Designing a seamless P1/P2a open enrollment CRM dose escalation study

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Trial Background

- Fictitious, but using learnings from actual trials BC has designed
- First-in-human study of novel compound
- Animal data and first PK/PD data exist
- Preparing for IND submission
- Not a small Biotech – not interested in only P1 PoC
- Keeping in mind Project Optimus and learning not only about MTD but also about optimal dose as soon as possible and seamlessly
- Ideally skip P2 altogether and at the end of this P1/P2a go to a seamless P2/P3

General Design Requirements

- Have at most three trial participants simultaneously in DLT period at new dose levels or MTD estimate (coming from 3+3)
- If models permits, ready to escalate after 3 completers
- Starting dose 100mg, available doses 100mg – 350mg in 25mg steps
  - Aim is to identify “correct” dose +-25mg
- Maximum sample size to determine MTD of 60 (phase 1)
  - *Another (up to) 50 trial participants available to determine dose-response (phase 2a)*
  - *Optional cohort expansion after that*
- DLT observation period 14 days
- TTL of 25%
- Minimally effective dose (MED) a priori assumed to be around 175mg

Basics of Continual Reassessment Method[1]

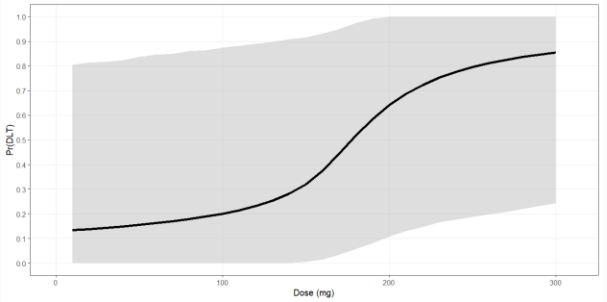
- Model based dose escalation method
  (as opposed to rule based dose escalation method)
- Uses all available data to estimate dose-toxicity relationship
- Different parametric models possible
  (hyperbolic tangent, one/two parameter logistic regression, …)
- Arriving trial participants assigned to current estimate of MTD

[1] O'Quigley, John, and Larry Z. Shen. "Continual reassessment method: a likelihood approach." Biometrics (1996).

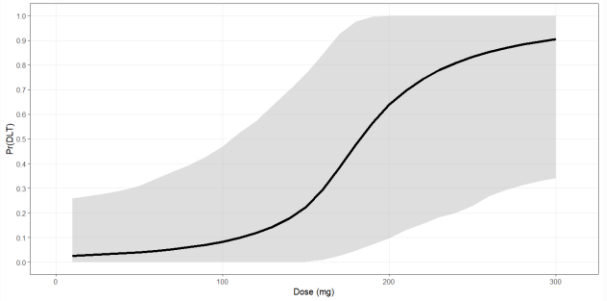
Statistical Model

- Example: Two parameter Bayesian logistic regression model
- Start with reasonably uninformative prior
- Parameters re-estimated after every patient with complete DLT information
- As MTD we choose the highest dose for which P(DLT) is “close” to the target toxicity rate (different definitions)
- Can be extended in many ways
- EWOC – Escalation With Overdose Control
  - Exclude doses from allocation that have too high probability of “unacceptable” toxicity
  - Can become stricter as trial progresses

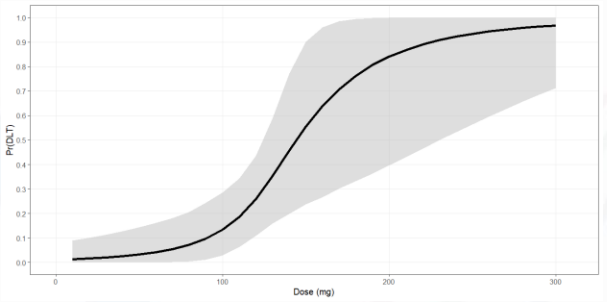
Prior



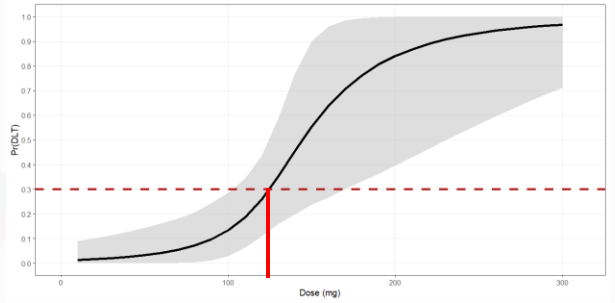
After 6 pts



After 39 pts



Choosing a final dose



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Various possible adaptations of CRM[2]

- Ad-hoc rules:
  - Don't skip dose levels in escalation / Skip at most X (1) dose levels
  - Start at the lowest dose
- Open enrollment
- Backfilling/Frontfilling
- Early stopping rules
- Target toxicity intervals
- Escalation with overdose control (EWOC)
- Switch between MTD/MED hunt if new emerging data suggests necessity
- …

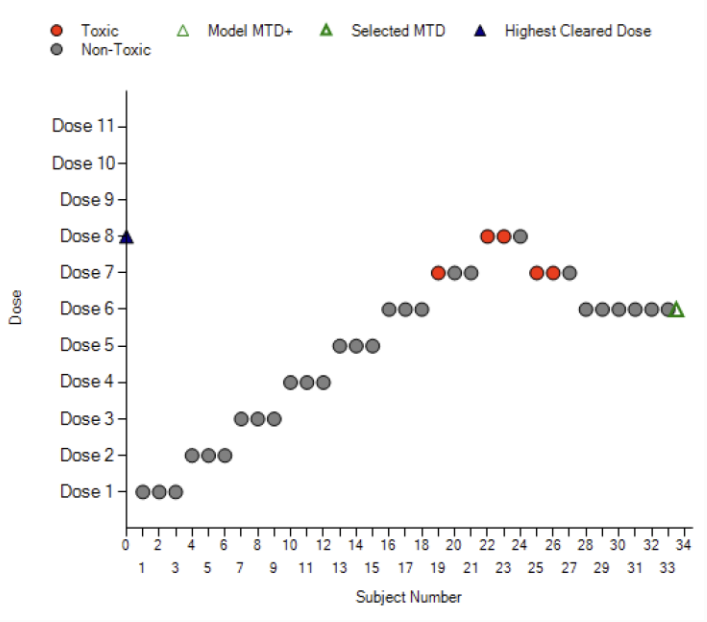
[2] Neuenschwander, Beat, Michael Branson, and Thomas Gsponer. "Critical aspects of the Bayesian approach to phase I cancer trials." Statistics in medicine 27.13 (2008).

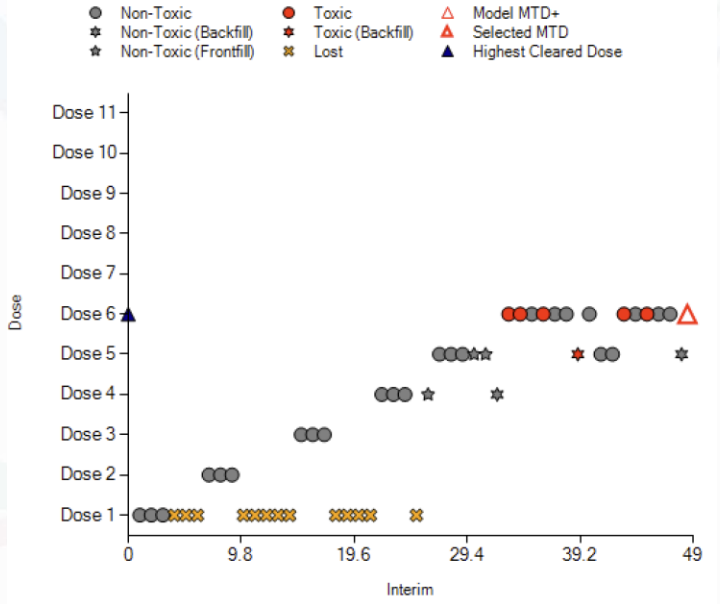
Open enrollment[3]

- Cohort enrollment: fixed number of trial participants per dose, trial is paused until results available

- Open enrollment: Trial participants may be enrolled while the current “cohort” is completing
  - Requires additional rules and risk management, but can offer many advantages

[3] Broglio, Kristine R., et al. "Bayesian dose escalation in oncology with sharing of information between patient populations." Contemporary clinical trials 44 (2015).





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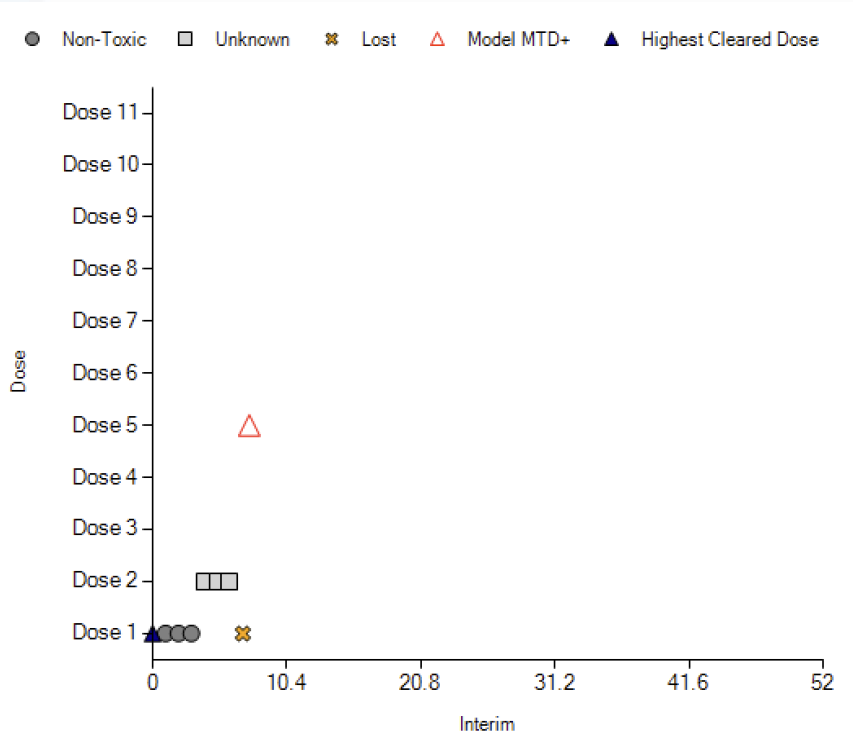
Rules for open enrollment

- Three queue concepts govern how many trial participants without DLT results can be allocated at a given dose:
  - Uncleared doses
  - Cleared doses below MTD
  - Cleared doses at MTD
- Concept of clearing doses is separate from queue lengths
  - Typically requiring a certain number of completers, but possibly also certain maximum toxicity rate

Open Enrollment:

Max subjects:	60
Time unit:	week
Mean recruitment rate (1/week):	2
Time until final result (week):	2
Maximum subjects without final results if dose is uncleared:	3
Max subjects without final results if dose is cleared and below MTD:	6
Max subjects without final results if dose is cleared and at MTD:	3



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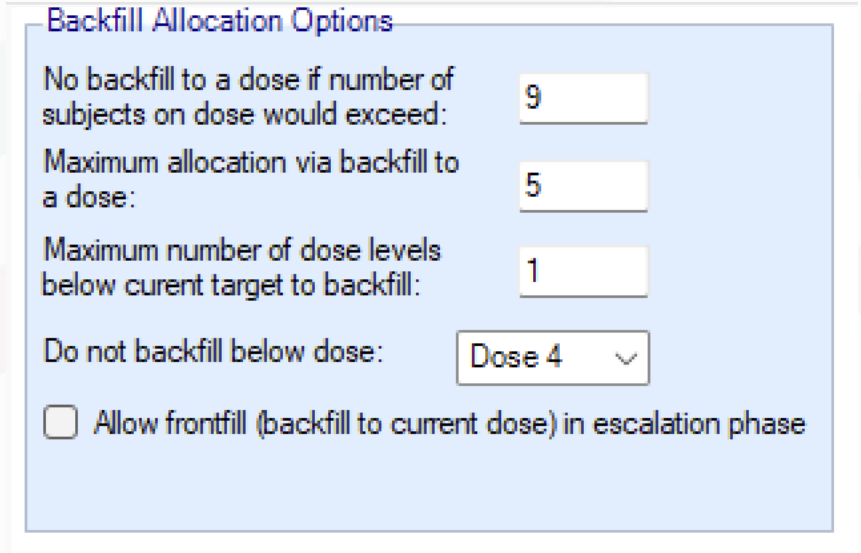
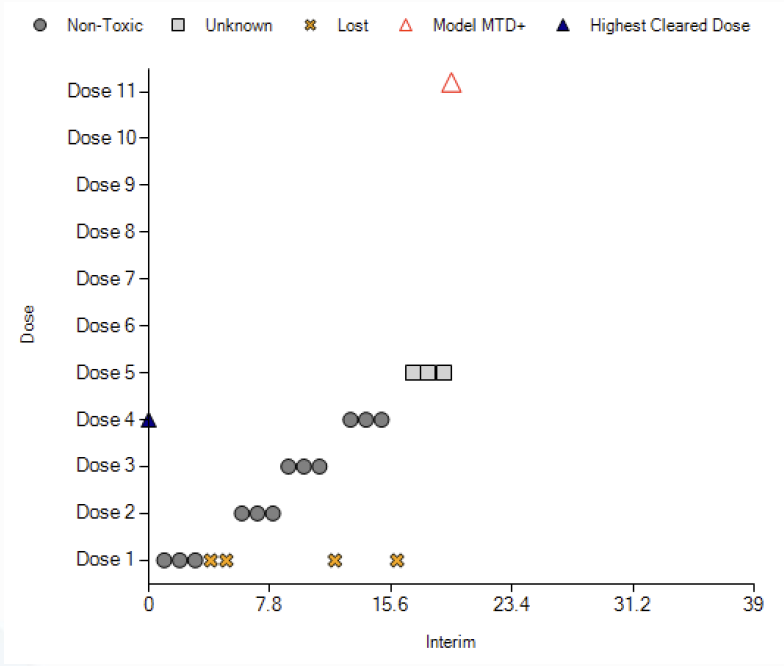
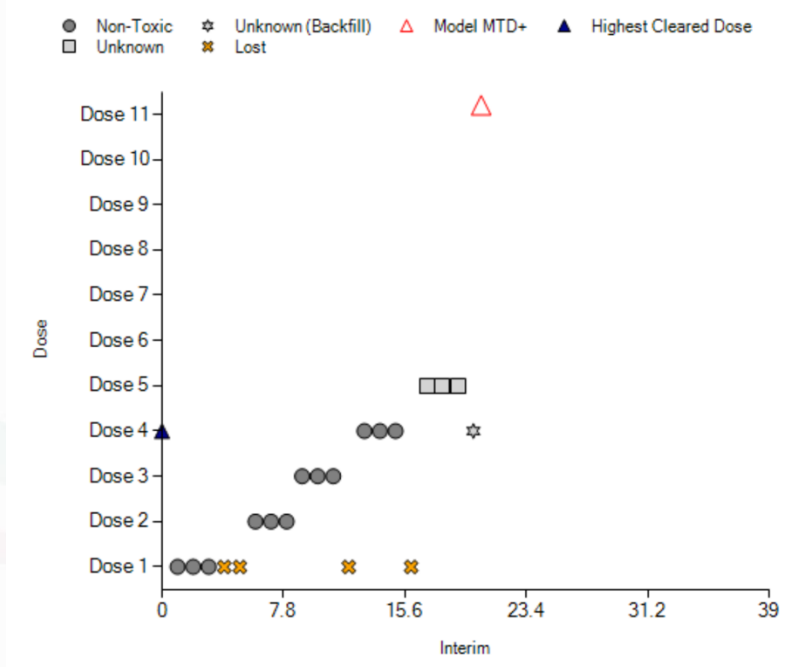
Backfilling

- When the highest dose is unavailable for assignment (according to open enrollment queues), patients are either not assigned, or assigned to lower doses (backfilling)

- Several backfilling rules can be specified:







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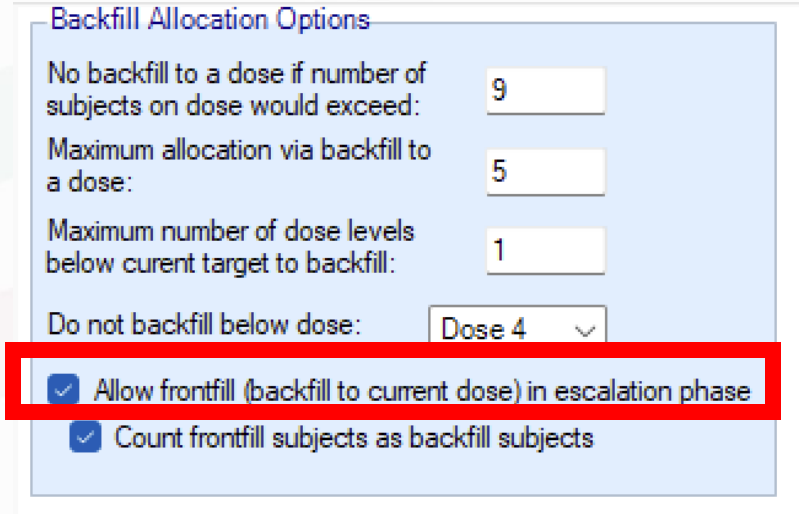
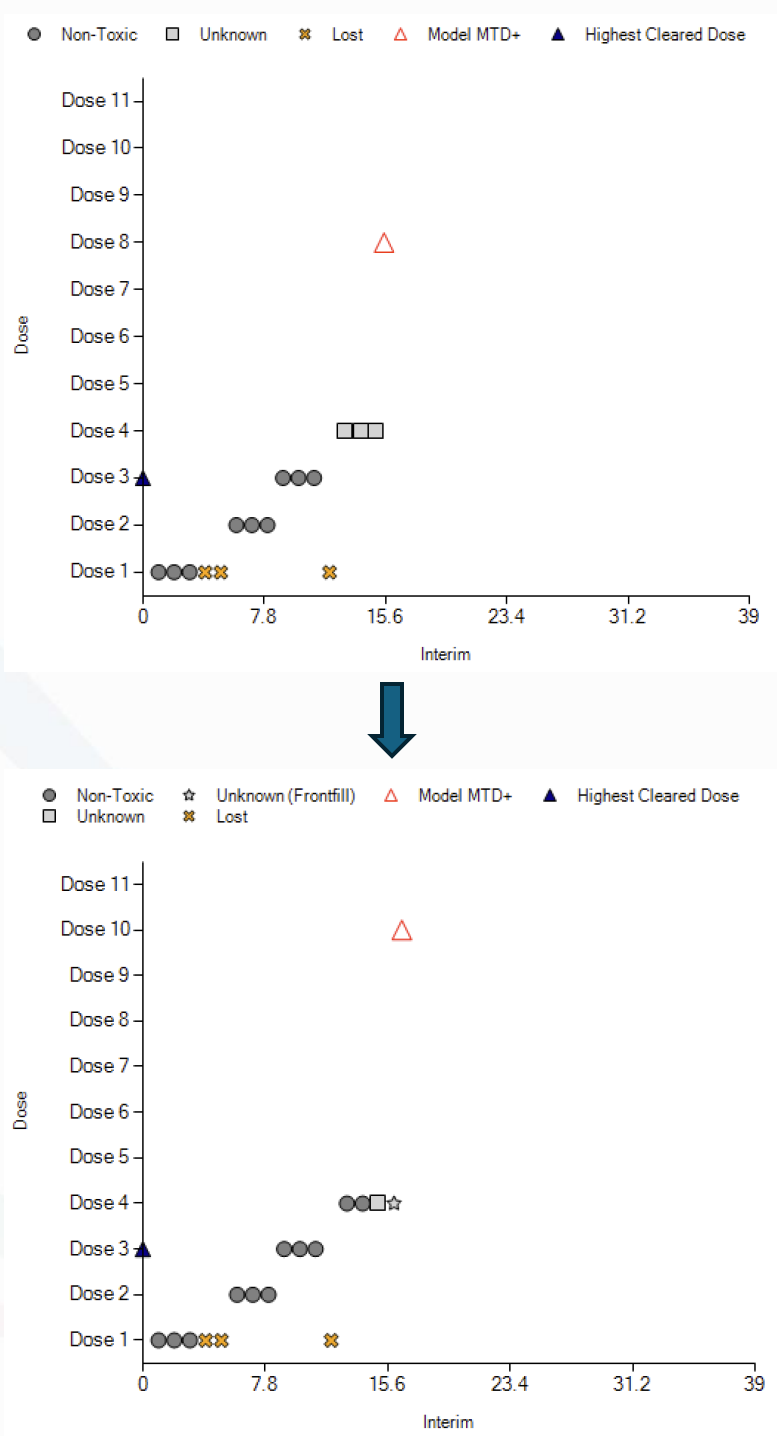
Frontfilling

- Backfilling to front dose (assign more patients to current escalation dose despite open enrollment queue)

- Behaves similarly to backfill:





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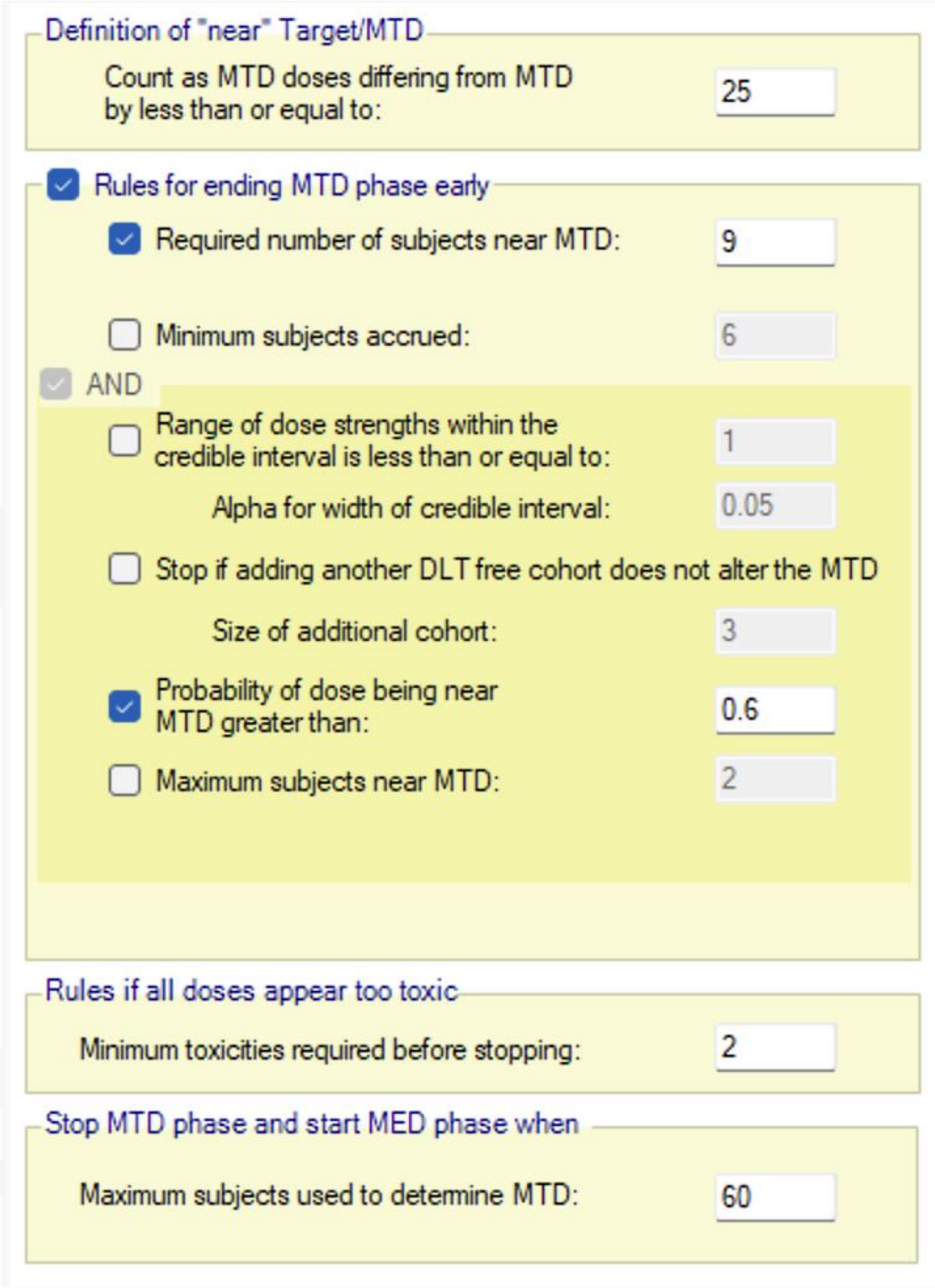
Early stopping rules

- In general, maximum sample size is 60
- If there are 9 DLT completers on the (model estimated) MTD or ±25mg, stop the trial
- Stop only if probability of being near (±25mg) true MTD greater than threshold (here 60%)
- Many other rules possible
- Similar rules for MED search - can switch between MED search and MTD search
- In practice, the DMC/SRC or sponsor may overrule and continue assignment of patients



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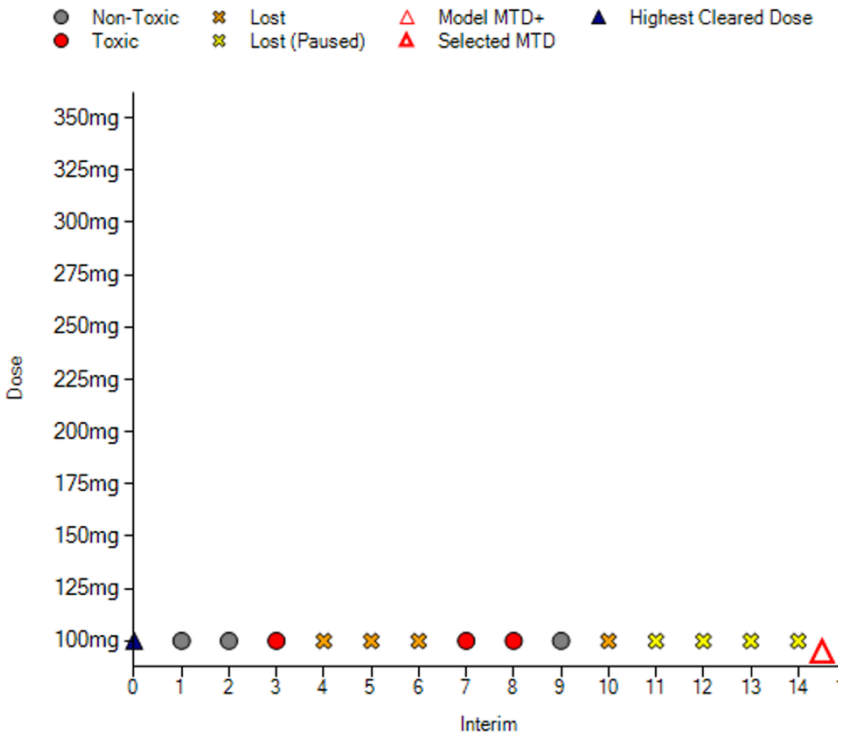
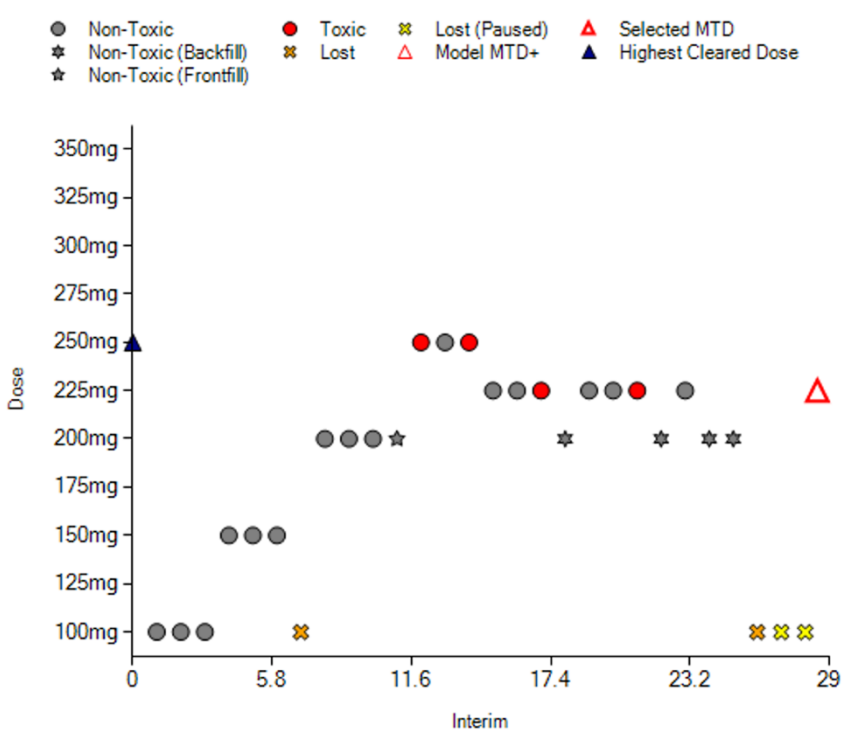
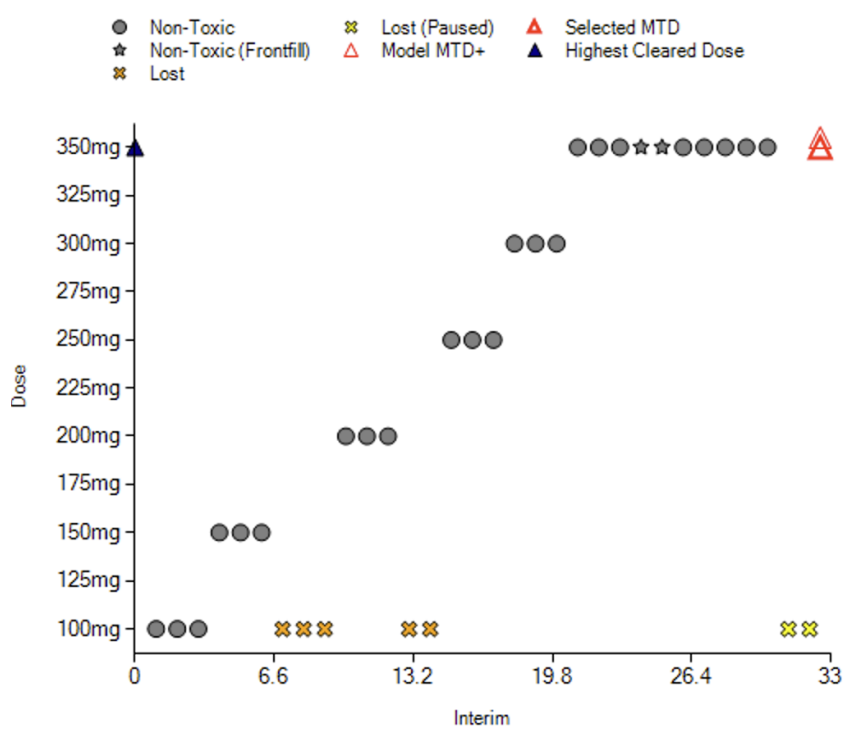
Individual Simulations (P1 part)







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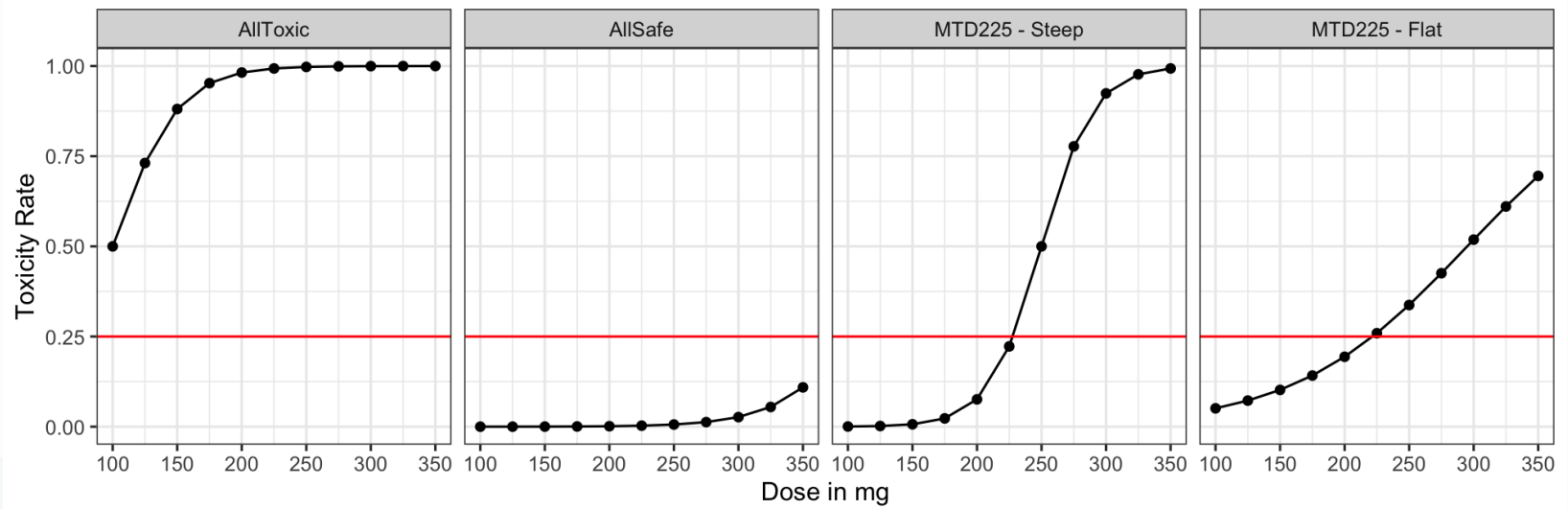
(Some) Things to look out for

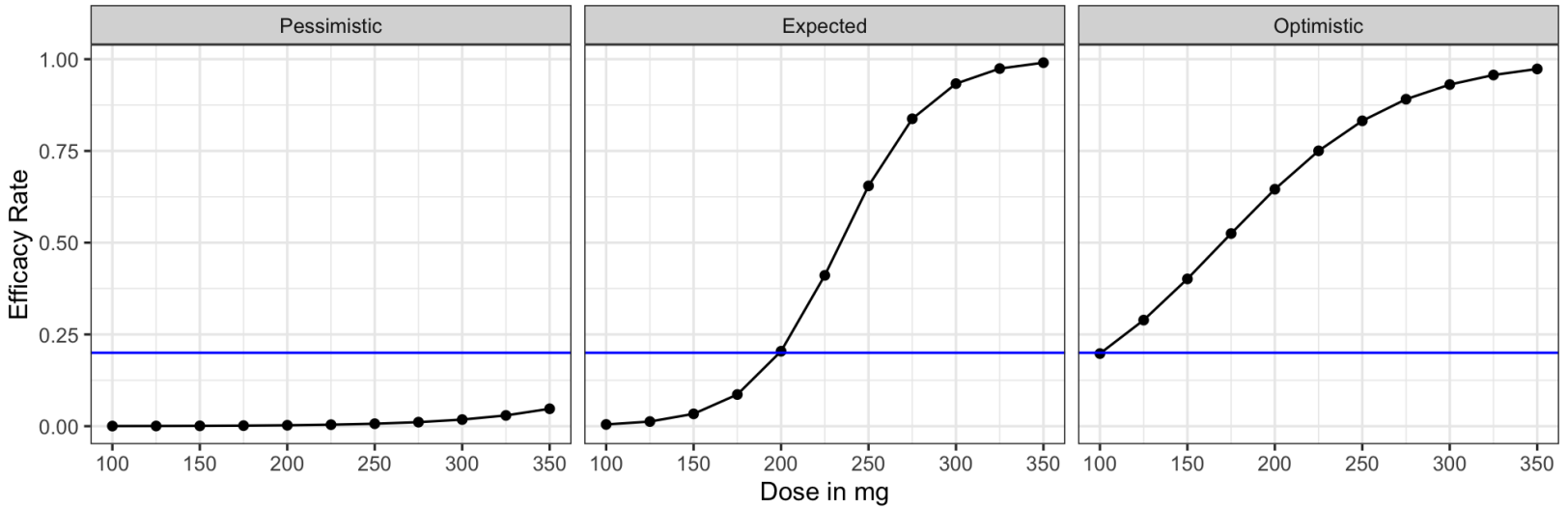
- Is the CRM allocating, estimating and stopping “sensibly”:
  - Suggesting escalation after 3/3 DLTs? Suggesting not to escalate after 0/6 DLTs?
    Might have to tweak prior or include pseudo subjects or look at EWOC rules.
  - Assigning patients 31-60 to the same dose with no change in estimated MTD?
    Might have to tweak stopping rules.
  - Fast recruitment and either many lost subjects or too many backfilled subjects?
    Might have to tweak backfill rules.
  - Assigning too many patients to previously untested doses?
    Might have to tweak open enrollment queue lengths.
  - Jumping back and forth between 225mg and 250mg for too long?
    Might have to tweak stopping rules and consider ±25mg as “near”
  - …

Selected MTD – 3+3 vs. CRM P1



Sample Size / Percentage of correct pick	**3+3**	**CRM**	**Correct Pick**
All Toxic	5 / 80%	5 / 91%	No Dose
All Safe	34 / 87%	29 / 100%	Highest Dose
MTD225 - Steep	23 / 93% / 8% (250mg)	24 / 99% / 5% (250mg)	225mg +/- 25mg
MTD225 - Flat	20 / 47%	33 / 73%	225mg +/- 25mg

Selected MED – CRM P1/2a



MED: Sample Size / Percentage of correct pick	**Pessimistic**	**Expected**	**Optimistic**
All Toxic	6 / 33%	6 / 2%	6 / 58%
All Safe	45 / 99%	63 / 100%	60 / 98%
MTD225 - Steep	27 / 99%	63 / 95%	54 / 100%
MTD225 - Flat	38 / 99%	62 / 87%	69 / 97%
Truth	Pick None	Pick 175-225 mg	Pick 100-125mg

Selected “optimal dose”

- Optimal dose here defined as MED, if MED <= MTD, and None, otherwise

Sample Size / Percentage of correct pick / True Optimal Dose	**Pessimistic**	**Expected**	**Optimistic**
All Safe	45 / 99% / None	63 / 100% / 175-225mg	60 / 98% / 100-125mg
All Toxic	6 / 97% / None	6 / 97% / None	6 / 98% / None
Flat DT Curve	38 / 99% / None	62 / 93% / 175-225mg	69 / 98% / 100-125mg
Steep DT Curve	27 / 99% / None	63 / 100% / 175-225mg	54 / 100% / 100-125mg

What else could we explore?

- Is *"correct" dose +-25mg* too lenient?
- Tweak dose standardizations and prior to further improve OCs
- Consider small cohort run-in
- Consider expansion cohorts
- Investigate more scenarios of varying dose-toxicity relationships
- Investigate effect of recruitment rate and possibly tweak backfill
- Compare with other rule-based DE schemes such as BOIN, mTPI(2) and i3+3 (will be added to FACTS in 2025)

- Questions? Reach out to me at elias@berryconsultants.com