Statistical Methods for Early Phase Clinical Trials

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Some methodological questions

- Schedules / several groups
- Bridging studies, eg. pediatrics
- Multidrug problems / partial ordering
- Analyzing expansion cohorts
- Recording errors - non drug-related toxicities.

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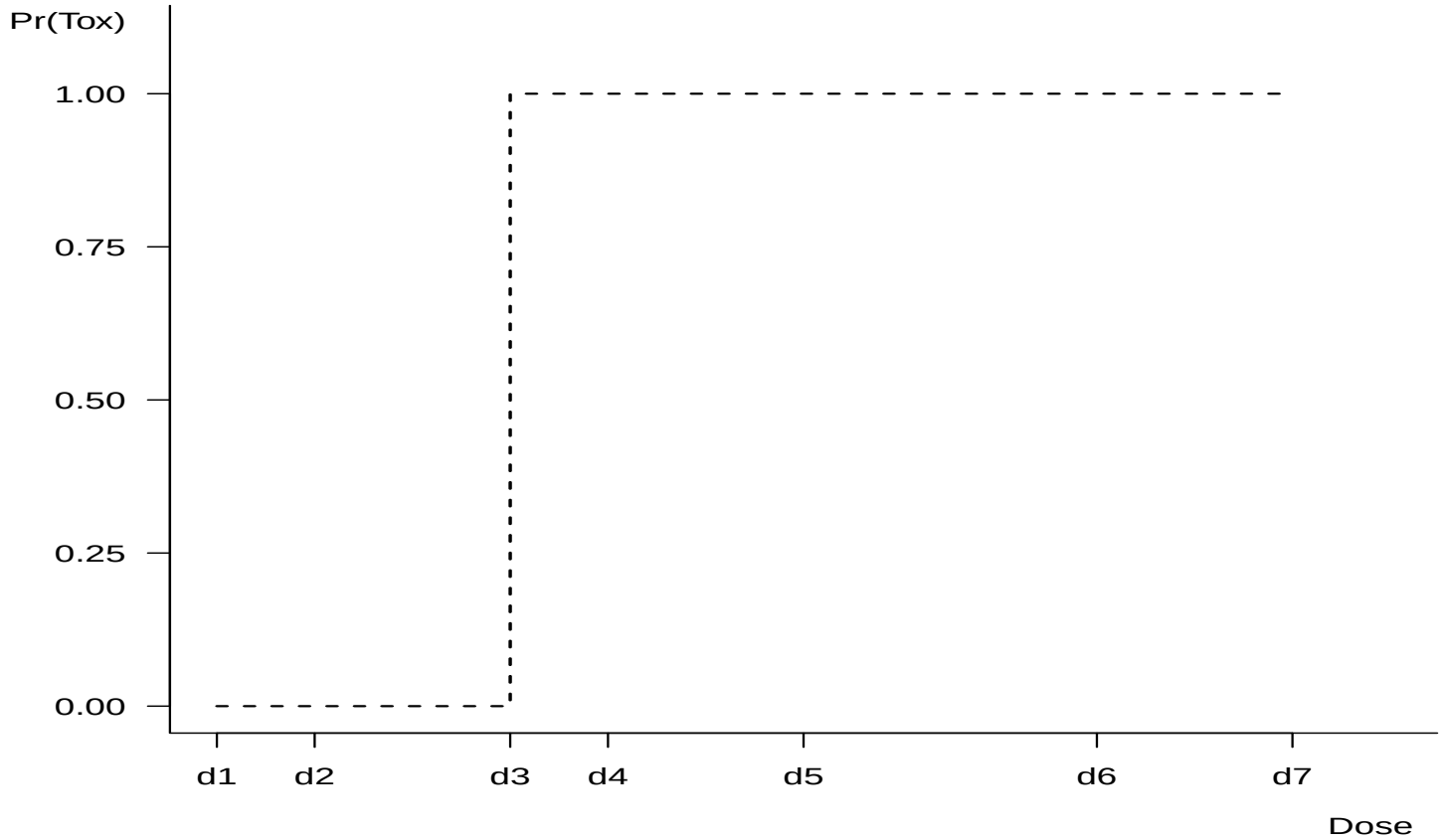
Model for cytotoxics (3 patients)



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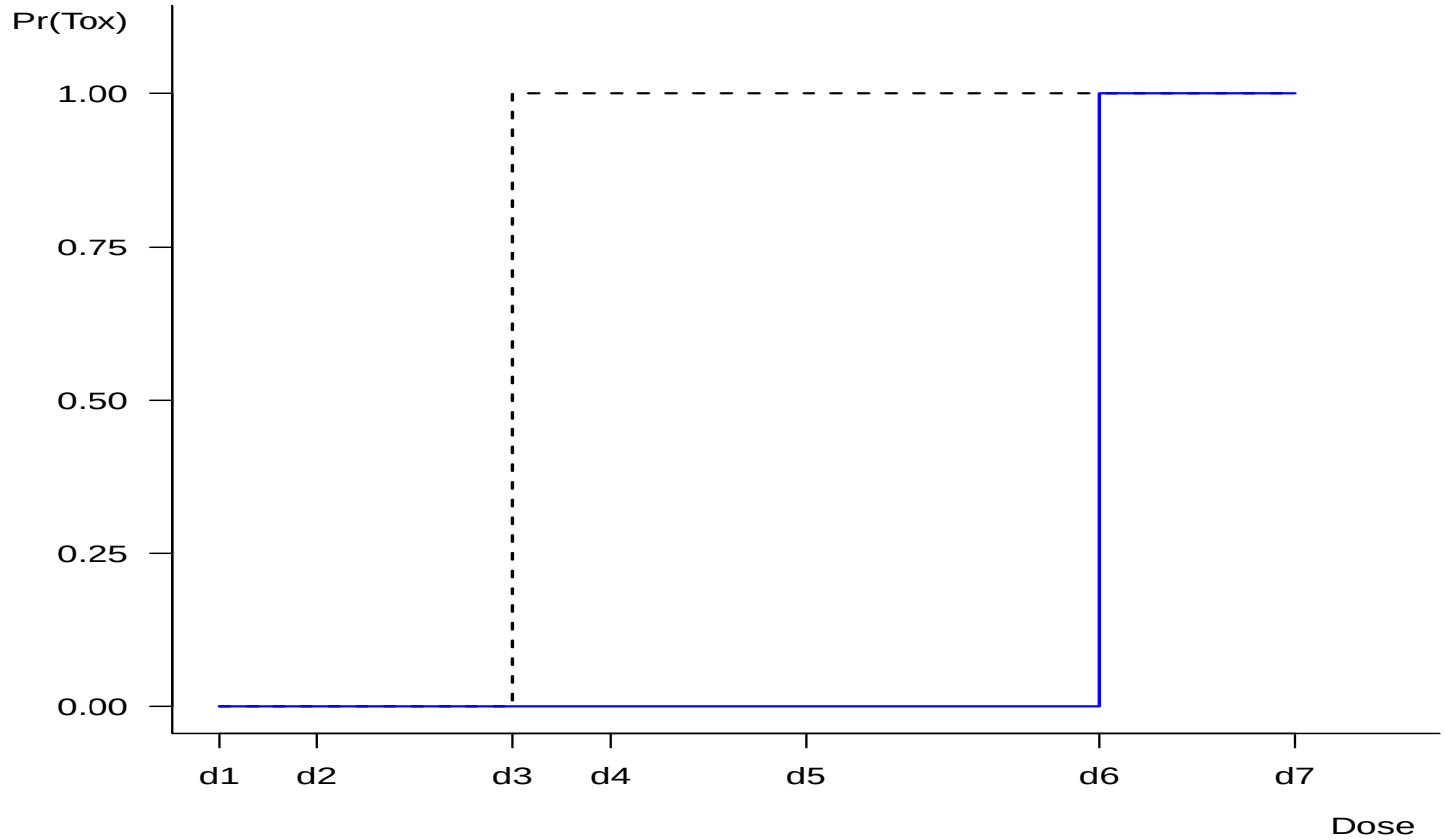

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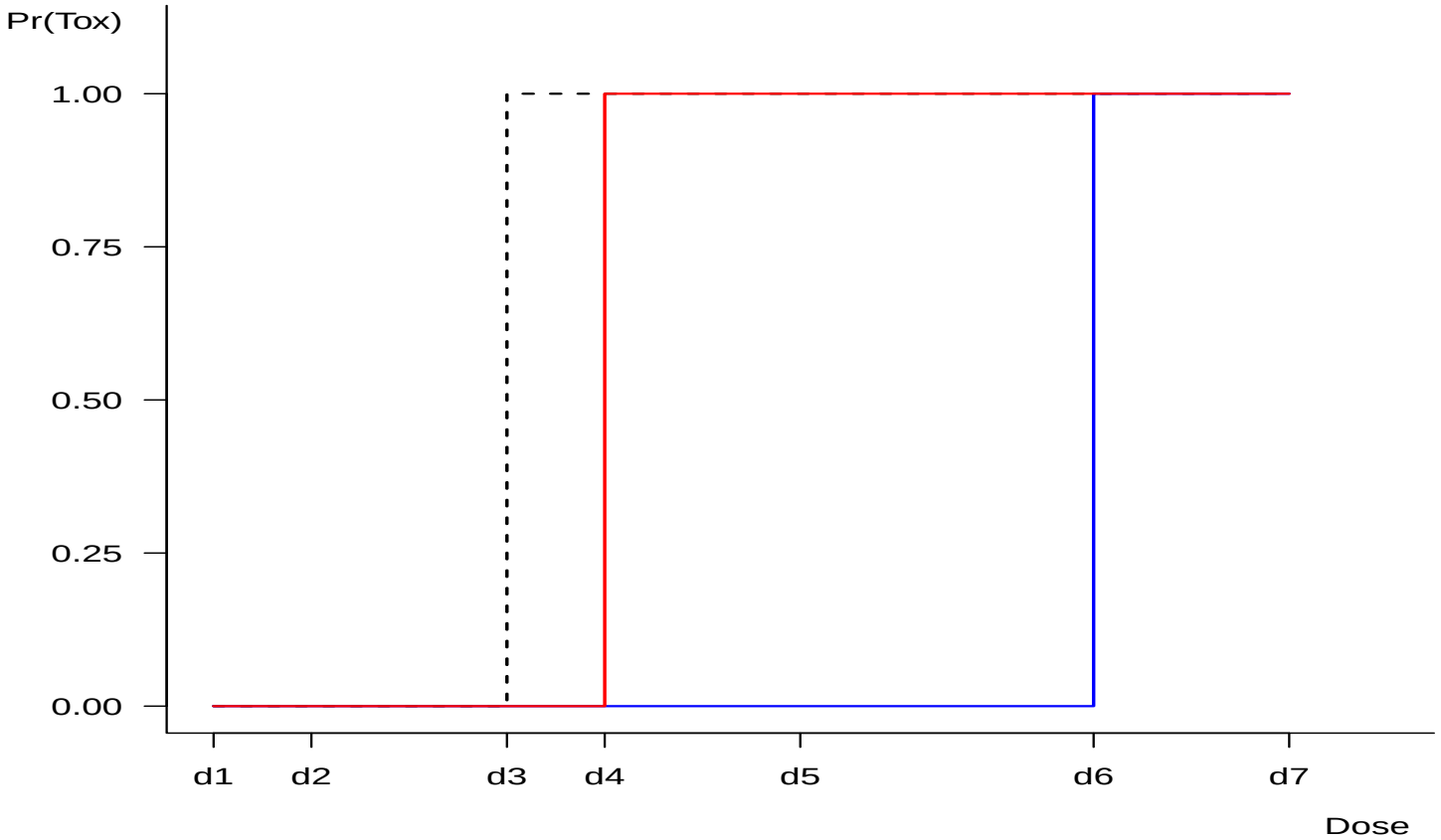
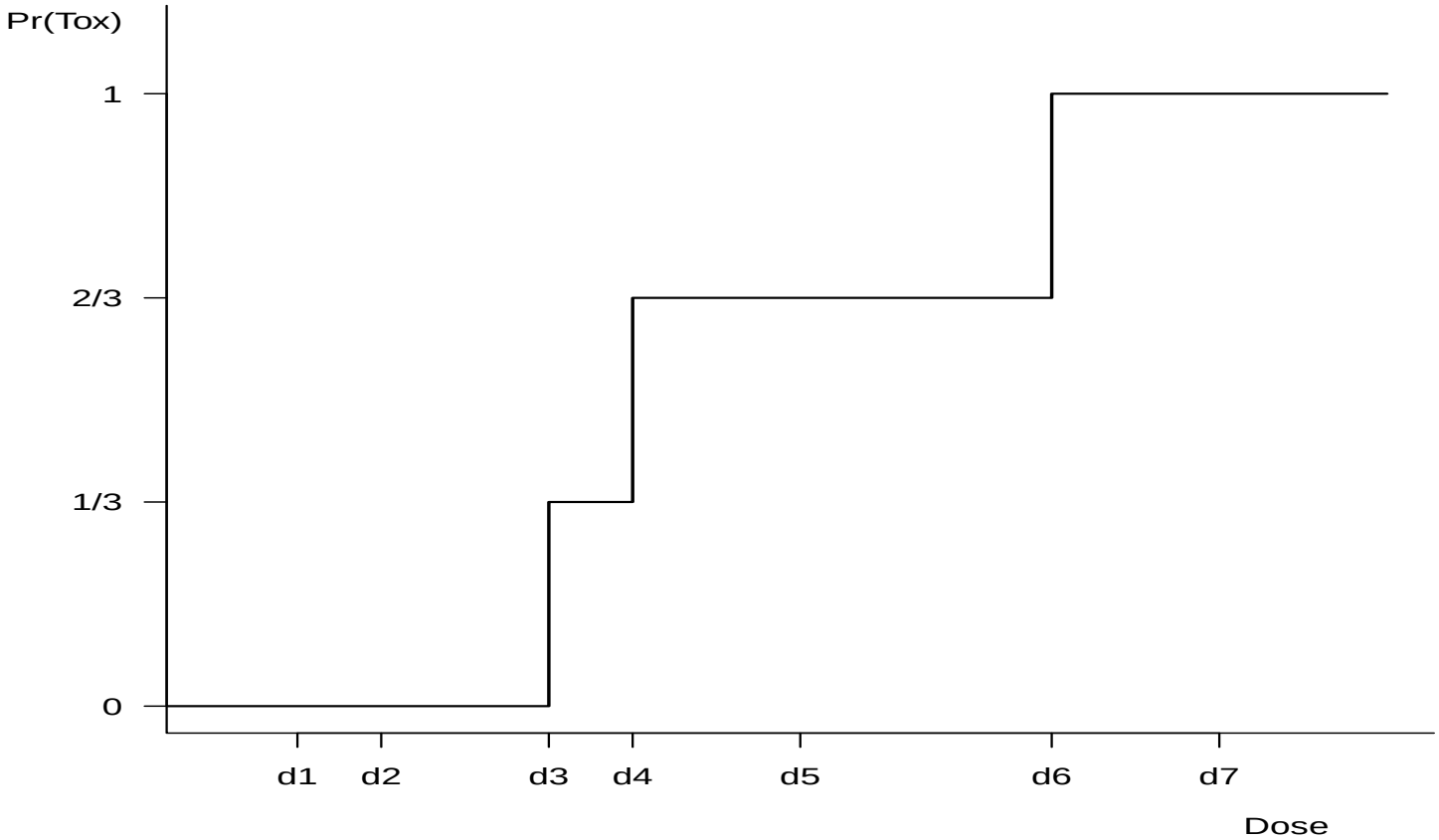
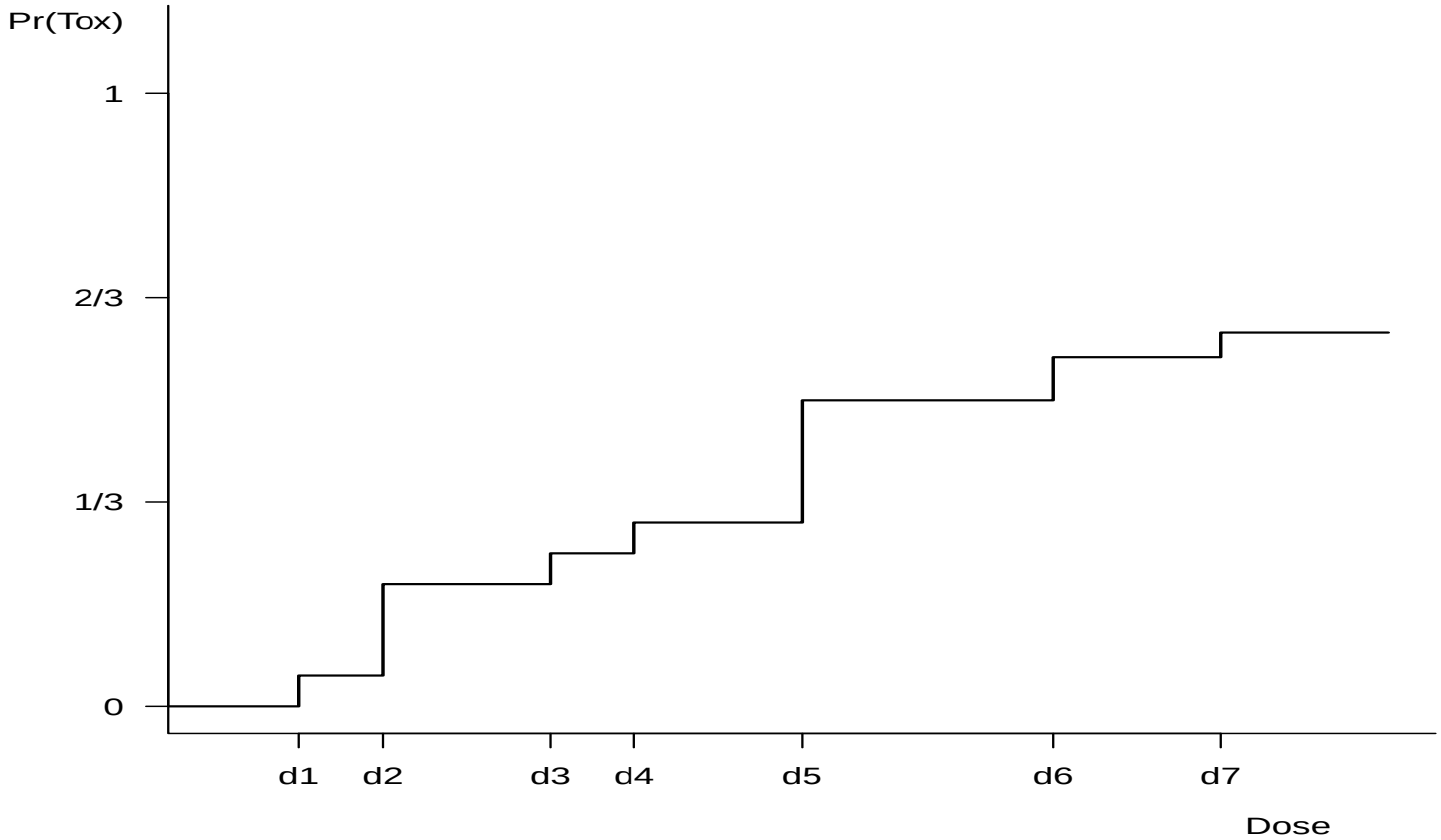


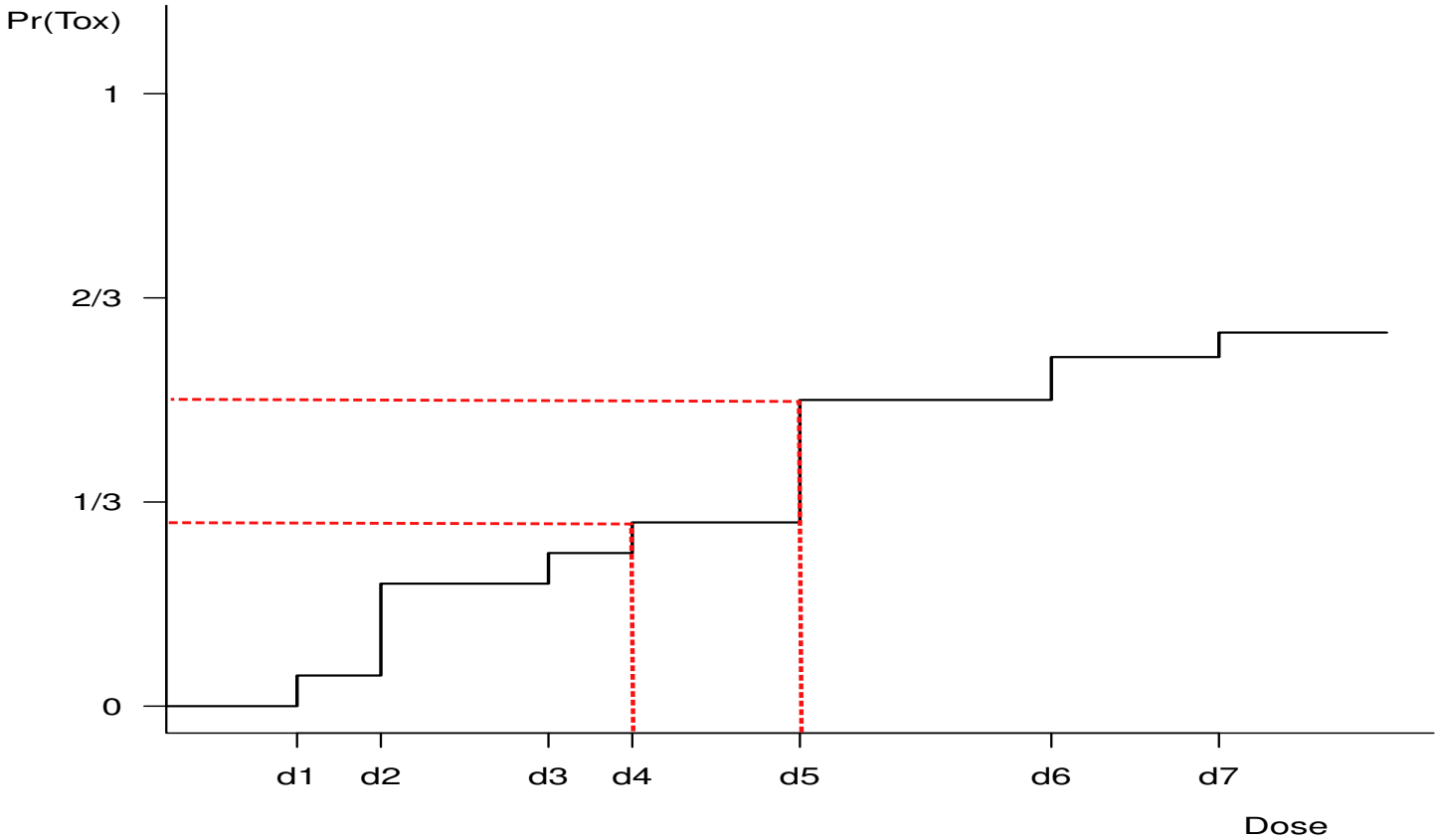
Empirical distribution for 3 patients



Model for cytotoxics (population)



Relating target to dose



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Ethical considerations for a Phase I trial

1. We do not want to “undertreat”

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3. Use as few patients as possible (efficiency).

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2. Rigidity: Probability of escalation (de-escalation) tends to one as rate of toxicity tends to zero (one).
3. Efficiency: Final recommendation / allocation as close to optimal as possible.

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Up and Down Designs (Storer *Biometrics* (1989, 1993)

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1. Random walk (no memory)
2. Decision rule uses only part of data.
3. Standard design is 3+3 design + stopping rule.
4. Fails all 3 ethical criteria;
    1. More patients under-treated than necessary.
    2. More patients over-treated than necessary.
    3. Poor (inefficient) estimate of MTD.

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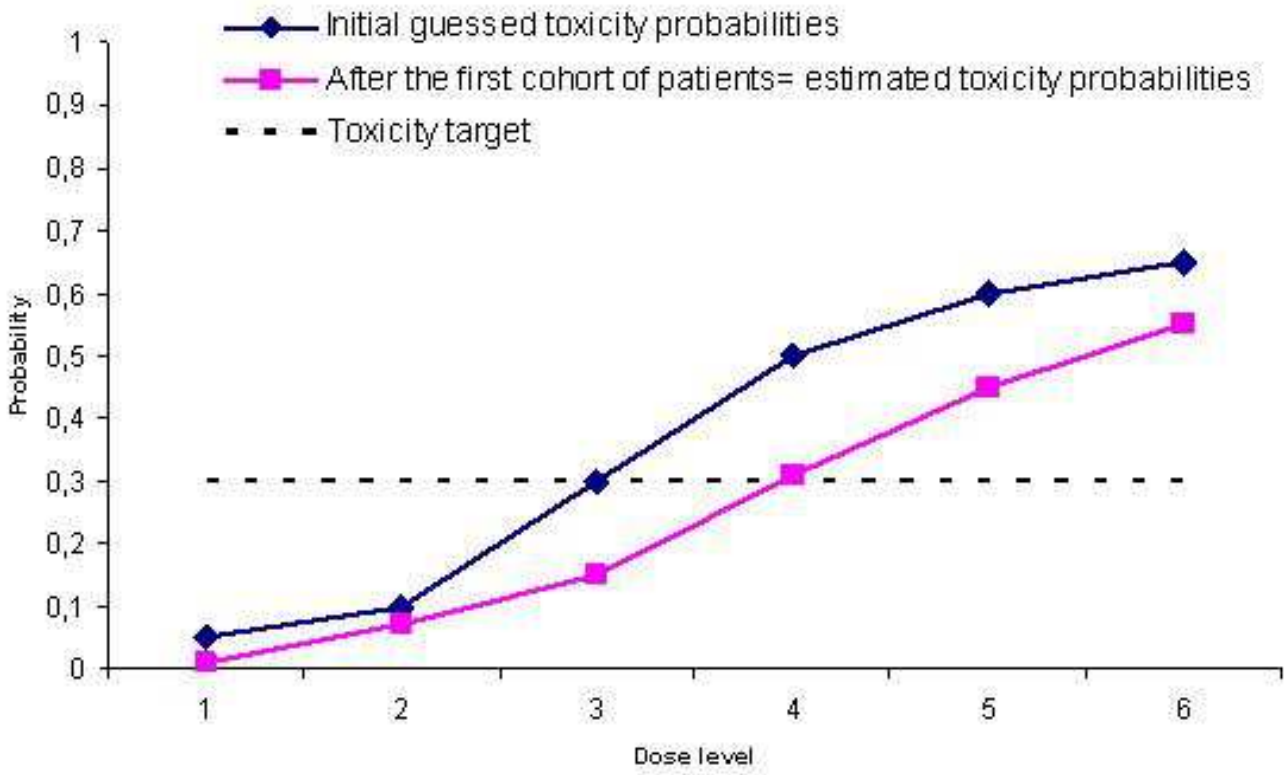
Continual Reassessment Method

Two operational features:

1. An allocation rule to assign sequentially the incoming patients to one of the possible doses, with the intent of assigning doses ever closer to, and eventually recommending, the MTD.
2. A statistical procedure that updates the information on the probabilities of toxicity in light of the results obtained for the patients already observed

Same idea for MCRM (Faries 1994), GCRM (Goodman 1995, Heyd and Carlin 1998), RCRM, ECRM (Moller 1995).

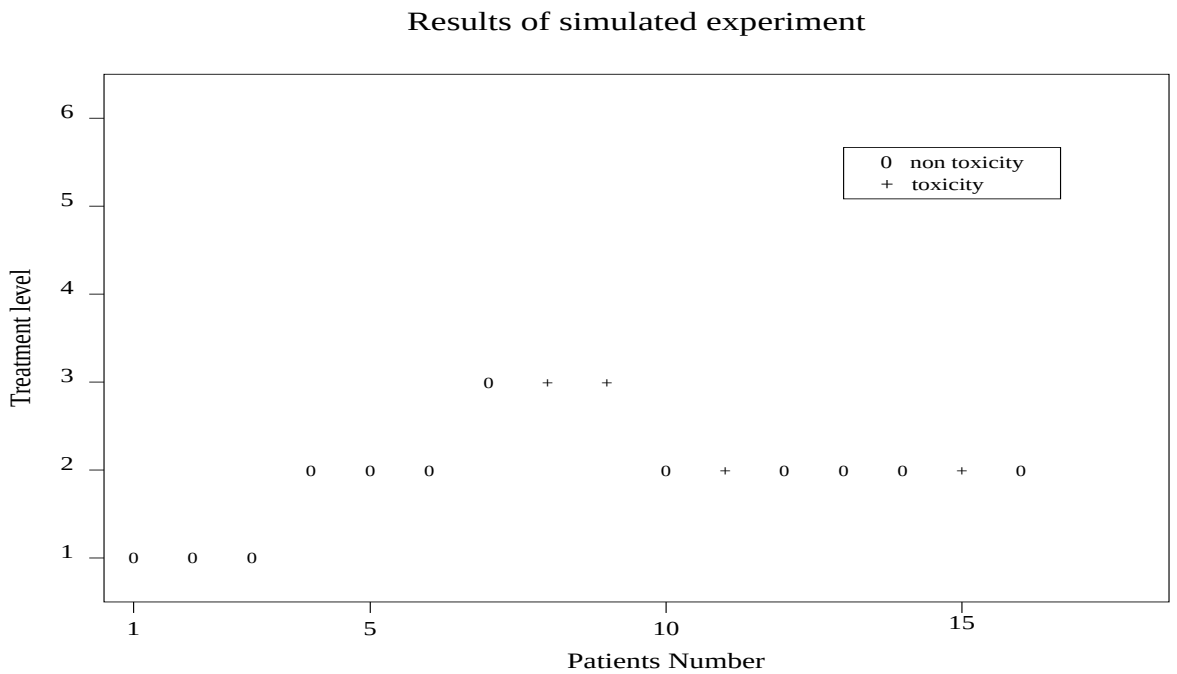
Continual Reassessment Method



1	-0.69	d_1	0.2	0	–	d_1	–	0
2	-0.27	d_2	0.13	0	–	d_2	–	0
3	-0.03	d_3	0.21	0	–	d_3	–	0
4	0.23	d_3	0.13	0	–	d_4	–	0
5	0.40	d_4	0.21	0	–	d_5	–	1
6	0.61	d_4	0.14	1	0.34	d_4	0.23	0
7	0.08	d_3	0.18	0	0.52	d_4	0.17	0
8	0.17	d_3	0.15	0	0.64	d_4	0.14	0
9	0.25	d_4	0.26	0	0.74	d_5	0.29	0
10	0.35	d_4	0.23	0	0.87	d_5	0.24	1
11	0.42	d_4	0.20	0	0.58	d_4	0.15	0
12	0.50	d_4	0.18	1	0.65	d_4	0.13	1
13	0.26	d_4	0.26	0	0.35	d_4	0.23	0
14	0.32	d_4	0.23	0	0.42	d_4	0.20	0
15	0.37	d_4	0.22	0	0.47	d_4	0.19	0
16	0.42	d_4	0.20	0	0.52	d_4	0.17	0
17	0.47	d_4	0.19		0.56	d_4	0.16	

Illustration. Groups of 3

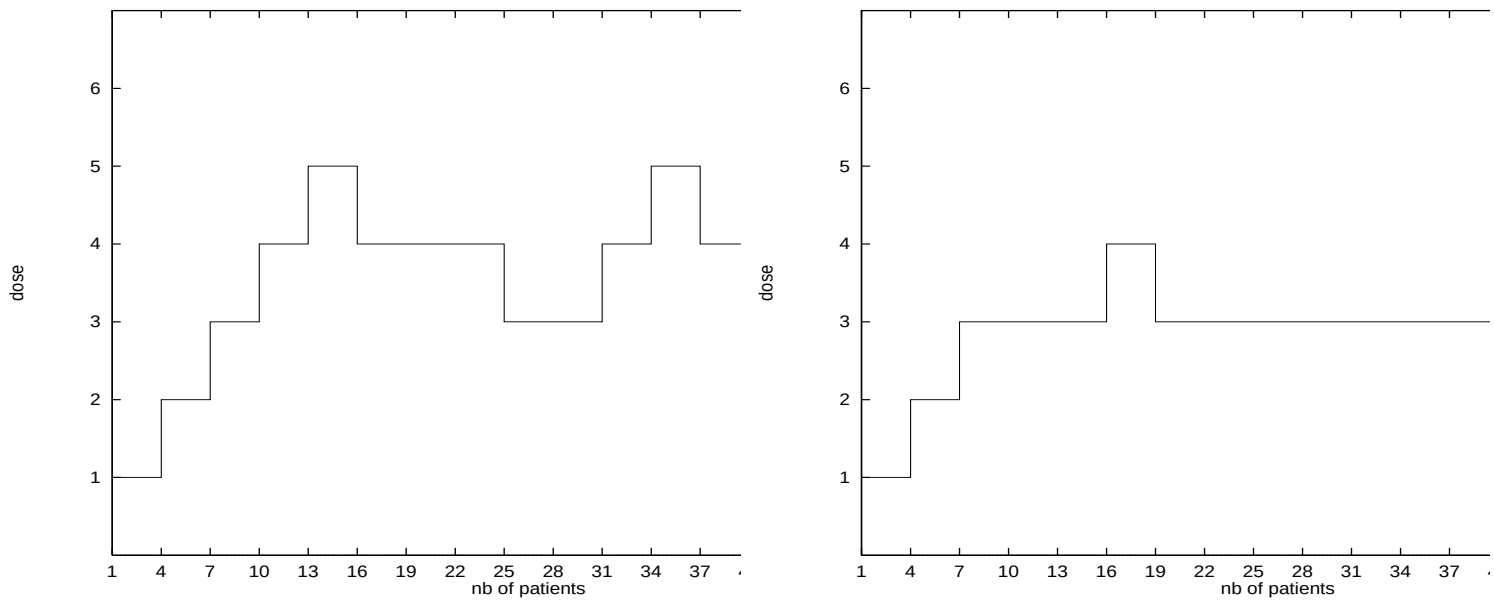
unknown probabilities at level i						
R_i	.05	.22	.31	.37	.45	.53



MTD=level 2 , $\hat{\psi}(2) = .212$ 90%CI $= (.07, .39)$

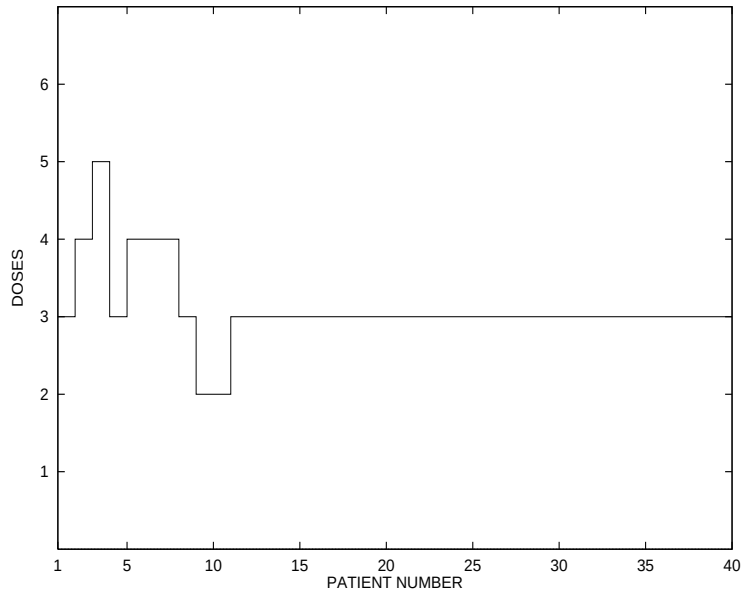
Behaviour of SM (no stopping rule) and CRM

unknown probabilities at level i						
R_i	.04	.11	.23	.34	.42	.61

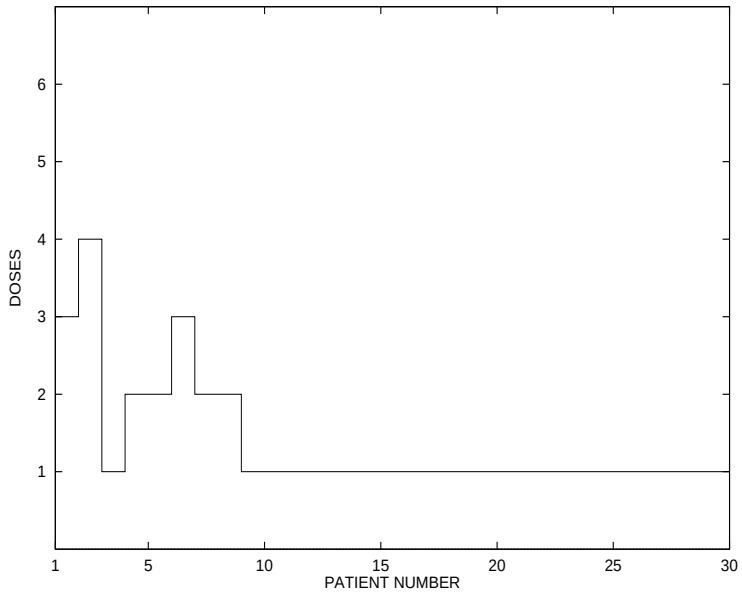


CRM examples, no stopping rule

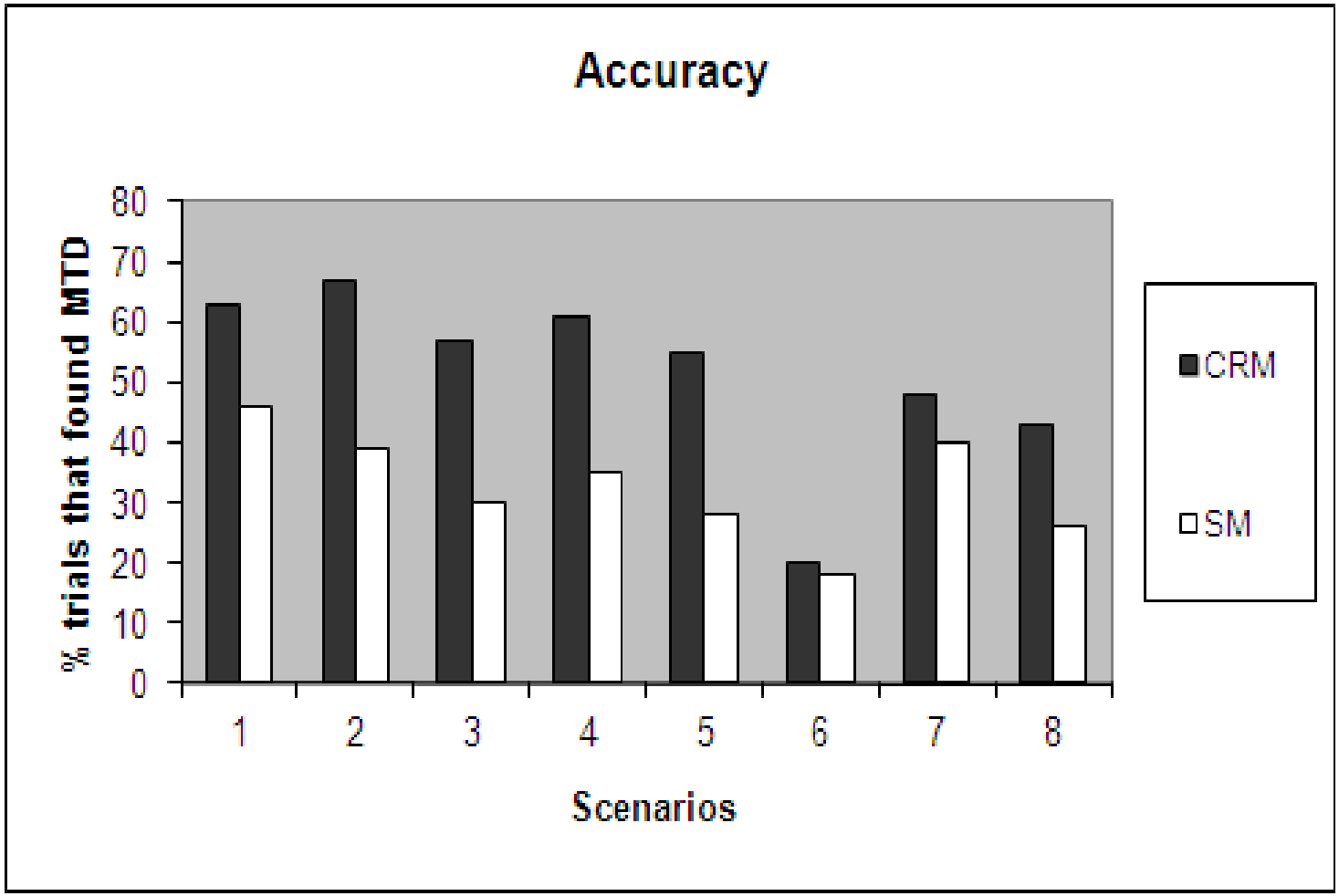
MTD = level 3



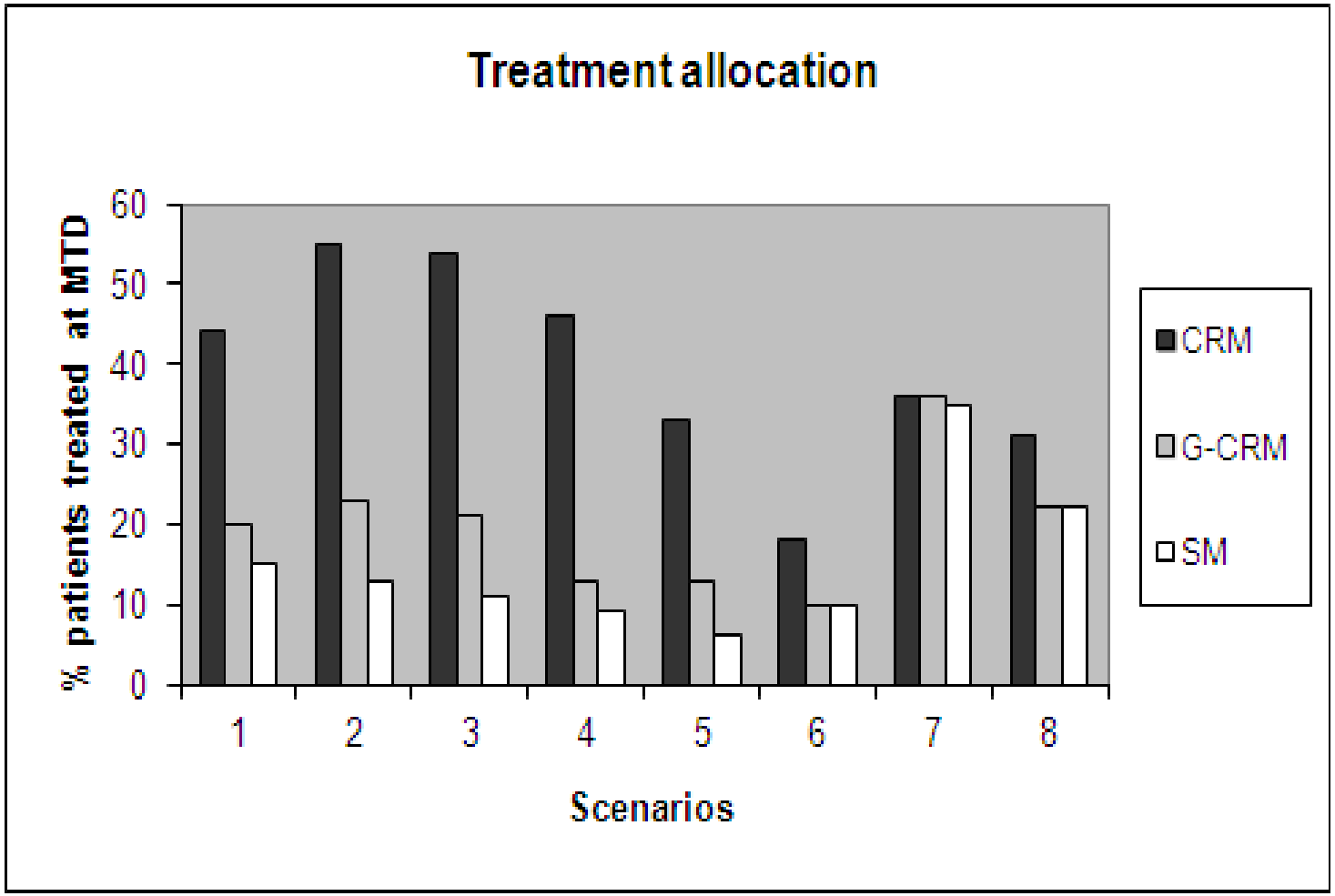
MTD = level 1



Percentage correct recommendation of MTD



In trial allocation at MTD



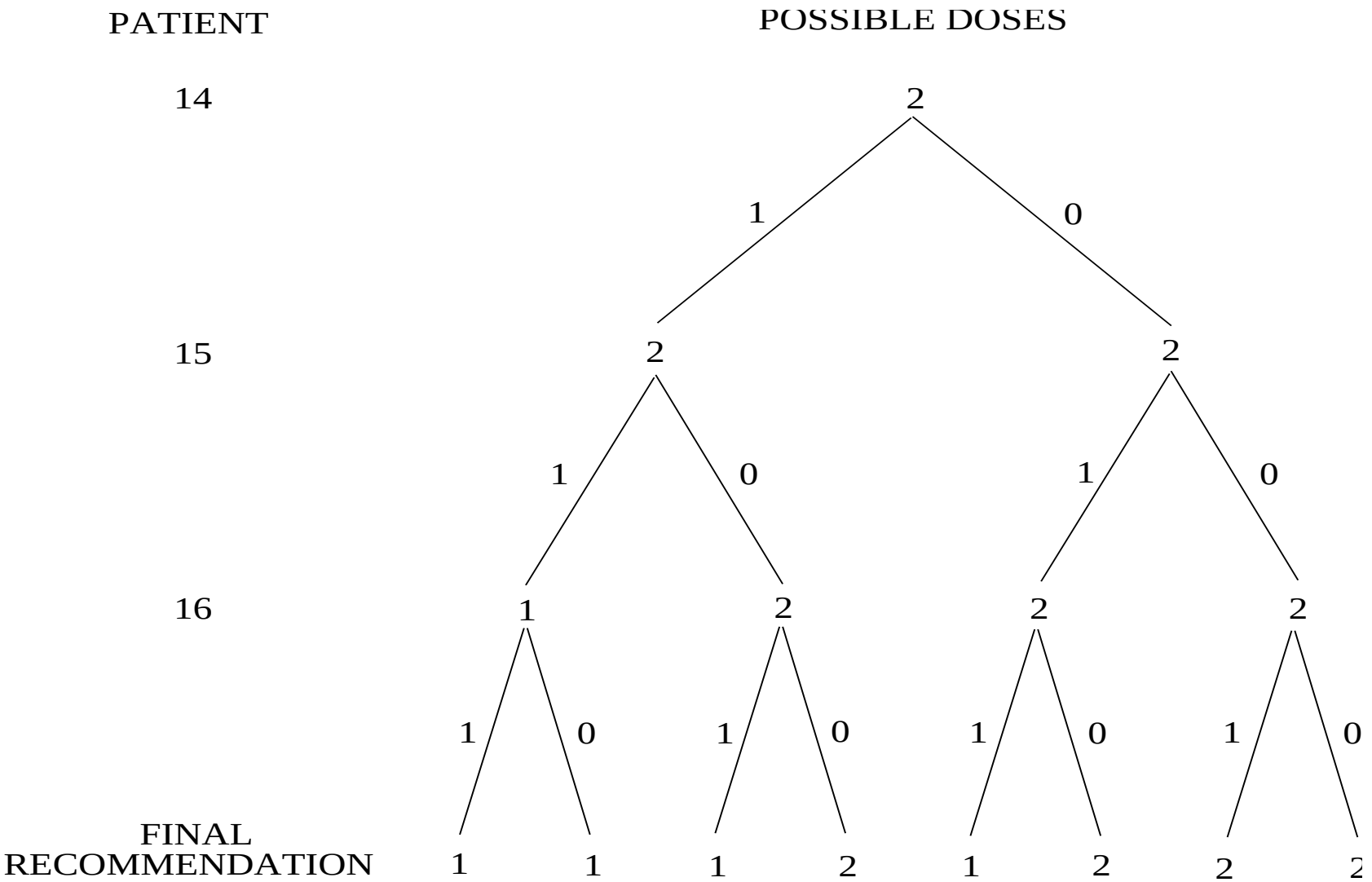
Studies in Br. J. Cancer

In 2006 review of published studies in Br. J. Cancer, percentage allocation to MTD

Published trial	3+3	CRM
Lurotecan trial	30%	49%
AMD473 and docetaxel trial	30%	53%
Topotecan trial	28%	51%
Amrubicin trial	40%	60%

Table: Percentage of patients treated at estimated MTD

Potential sample paths



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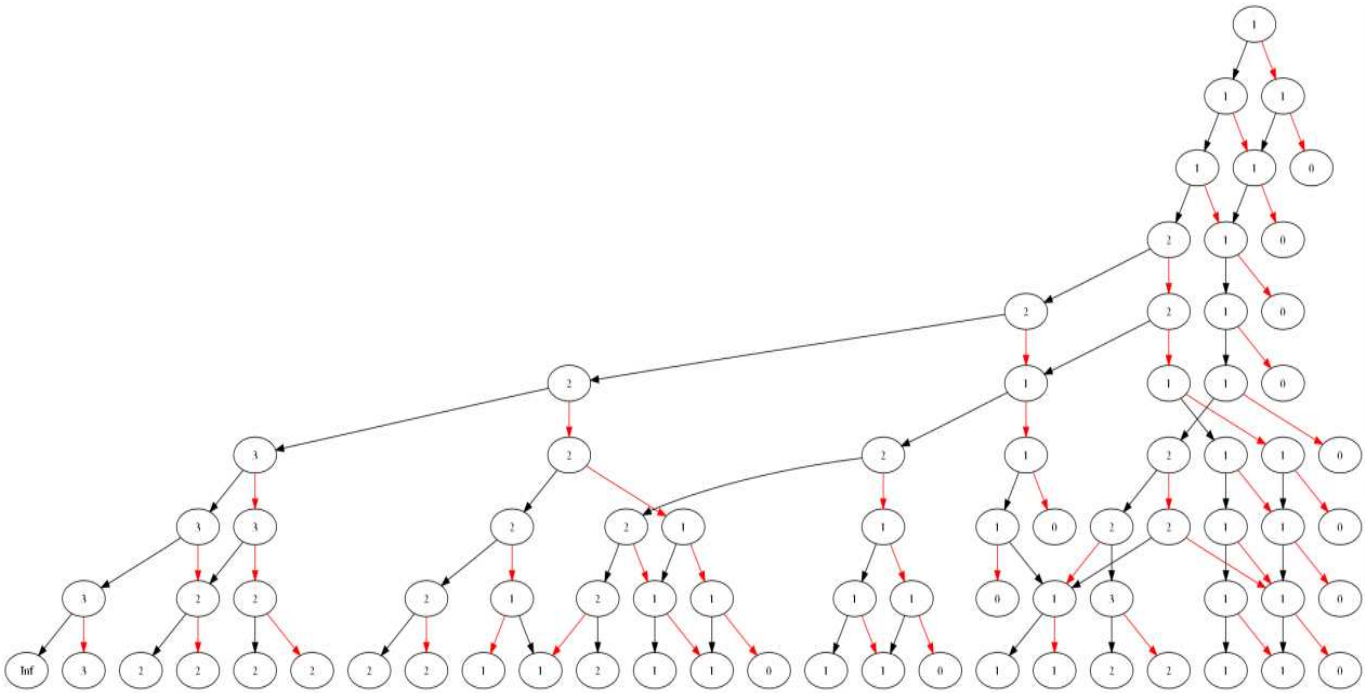

Simple take home message

1-param CRM satisfies all ethical criteria

1-param CRM is coherent

1-param CRM is not rigid

1-param CRM is efficient

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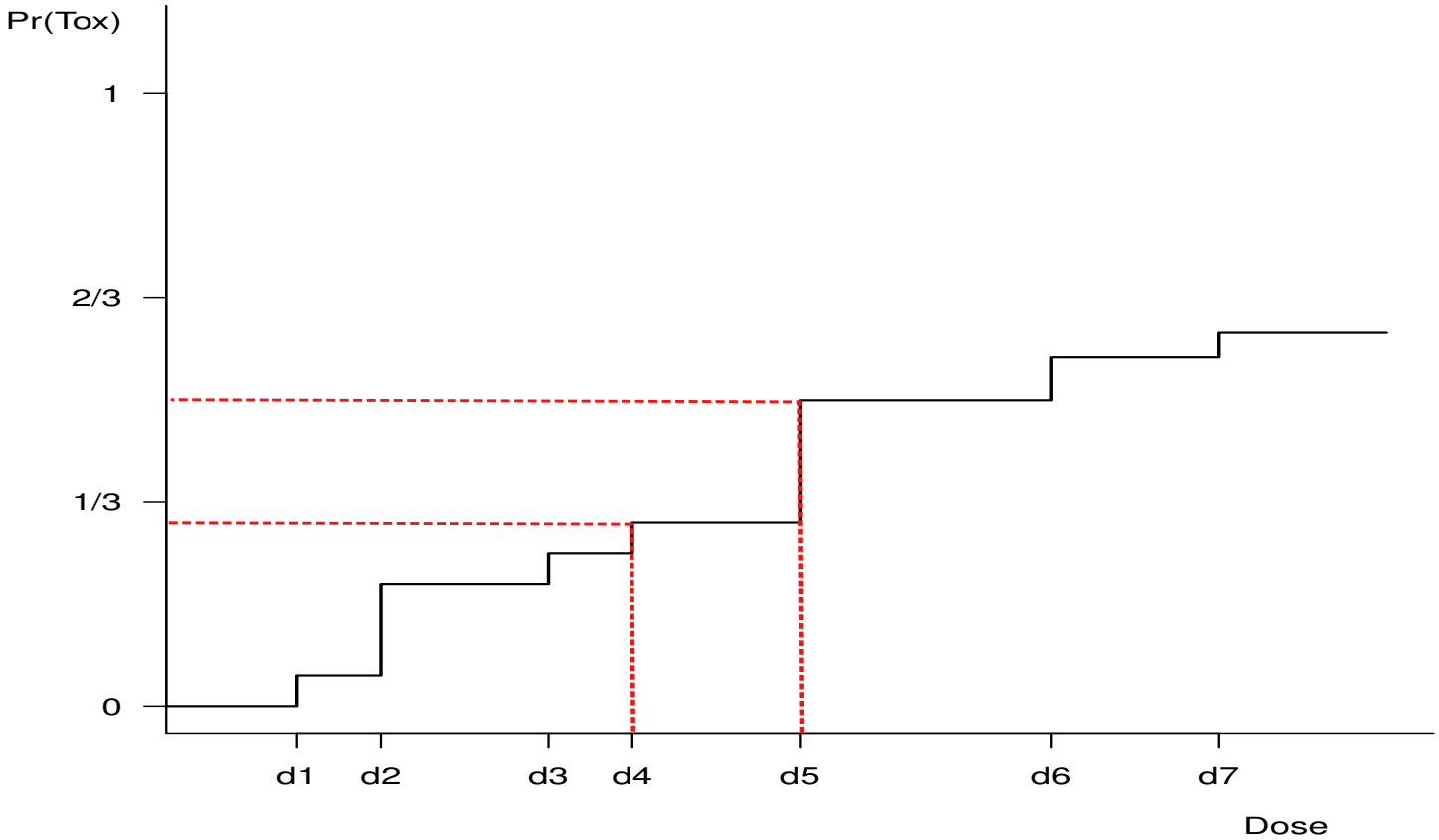
Interval methods: mTPI, BOIN, CCD



TPI design Ji et al (2007)

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5. Implementation very complex. Stopping rule very complex. Poor behaviour.

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5. At completion, use isotonic regression.
6. Global BOIN $\equiv$ mTPI

Related designs

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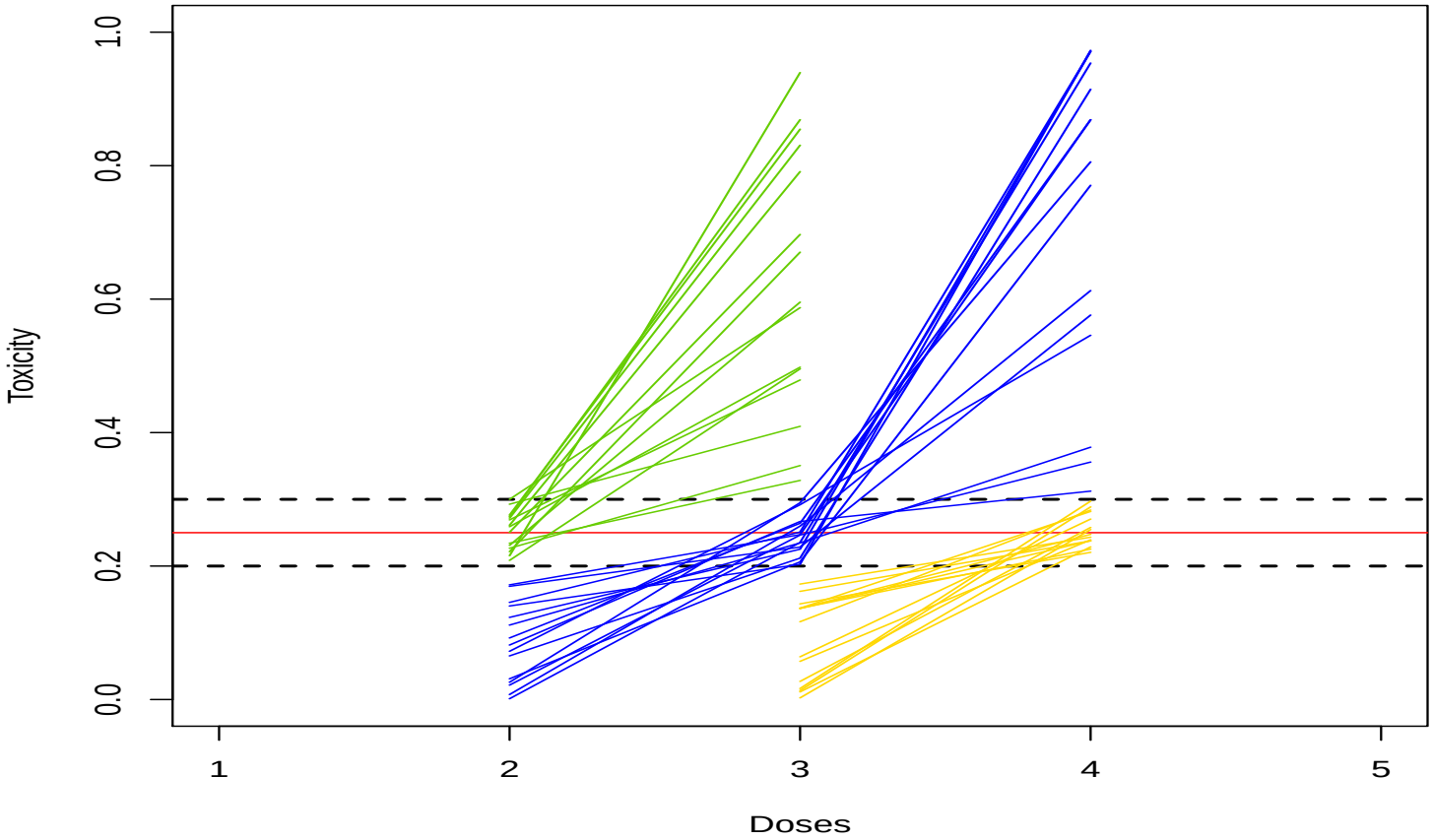
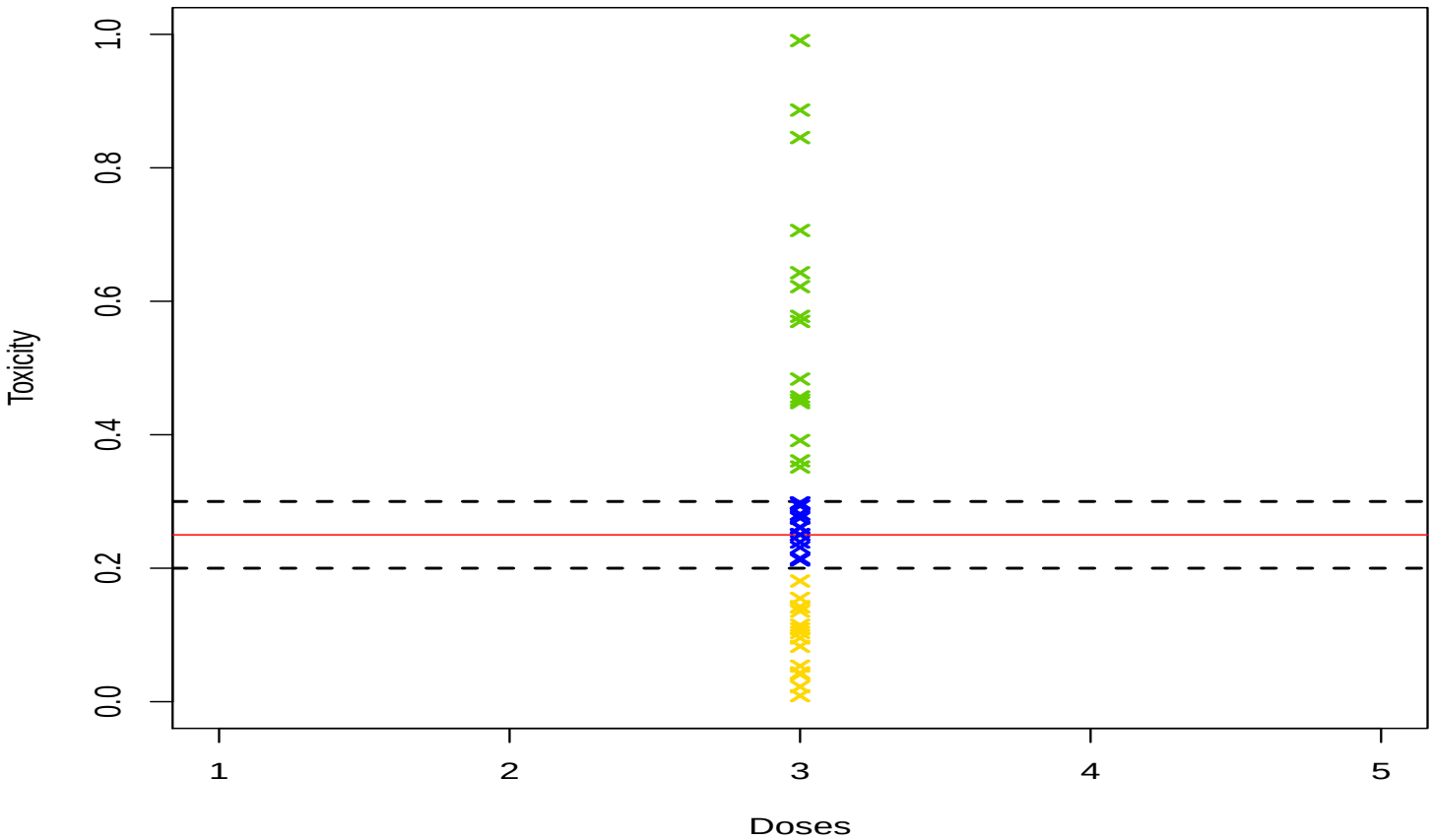
3. ALL of these designs are special cases of SPM

Semi-parametric context to mTPI/BOIN/CCD




Toxicity
0.0
0.2
0.4
0.6
0.8
1.0
1
2
3
4
5
Doses

Some mistaken beliefs

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Some mistaken beliefs

- mTPI/BOIN have comparable performance to CRM Not true
- mTPI/BOIN are very easy to implement. Not true
- BOIN is a different design to mTPI. Not true
- Little input needed from clinicians. Not true
- mTPI/BOIN limited to simplest case. True

Simple take home message

mTPI / BOIN / CCD need rules to meet ethical criteria

mTPI / BOIN / CCD are not coherent

mTPI / BOIN / CCD are not rigid

mTPI / BOIN / CCD are not efficient