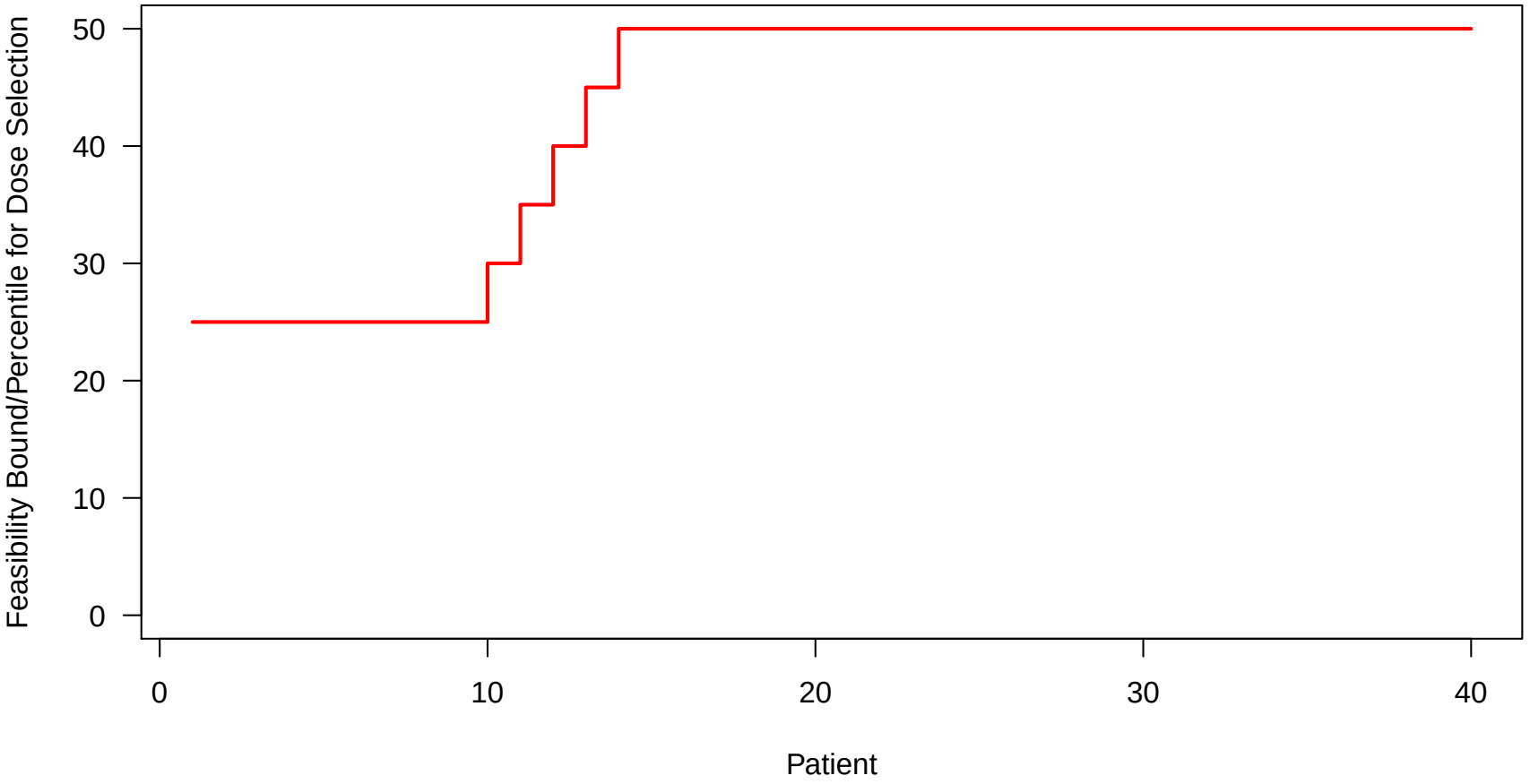
A Simulation Study

1) EWOC — feasibility bound is always 25^{th} percentile;



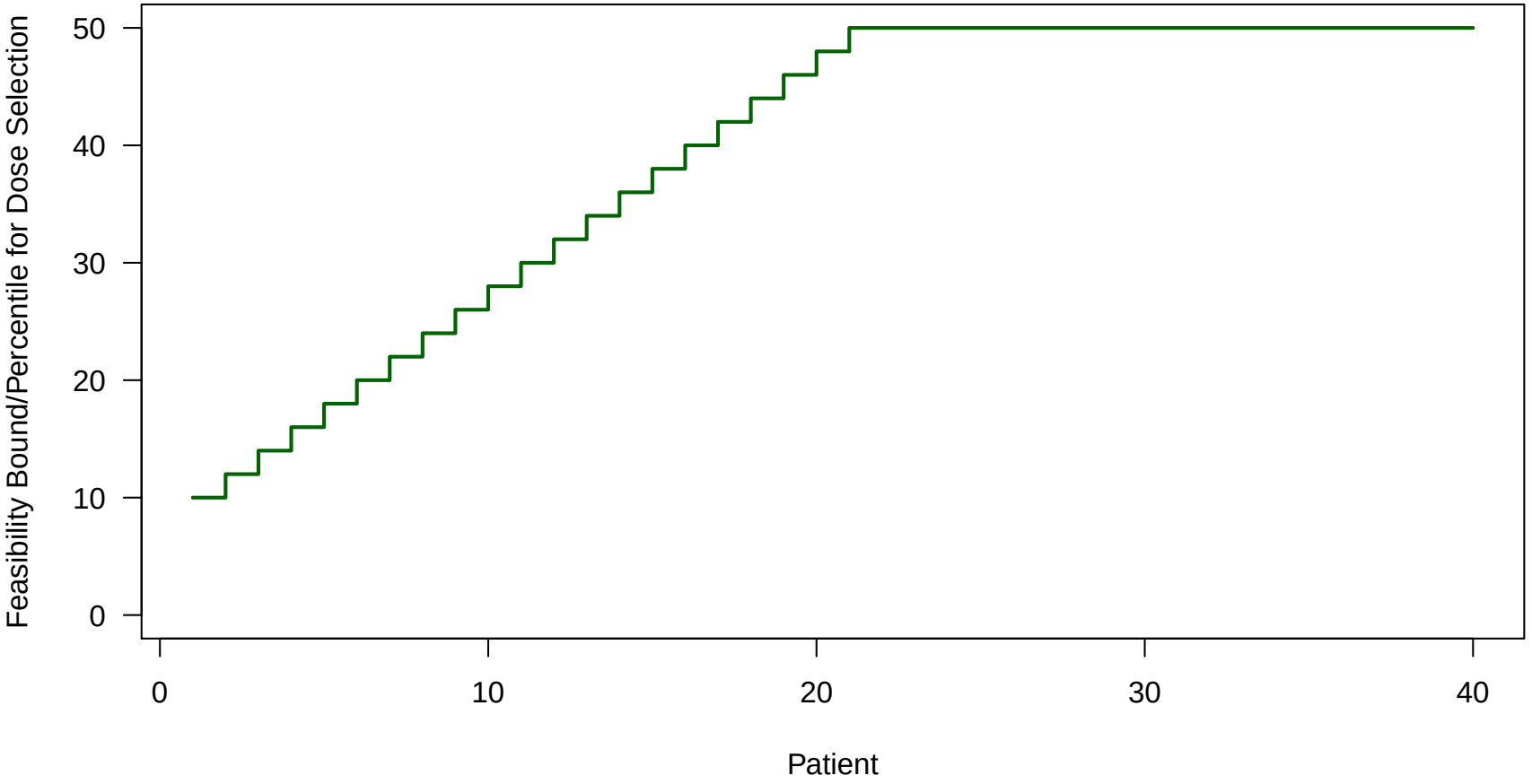
A Simulation Study

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



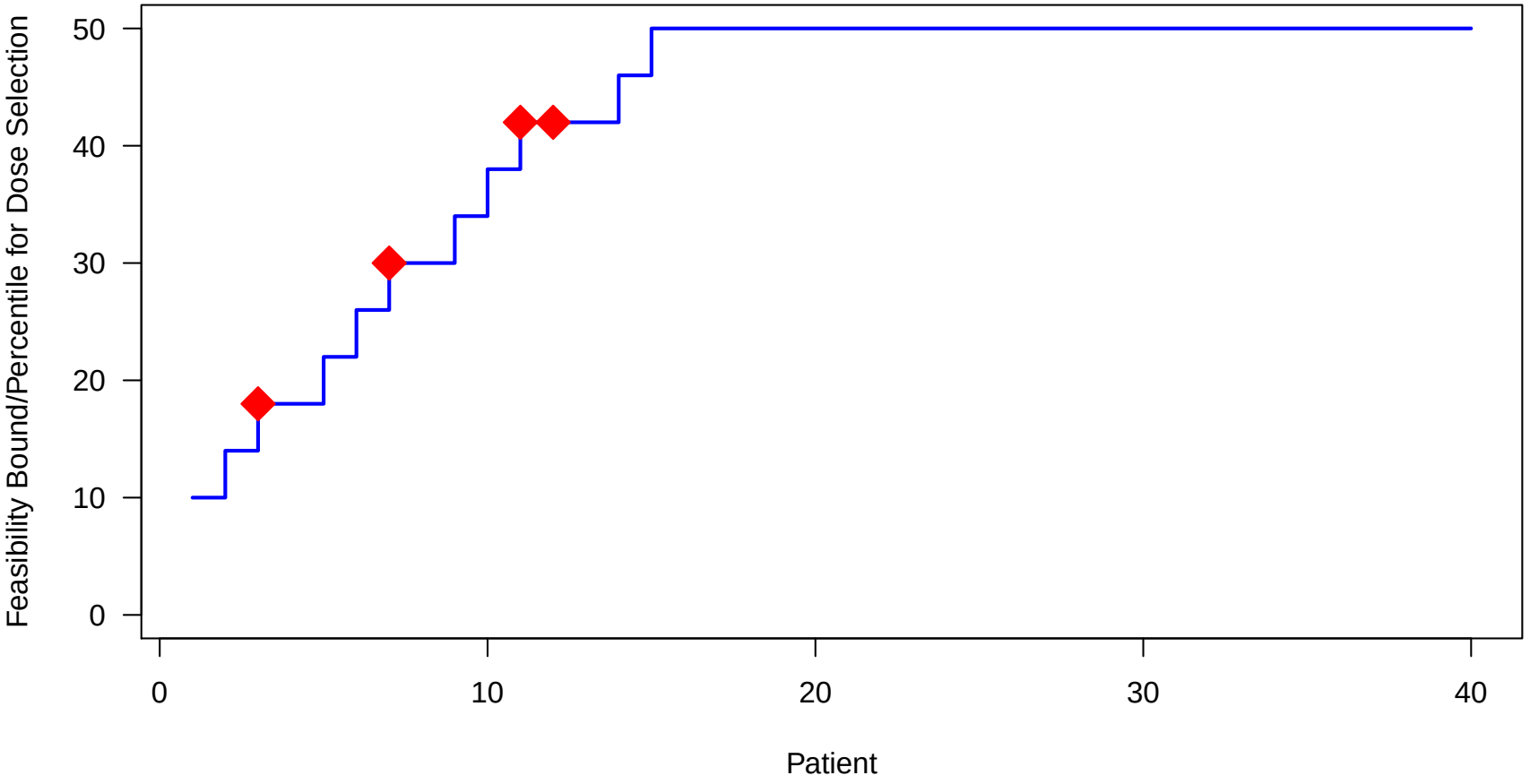
A Simulation Study

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



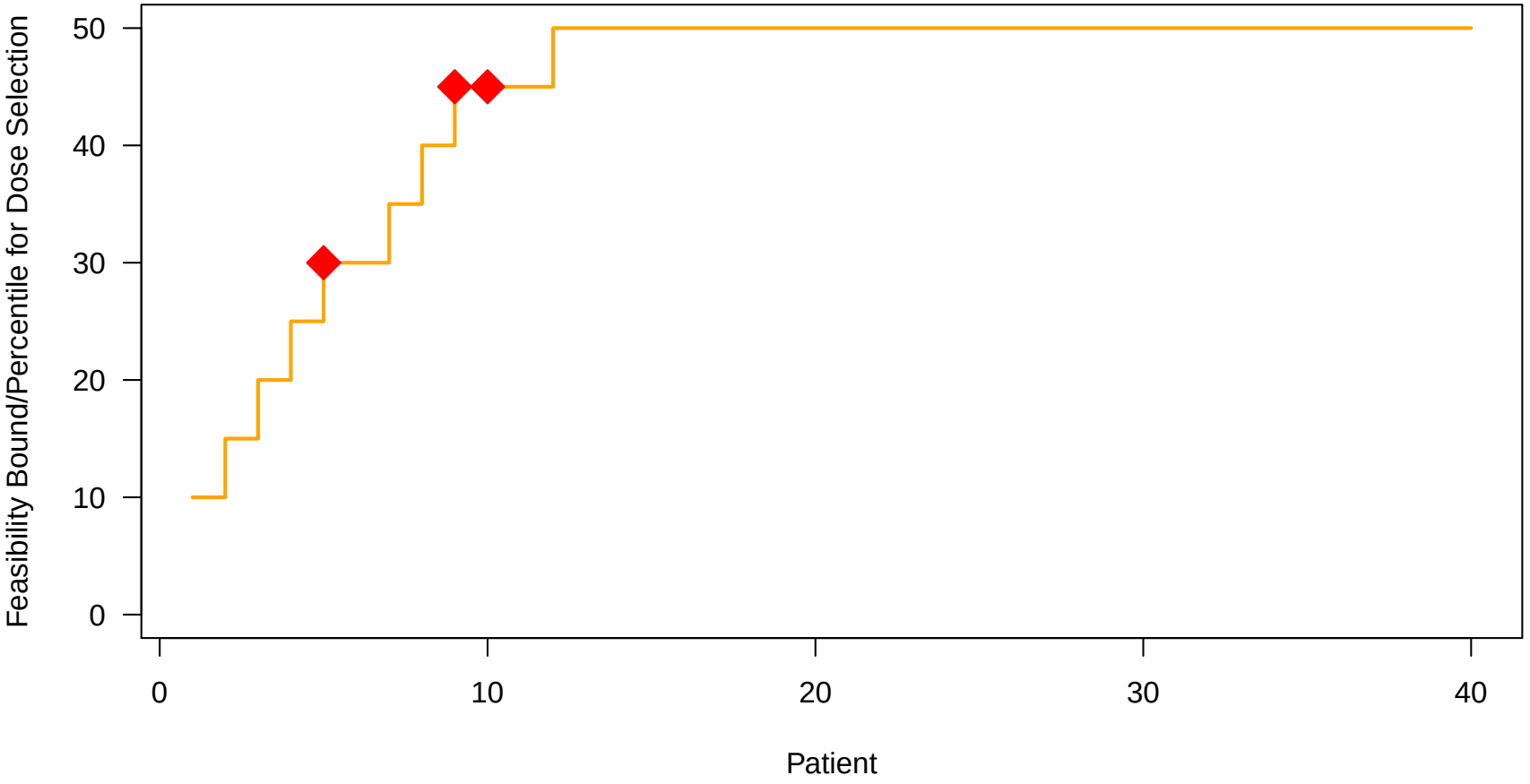
A Simulation Study

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

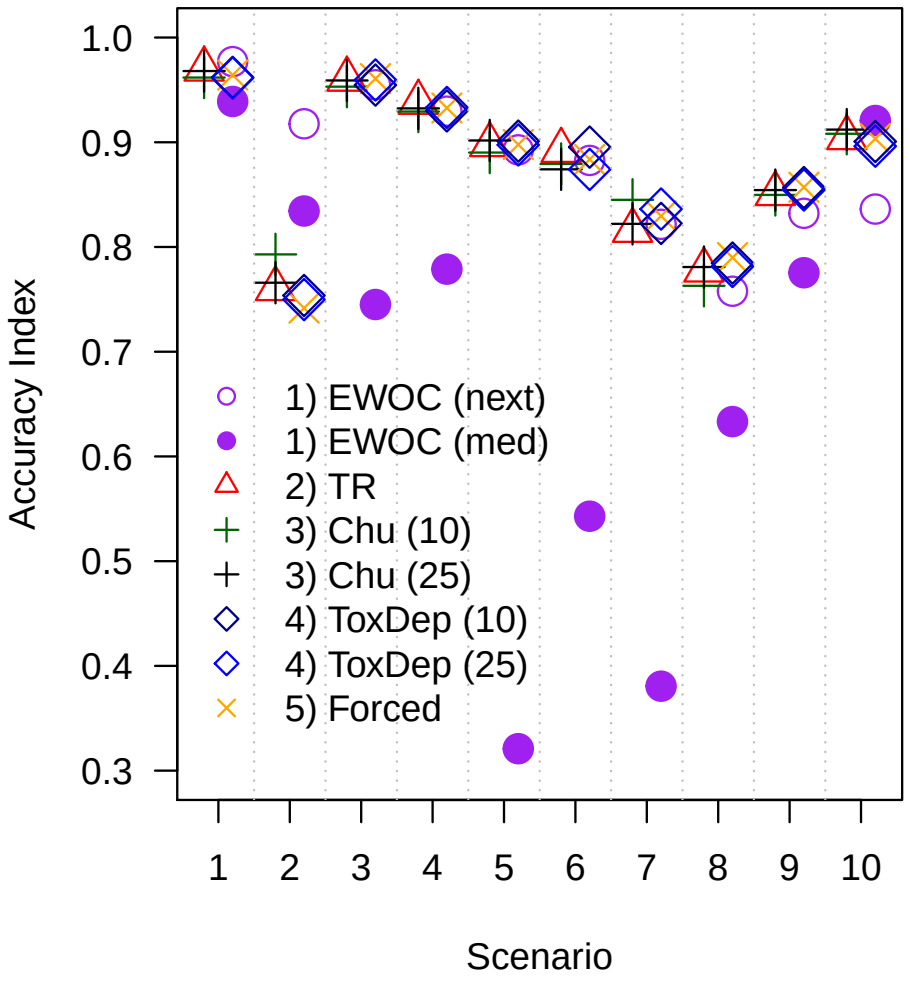


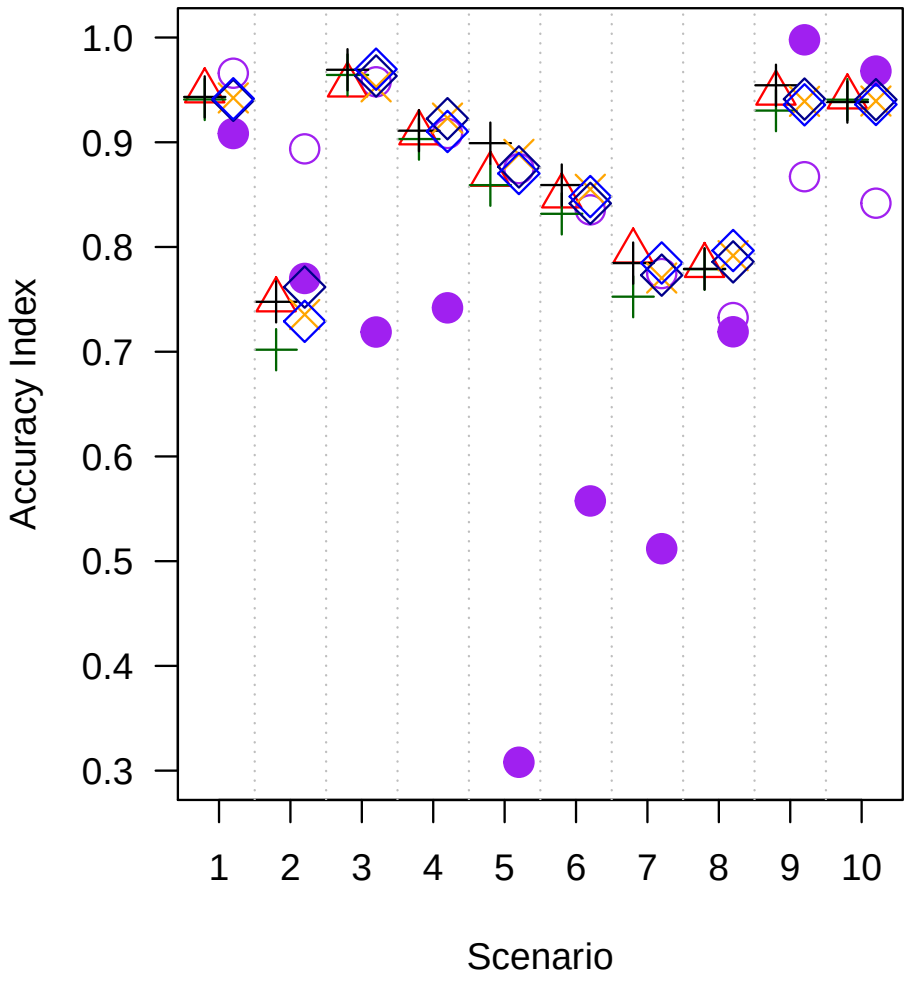
A Simulation Study

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



Results (Accuracy Index)





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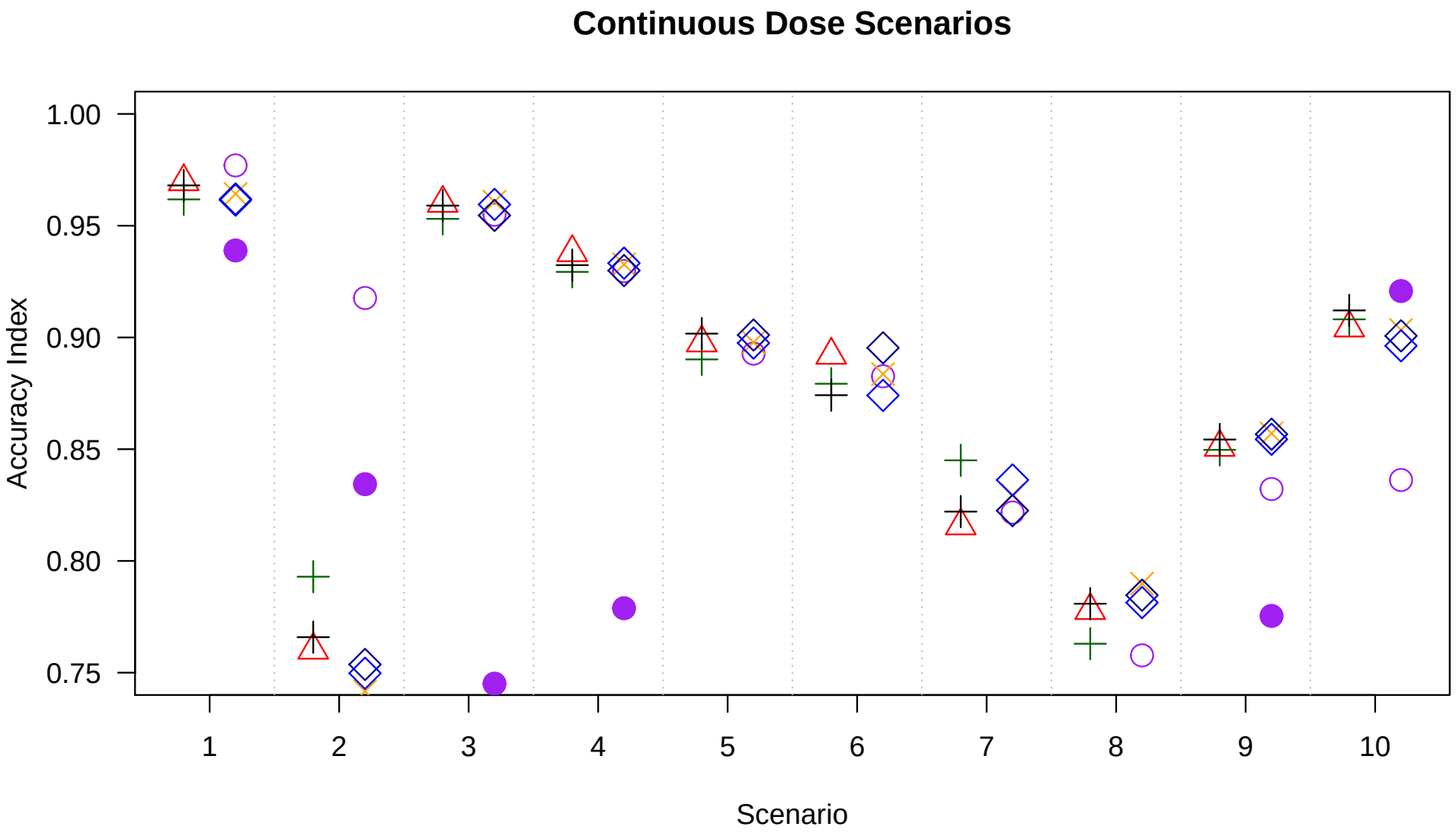

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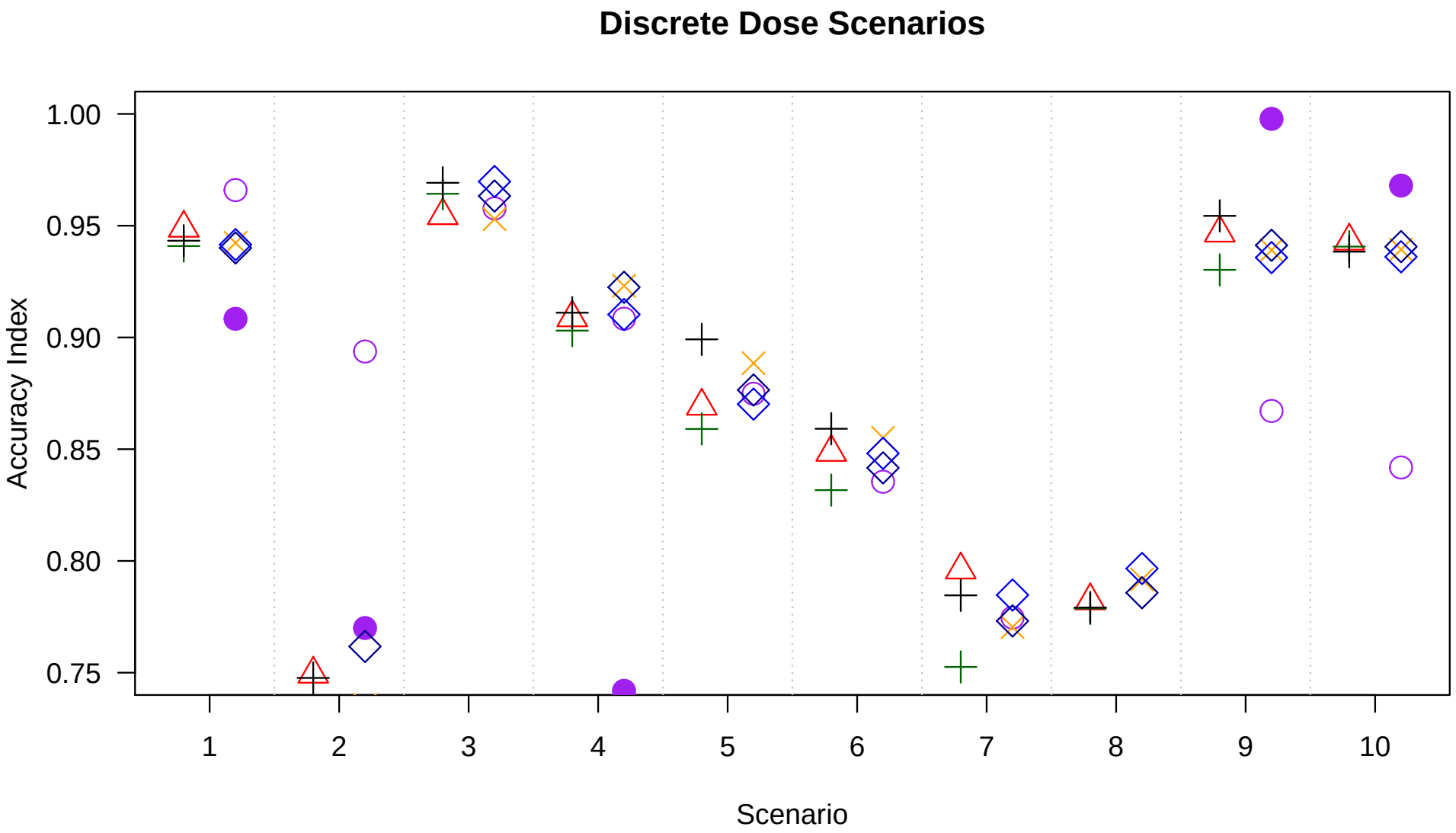

Results

Coherence

- Across simulations for continuous doses scenarios, 2-21 incoherent escalations per scenario observed for designs 2) and 3)
- 1-11mg/m^2 — Mean 3.5mg/m^2
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Experimentation

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

Discussion

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

Using posterior median of MTD with EWOC approach is unwise

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- UK Medical Research Council
- Cancer Research UK and UCL Cancer Trials Centre

References

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