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Introduction to Designing Adaptive Trials using FACTS : Dose Escalation

Tom Parke

- Introduction to the problem
- An example designing a trial: FACTS, i3+3 and BOIN
- FDA project Optimus – the need to target efficacy
- What can we do currently in FACTS to target efficacy in dose escalation?
- What in the future?

INTRODUCING THE PROBLEM

Conventionally

- Dose escalation is done in small cohorts (typically 3 participants at a time)
- The cohort's results are collected
- A decision is made as to what dose the next cohort is to be given. In some settings the decision is limited to:
  a) escalate to the next dose,
  b) stay at the same dose, or
  c) de-escalate to the previous dose.

  Other designs could allow bigger jumps up or down

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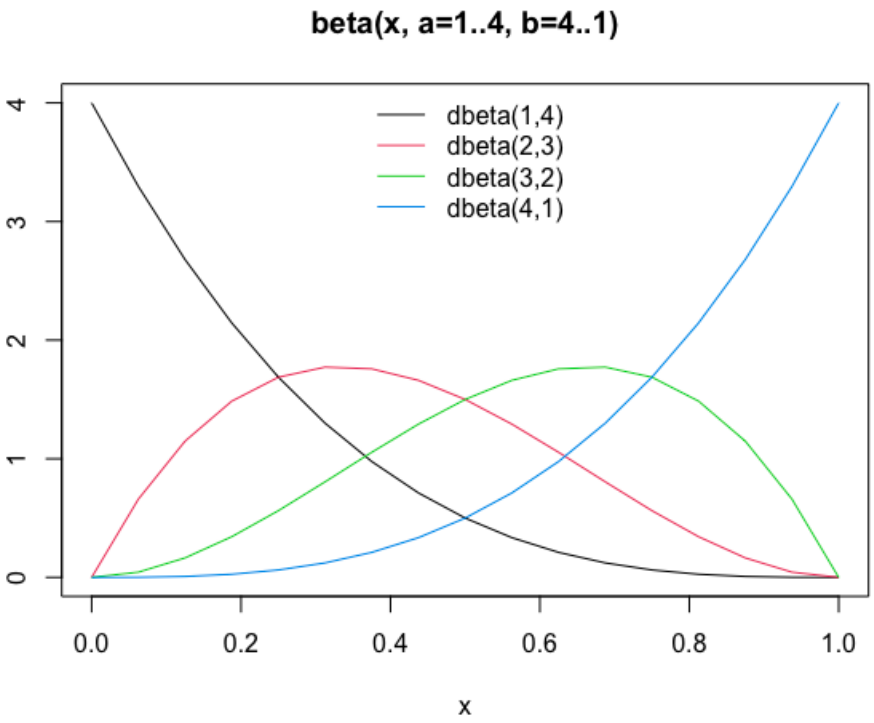
Data from cohort of 3

- 4 Beta distributions corresponding to seeing 0, 1, 2, 3 toxicities from a cohort of 3



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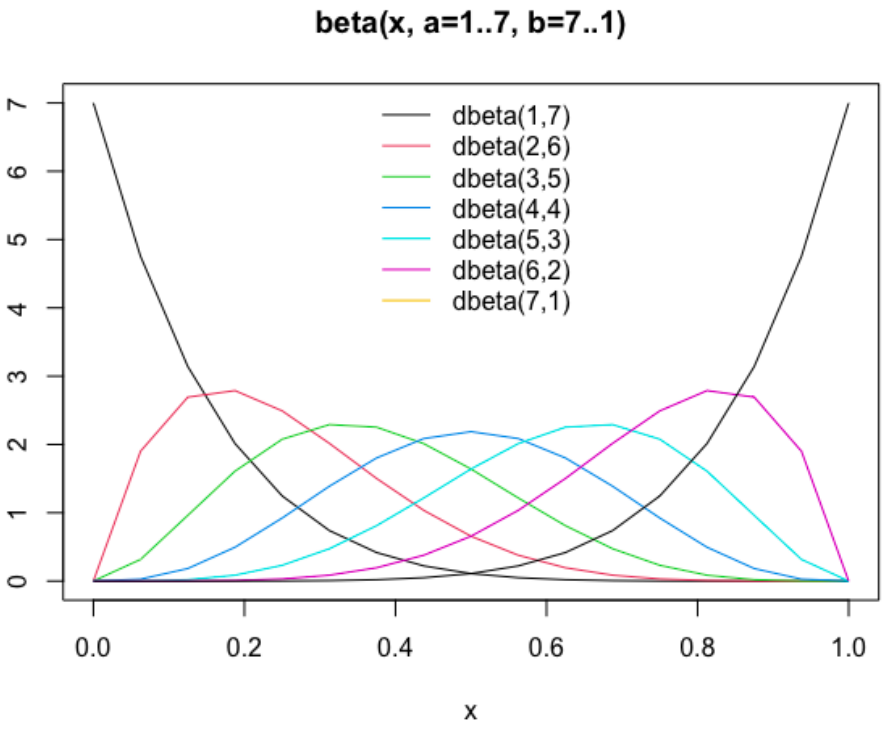
Data from 6 subjects

- 7 Beta distributions corresponding to seeing 0, 1, 2, 3, 4, 5, 6 toxicities from 2 cohorts of 3



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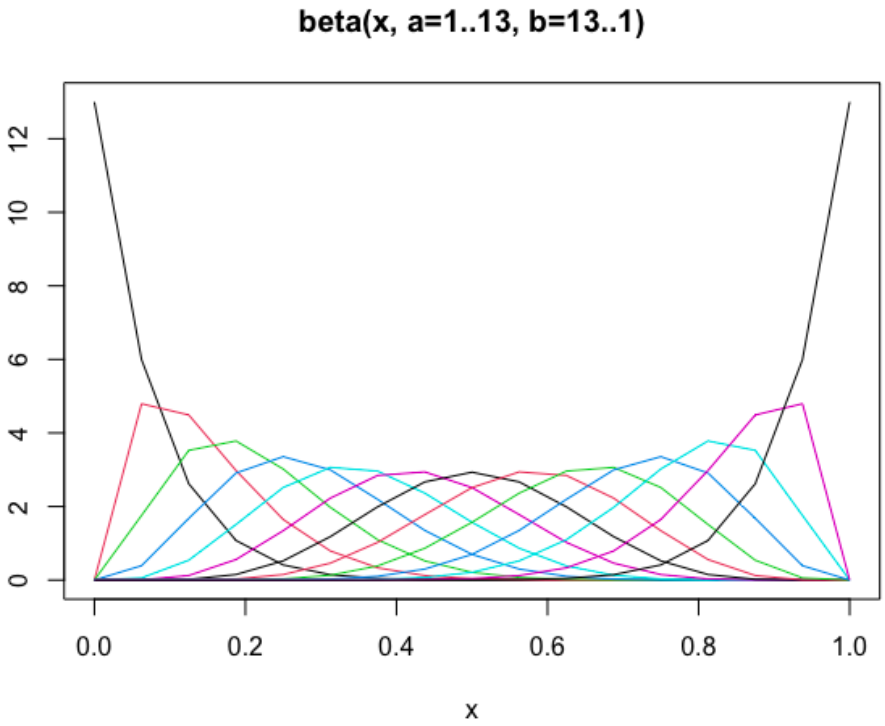
Data from 12 subjects

- 13 Beta distributions corresponding to seeing 0, 1, … 13 toxicities from 4 cohorts of 3



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Probability of seeing t toxicities | true toxicity rate

:	Number of Toxicities			
True tox	0	1	2	3
0.01	0.97	0.03	0.00	0.00
0.05	0.86	0.14	0.01	0.00
0.1	0.73	0.24	0.03	0.00
0.15	0.61	0.33	0.06	0.00
0.2	0.51	0.38	0.10	0.01
0.25	0.42	0.42	0.14	0.02
0.3	0.34	0.44	0.19	0.03
0.35	0.27	0.44	0.24	0.04
0.4	0.22	0.43	0.29	0.06
0.5	0.13	0.38	0.38	0.13
0.6	0.06	0.29	0.43	0.22
0.7	0.03	0.19	0.44	0.34
0.8	0.01	0.10	0.38	0.51

At a true tox rate of 0.1, there is still > 25% chance of 1 or more toxicities

At a true tox rate of 0.3 there is > 20% chance of 2+ toxicities

At a true tox rate of 0.6 there is still 35% chance of 1 or no toxicities.

Design

- The first questions for the design are:
  - What's the target toxicity rate (for what type of toxicities)
    - What's the target band for the toxicity
    - What's an unacceptable probability that a dose may have a toxicity rate above the target band?
  - How many doses are are available to test?
  - How long does is it expected to take to recruit a cohort and how long are the patients observed after treatment for toxicity?
    - If the observation time is very long we might want to use larger cohorts

Enough Doses?

- Typically teams initially propose a very small number of doses, perhaps as few as 4.
- To challenge this we should ask:
  - If even at the top dose you saw no toxicities, what would you do? Is there a higher dose that could be tested?
  - If we saw 2 toxicities in the first 3 subjects on the first dose is your prior belief that this dose has v low toxicity sufficient that you would allow re-testing at this dose, or would you like to include an additional dose below the starting dose?

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How widely spaced are the doses?

- Say we are targeting toxicity rate of 0.25, acknowledging the uncertainty in the estimate we define the target band to be the range (0.16, 0.33).
- We'd like doses spaced so that if there is a dose with a rate < 0.16, the next dose won't have a toxicity > 0.33.
- Say for convenience we say that our doses have effective dose strengths $\widehat{x_i}$ of 0, 1, 2, 3, …
- If using the BLRM we'd like to be able to say that if there is a dose *i* such that $p_i < 0.16$, the maximum change in toxicity to p_{i+1} is such that $p_{i+1} < 0.33$
- So the slope in the BLRM $\beta < \ln(\frac{0.33}{1-0.33}) - \ln(\frac{0.16}{1-0.16})$ ~= 0.95
- So we're asking that the maximum expected change in log odds from dose to dose is about 1 (β re-scaled if the $\widehat{x_i}$ values are not 0,1,2, …)

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This implies (with max slope):

Two scenarios with slope 1 [chance in log-odds between doses]. The maximum slope we would like to be credible.

Scenario	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7
#1 p_i	0.016	0.043	0.109	0.250	0.475	0.711	0.879
#1 Logit(p_i)	-4.099	-3.099	-2.099	-1.099	-0.099	0.901	1.901
#2 p_i	0.025	0.065	0.160	0.330	0.572	0.748	0.908
#2 Logit(p_i)	-3.658	-2.658	-1.658	-0.708	0.292	1.292	2.292

Starting dose

'safe' fallback dose

Target doses

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This implies (with min slope):

Scenarios with slope 0.66 and 0.33 [chance in log-odds between doses].

Scenario	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	Dose 8
#3 p_i	0.023	0.044	0.082	0.147	0.250	0.392	0.555	0.707
#3 Logit(p_i)	-3.739	-3.079	-2.419	-1.759	-1.099	-0.439	0.221	0.881
#4 p_i	0.032	0.044	0.060	0.082	0.110	0.147	0.193	0.25
#4 Logit(p_i)	-3.409	-3.079	-2.749	-2.419	-2.089	-1.759	-1.429	-1.099

Starting dose

'safe' fallback dose

Target doses

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Other scenarios to consider

- What if starting dose mis-identified (response shifted left or right) (#1 and #2 are already examples of same slope shifted start)
- What if slope is not constant in log-odds? Perhaps add scenarios with increasing and decreasing slope.
- This could easily yield at least 3x3x3 scenarios, which is probably too many for most stages of simulation (perhaps use in a sensitivity analysis at some point?)
- Perhaps use 7 scenarios?
  - (1) Median starting toxicity, median slope, constant slope, (2, 3) +/- starting tox, (4, 5) +/- slope, (6, 7) increasing/decreasing slope.

Scenario selection

- Key part of the ‘art’ of adaptive design
- Don’t ignore any uncertainty
- But don’t get bogged down with too many scenarios
- The more dimensions of uncertainty you have, the more combinations of values will have multiple values at extremes on different dimensions
- Ideally we eliminate scenarios where the simulation results are similar and can concentrate on a smaller set of key ‘exemplar’ scenarios.

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Escalation rules, stopping rules and sample size

- Sample size:
  - As many cohorts as doses (in order to be able to escalate to the top dose)
  - Plus as many cohorts as you want on the final dose
  - Plus two more cohorts in case the trial reaches the top dose and has to de-escalate, and/or encounters toxicity on the way up and has to allocate a second cohort before continuing
- Allocation – typical is to require one cohort per dose, possible modifications are
  - If the trial include intermediate doses, possible escalation is two dose strengths
  - This might be modified to one dose strength at higher doses, or after the first toxicity observed
  - Possibly the trial includes a “run in” using small cohorts (1 or 2) until the first toxicity is seen (ethically this should be a moderate toxicity not DLT)

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Escalation rules, stopping rules and sample size

- Stopping rule – typically the number of participants tested at the current estimate of MTD, 9 should be regarded as the minimum
- Some nice stopping rule options with BLRM (N-CRM):
  - Requiring the posterior probability the current dose has a toxicity in the target band > T (where T might be .5, 0.6, …)
  - Stopping if another cohort with no toxicities would not cause escalation or de-escalation.
- Sample size:
  - Simulate the trial with a large potential maximum and review the individual simulations to see the largest sample size actually required.

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EXAMPLE AND COMPARISON OF I3+3, BOIN AND BLRM (N-CRM IN FACTS)

Overview

- Compare i3+3, BOIN, mTPI and N-CRM
- Pre-define simulation study .. No cheating ;-)
- Expectations:
  1. That i3+3, BOIN & mTPI will be similar
  2. That in trials with small numbers of doses that N-CRM will be similar too
  3. That in trials with larger numbers of doses N-CRM will be superior – when the simulated MTD is at a high dose.

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I3+3, mTPI and BOIN

- All similar in that they just look at the data on the current dose and determine from that whether for the next cohort we should escalate to the next dose, stay at the same dose or de-escalate to the previous dose.
- I3+3 simply looks at the tox/number tested ratios x/d and (x-1)/d.
  - If x/d < target tox band then escalate
  - If x/d in target tox band then stay
  - If x/d above target tox band and (x-1)/d below then stay otherwise de-escalate
- BOIN is similar with two differences, 1) rather than being used directly, the upper and lower bounds are converted to boundaries to be tested against that minimise the expected decision error and 2) the final MTD is selected after applying isotonic regression to all the data.

I3+3, mTPI and BOIN

- mTPI is slightly different, once again it divides the probability of toxicity into three bands – below target, target and above target. It then uses the unit probability mass (the probability of the interval / interval length).
- After each cohort, calculate the upm at the current dose for being in the below target, target or above target bands and escalate, stay or de-escalate accordingly.
- There is a modified mTPI-2 that for typical values creates better decision rules. This has not yet been implemented in FACTS and has not been used in this example.

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Compared to BLRM

- Compared to Bayesian Logistic Regression such as N-CRM all these 3 methods are easier to use, they generate pre-trial decision tables.
- BLRM (N-CRM) analyses the totality of the data after each cohort (not just the last dose tested) and returns an estimate for each dose that it is below, in or above the target toxicity band.

Num Toxic	3	6	9
0	E / E / E	E /E / E	E / E / E
1	S / D / S	S / E / S	E / E / E
2	X / X / X	S / D / D	S / S / S
3	X / X / X	X /X / X	S / D /D
4		X / X / X	D / D / D
5		X / X / X	X / X / X
6		X / X / X	X / X / X
7			X / X / X
8			X / X / X
9			X / X / X

- 7 doses: 25mg, 50mg, 100mg, 200mg, 400mg, 600mg, 800mg
- 11 doses: 25mg, 37.5mg, 50mg, 75mg, 100mg, 150mg, 200mg, 300mg, 400mg, 600mg, 800mg
- Originally planned to do 4 dose example too (50mg, 100mg, 200mg, 400mg)
  - but decided this was would no likely be interesting enough for the amount of work to do and present the results
- Target: target DLT of 0.15-0.3
- 10 scenarios:
  - MTD at 37.5mg, 50mg, … , 800mg – at each dose except 25mg.
  - Mixing steep and shallow gradients, created using FACTS 4 different parametric models (for response generation) – only 1 matches the BLRM model for analysis

Rules

- Note: some designs have additional options, but here we want to compare on a ‘level’ playing field.
- Cohorts of size 3
- Max of 15 cohorts
- Stop when 3 cohorts (9 subjects) on MTD
- Start at second dose, reserve 25mg dose as a ‘fallback’.
- Only increase by at most one dose strength at a time
- N-CRM overdose control:
  - $Pr(tox > 0.3) < 0.5$
  - $Pr(tox > 0.6) < 0.05$

Rules

- mTPI:
  - 11 doses
  - Starting dose 2
  - Cohort size 3
  - Max 15 cohorts
  - Max probability dose exceeds target toxicity: 0.95

- BOIN (www.trialdesign.org):
  - 11 doses
  - Starting dose 2
  - Cohorts size 3
  - Max 15 cohorts
  - Stop trial when 9 subjects on MTD
  - Target toxicity: 0.225 (middle of range 0.15-0.3)
  - Use the default alternatives to minimize decision error
  - No accelerated titration
  - Eliminate dose if $\Pr(p_i > \phi) > 0.95$

Rules

- I3+3 (i3design.shinyapps.io):
  - 11 doses
  - Starting dose 2
  - Cohorts size 3
  - Max 45 subjects (15 cohorts)
  - Target toxicity: 0.225 (middle of range 0.15-0.3)

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Rules

- N-CRM – simple setup, no tuning
  - 11 doses (dose strengths 25, 37.5, 50, 75, 100, 150, 200, 300, 400, 600, 800)
  - Starting dose 2 (37.5)
  - Cohorts size 3
  - Max 15 cohorts
  - Target DLT range 0.15-0.3
  - Overdose control Excess+Unacceptable < 0.5, Unacceptable < 0.05
  - First dose is ref dose, x-hats are ln(dose/ref dose)
  - Prior derived from scenarios: $\theta \sim N(-3.8, 1.4^2)$ $\ln(\beta) \sim N(0.33, 0.54^2)$ $\rho=-0.13$
  - Allocation: Start dose 2, increment at most 1 dose level at a time
  - Stop: when 3 cohorts on MTD, and at least 2 toxicities observed

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Comments

- Boin
  - Could save design, could load scenarios from file
  - Would sometimes time out or go to a page where ‘back’ meant start again
  - Desktop app available I got exceptions no explanation but deduced to be due to Windows security
  - Could view some individual simulations as ‘animations’ on r-shiny version (not desktop), (not sure stopping rule obeyed)
  - Reports patient allocation as % of total

Comments

- i3+3
  - Could NOT save design, could NOT load scenarios from file
  - Would sometimes time out => start again
  - Entry of scenarios unnecessarily fiddly
  - Results only summarised for first 10 doses
  - No stopping rule (used 45 subjects unless all doses too toxic)
  - Could NOT view some individual simulations as ‘animations’ (not sure stopping rule obeyed)
  - Didn’t share parameters with ‘decision table’ tab

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Scenarios

Scenario	Model	Slope	ED50
37.5 f	Logistic	0.050	70
50 f	Emax	N/A	175
75 s	Log-logistic	2.200	125
100 s	Logistic	0.030	150
150 f	Emax	N/A	400
200 f	Log-logistic	1.300	500
300 s	Logistic	0.010	400
400 s	Log-logistic	4.000	550
600 f	Logistic	0.003	950
800 s	Log-Logistic	5.000	1000

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Scenarios

Scenario	25	37.5	50	75	100	150	200	300	400	600	800
37.5 f	0.095	**0.165**	**0.269**	0.562	0.818	0.982	0.999	0.9999	0.9999	0.9999	0.9999
50 f	0.125	**0.176**	**0.222**	**0.3**	0.364	0.461	0.533	0.631	0.696	0.774	0.82
75 s	0.028	0.066	0.118	**0.245**	0.38	0.599	0.738	0.873	0.928	0.969	0.983
100 s	0.023	0.033	0.047	0.095	**0.182**	0.5	0.818	0.989	0.999	0.9999	0.9999
150 f	0.059	0.086	0.111	**0.158**	**0.2**	**0.273**	0.333	0.429	0.5	0.6	0.667
200 f	0.002	0.033	0.048	0.078	0.11	**0.173**	**0.233**	0.34	0.428	0.559	0.648
300 s	0.023	0.026	0.029	0.037	0.047	0.076	0.119	**0.269**	0.5	0.881	0.982
400 s	0.0001	0.0001	0.0001	0.0001	0.001	0.006	0.017	0.081	**0.219**	0.586	0.817
600 f	0.059	0.061	0.063	0.068	0.072	0.083	0.095	0.124	**0.161**	**0.259**	0.389
800 s	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.002	0.01	0.072	**0.247**

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Decision Tables

Decision rules for mTPI / BOIN / i3+3

At 3, 6 and 9 subjects on a dose.

mTPI rules unchanged if target tox bounds changed to BOIN [0.177 – 0.268]

Note: BOIN has no 'stay' decision except if 9 subjects on dose with 2 DLTs

Num Toxic	3	6	9
0	E / E / E	E /E / E	E / E / E
1	S / D / S	S / E / S	E / E / E
2	X / X / X	S / D / D	S / S / S
3	X / X / X	X /X / X	S / D /D
4		X / X / X	D / D / D
5		X / X / X	X / X / X
6		X / X / X	X / X / X
7			X / X / X
8			X / X / X
9			X / X / X

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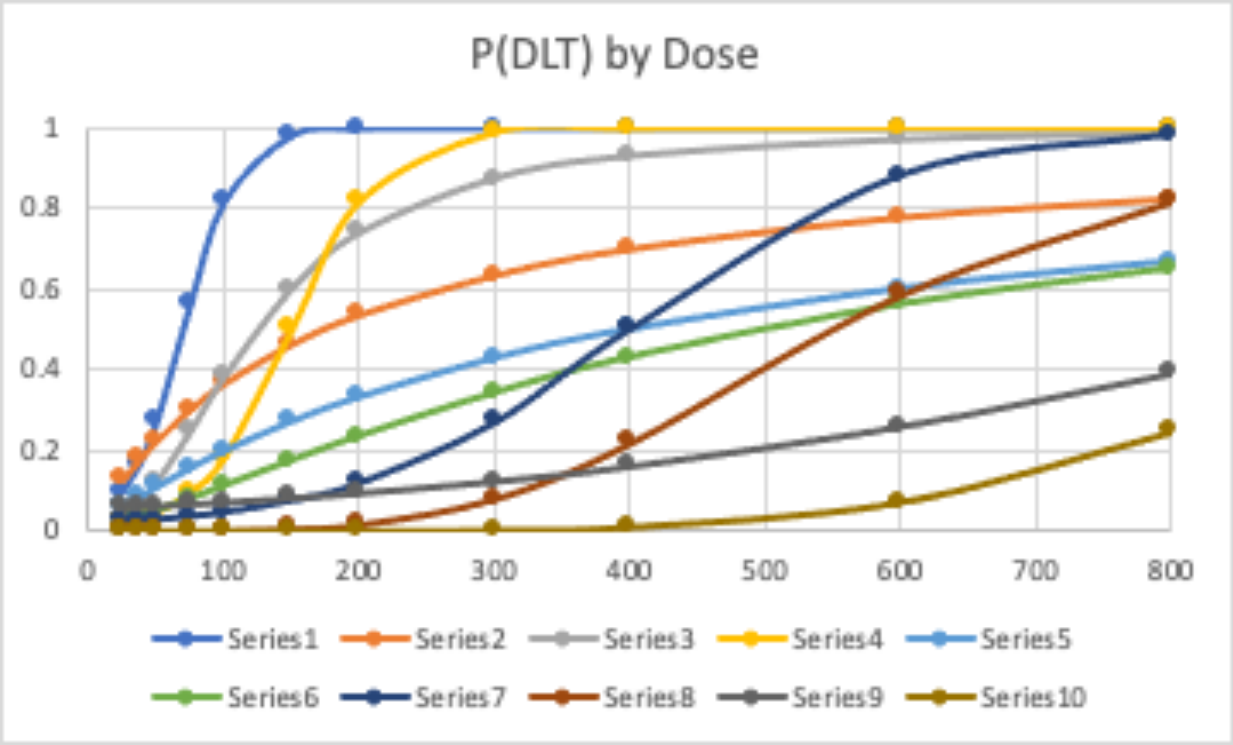
10 Scenarios

Note the mixture of locations of MTD and slopes



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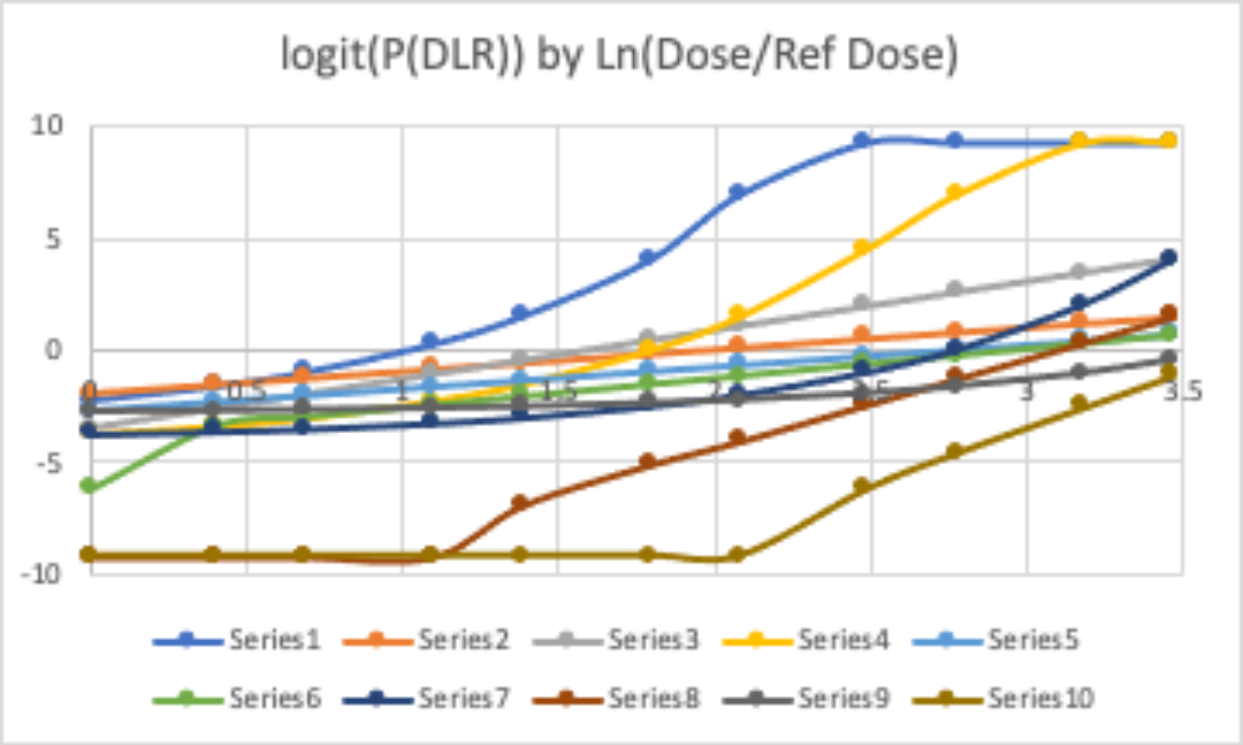
Logit plot of scenarios

Note a number of the scenarios are *not* linear in the logit – may cause N-CRM problems



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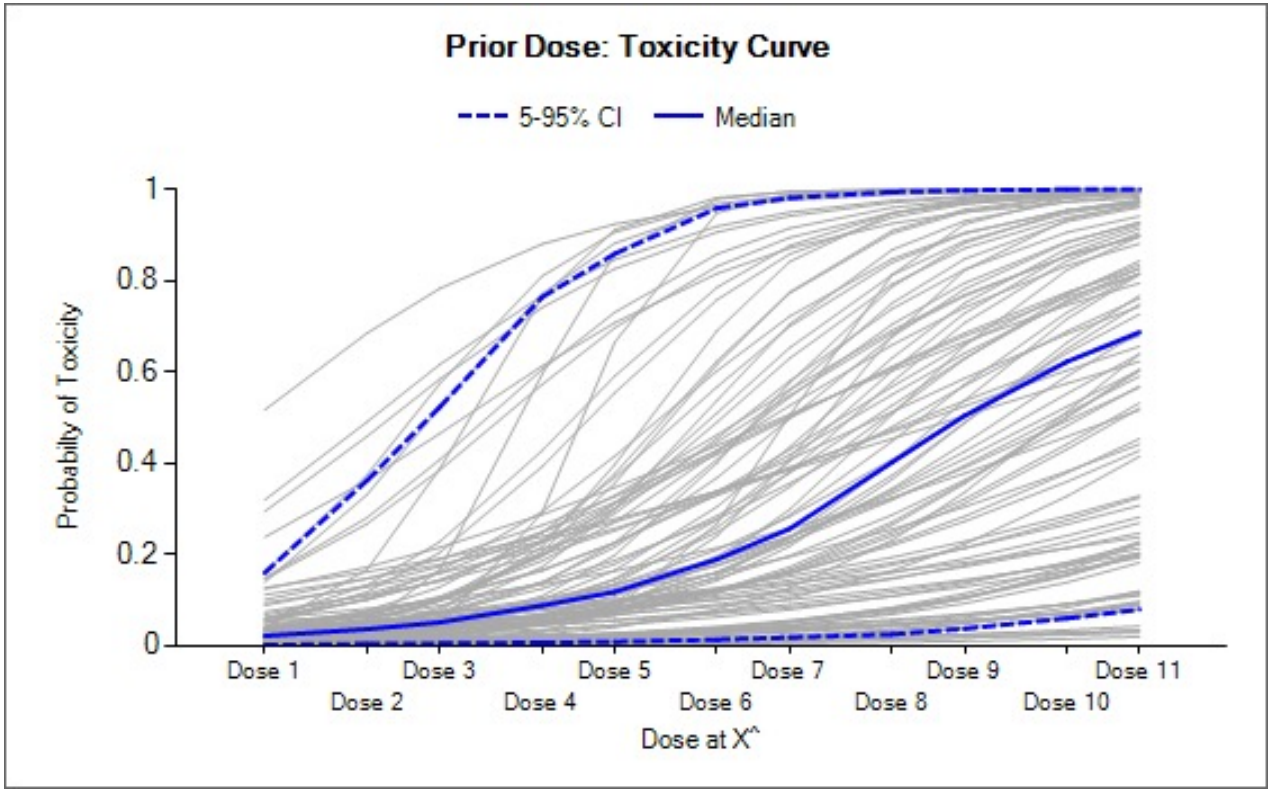
N-CRM Prior



How to assess?

- Want similar sample sizes
- To compare to i3+3 (the code had no early stopping option) a second N-CRM with an additional stopping criteria Pr(tox at MTD in target band) > 0.6 was simulated
- Then compare probability of selecting doses in the target range
  - Want to “punish” selecting non target doses
  - Selecting doses above target should be worse than selecting below
  - Some scenarios have doses with DLT rates close to the target, selecting these should not be as bad as selecting those with DLT rates far from the target.

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Loss function

- Sum over all doses
  - If DTL rate in target range, loss is: 0
  - If DLT rate is > target, loss is: ppn of times selected * 200 * (DLT rate – upper bound of target range)
  - If DLT rate is < target, loss is: ppn of times selected * 100 * (lower bound of target range – DLT rate)

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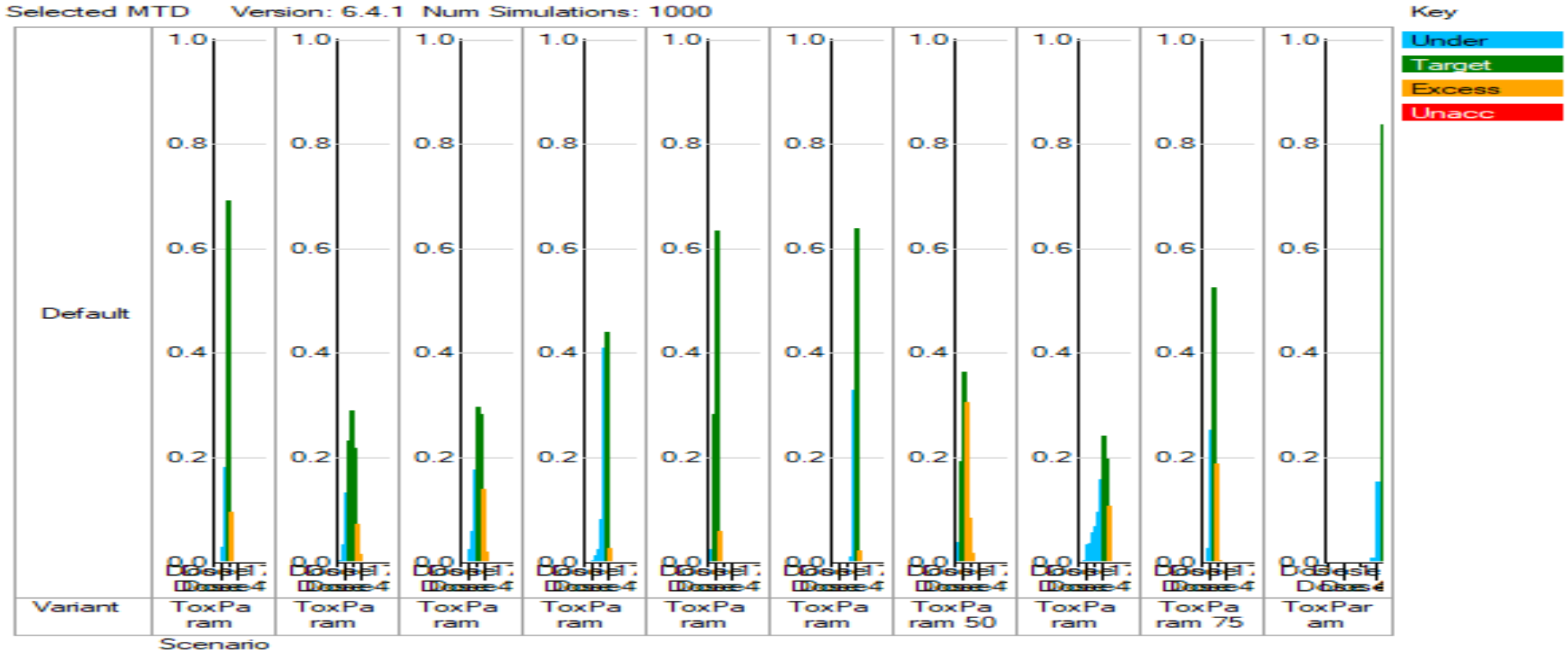
Results N-CRM



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Sample Sizes

	I3+3	N-CRM large	mTPI	BOIN	N-CRM
37.5 f	45	**26.4**	16.1	19.3	**16.0**
50 f	45	**28.1**	**16.2**	21.2	17.7
75 s	45	**30.2**	21.0	23.8	19.9
100 s	45	**31.6**	25.1	26.7	**23.5**
150 f	45	**33.1**	**22.5**	27	23.3
200 f	45	**37.0**	**28.6**	31.9	**28.6**
300 s	45	**38.8**	**32.7**	34.8	**32.7**
400 s	45	**40.0**	**35.9**	36.8	36.4
600 f	45	**42.4**	**31.7**	36	35.3
800 s	45	**44.7**	39.8	39.6	**37.5**

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Raw P(select dose in target range)

	Target Doses	I3+3	N-CRM large	mTPI	BOIN	N-CRM
37.5 f	37.5, 50	0.817	**0.975**	0.759	0.861	**0.916**
50 f	37.5, 50, 75	0.746	**0.883**	0.671	0.75	**0.862**
75 s	75	0.41	**0.644**	0.402	0.454	**0.526**
100 s	100	0.754	**0.813**	0.586	0.685	**0.692**
150 f	75, 100, 150	0.691	**0.831**	0.543	0.623	**0.741**
200 f	150, 200	0.619	**0.684**	0.492	0.539	0.581
300 s	300	0.357	**0.508**	0.420	0.424	**0.44**
400 s	400	0.588	**0.656**	0.671	**0.681**	0.638
600 f	400, 600	0.456	**0.538**	0.316	0.426	**0.439**
800 s	800	0.544	**0.800**	0.723	0.652	**0.838**

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Loss scores

	Target Doses	I3+3	N-CRM large	mTPI	BOIN	N-CRM
37.5 f	37.5, 50	1.13	**0.51**	**3.25**	**1.29**	3.23
50 f	37.5, 50, 75	**1.03**	1.30	1.62	**1.35**	**1.71**
75 s	75	3.24	**3.22**	**5.39**	**4.01**	4.25
100 s	100	**2.22**	3.17	**7.15**	**3.90**	5.14
150 f	75, 10, 150	1.91	**1.23**	**3.16**	2.43	**1.69**
200 f	150, 200	6.00	**2.46**	4.18	3.70	**2.98**
300 s	300	3.29	**3.19**	**5.67**	4.53	**3.39**
400 s	400	**3.28**	4.85	**5.83**	**3.33**	3.61
600 f	400, 600	**3.25**	3.39	**5.37**	**4.08**	4.38
800 s	800	3.72	**1.61**	2.31	2.82	**1.31**

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PROJECT OPTIMUS

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Growing concern about dose identification in oncology

- "Some examples of drugs whose doses or schedules were modified post-marketing include ceritinib, dasatinib, niraparib, ponatinib, cabazitaxel, and gemtuzumab-ozogamicin [19]. The FDA has recognized the drawbacks of the MTD/HTD approach. In 2021, the FDA Oncology Center of Excellence launched Project Optimus." - Apostolos Papchristos et al in Cancers, June 2023 https://doi.org/10.3390/cancers15123233
- "The Drug-Dosing Conundrum in Oncology – When Less Is More" – Mirat Shah et al NEJM, Oct 2021, DOI: 10.1056/NEJMp2109826
- "Project Optimus is an initiative to reform the dose optimization and dose selection paradigm in oncology drug development. Too often, the current paradigm for dose selection—based on cytotoxic chemotherapeutics—leads to doses and schedules of molecularly targeted therapies that are inadequately characterized before initiating registration trials." https://www.fda.gov/about-fda/oncology-center-excellence/project-optimus

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Impact on Phase 1 Dose Escalation in oncology

- Don’t just target MTD look at efficacy too.
- Look for MED (Minimal Efficacious Dose) or OBD (Optimal Biological Dose) – maximise benefit/risk or provide desired therapeutic effect whilst minimizing toxicity.
- Specific challenges:
  - Efficacy usually takes longer to observe than toxicity
  - Use low-grade toxicity
  - Identifying reliable early effect biomarkers is a big challenge
  - Don’t assume efficacy monotonicity
  - Efficacy may not be dichotomous
  - Identify not “a” dose but a range of doses for later phases

N-CRM can model Efficacy and Toxicity

- Current limitations, assumes:
  - Same time to efficacy and toxicity endpoint
  - Dichotomous efficacy endpoint
  - Monotonicity in efficacy
- However within those limitations FACTS already has an interesting capability

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N-CRM Toxicity and Efficacy

- Toxicity has all the features of “only toxicity” including
- Efficacy – target an MED
- Separate model for efficacy
- Allocation in 2 stages
  - Find MTD
  - Then find MED (while MED is < MTD)
  - All the time still estimating MTD and applying overdose control.
  - Modern requirement is no longer to find MTD, this can be simply achieved by setting max MTD phase size to 1 cohort.
- If using “open enrolment” can also use “backfill” to allocate subjects arriving before current cohort is complete to doses below current dose

Example

- 7 doses, effectively equally spaced
- 12 cohorts of 3, could explore larger cohorts to get larger sample size in similar time
- Target toxicity band [0.2-0.35]
- Overdose control: prob(toxicity > 0.35) < 0.5
- Efficacy target: nearest dose to efficacy rate of 0.5

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Example scenarios

	12.5mg	25mg	50mg	100mg	150mg	200mg	250mg
s2	0.076	0.2231	0.5	0.7769	0.8784	0.9238	0.9477
s4	0.00095	0.00658	0.0441	0.243	0.5	0.691	0.81
s6	0.00001	0.0001	0.0016	0.025	0.115	0.291	0.5
Param	0.00091	0.00247	0.00669	0.01799	0.04743	0.11920	0.26894

	12.5mg	25mg	50mg	100mg	150mg	200mg	250mg
Eff-d3	0.14000	0.35000	0.48462	0.56000	0.60345	0.63000	0.64717
Eff-d4	0.00854	0.11546	0.35000	0.53175	0.61969	0.65882	0.67716
Eff-d6	0.03166	0.12512	0.2428	0.35000	0.43422	0.49651	0.54181

Design

- X-hats: use reference dose of 0, dose strength – ref dose
- Toxicity response
  - Derive prior from scenarios then round and increase SD of ln(Beta).
  - Alpha ~ N(-5, 1.5), Ln(Beta) ~ N(-0.15, 0.5), Rho = 0.0905
- Efficacy response
  - re-scale to lie between 0 and 0.8,
  - Derive prior from scenarios then round, increase SD of Ln(Beta), and decrease Rho.
  - Alpha ~ N(-3, 1.2), Ln(Beta) ~ N(-0.5, 0.6), Rho = 0.8

Allocation

- Test 1 cohort to allow escalation
- Increment at most 1 dose
- Start at the first dose

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Stopping Rules

- Rules for MTD
  - Require 3 cohorts on MTD
  - Accrue at least 3 cohorts
  - Prob of MED being in target band > 0.4
  - Min 2 toxicities before stopping
  - Max 1 cohort used to determine MTD
- Rules for MED
  - Max 4 cohorts on MED
  - Prob of MED > 0.4
  - If MED > MTD continue until 6 cohorts on MTD

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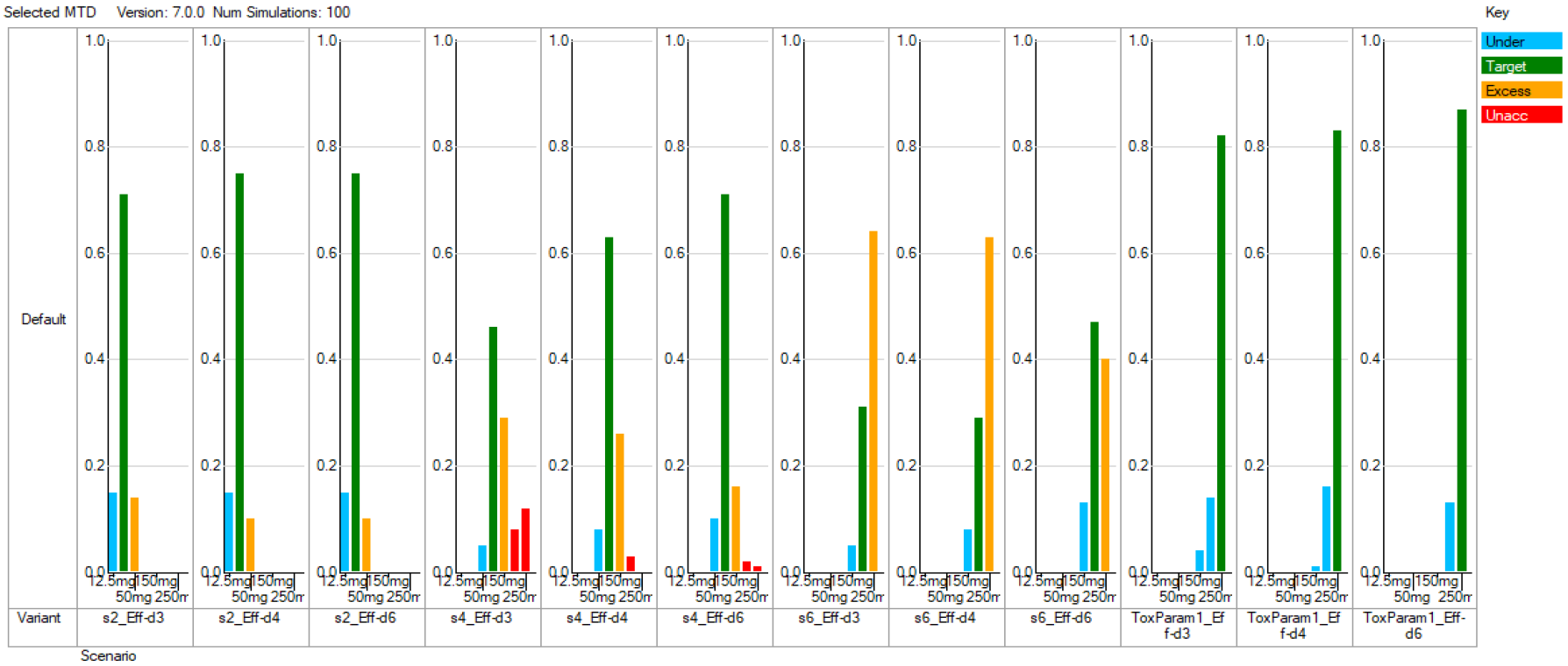
MTD



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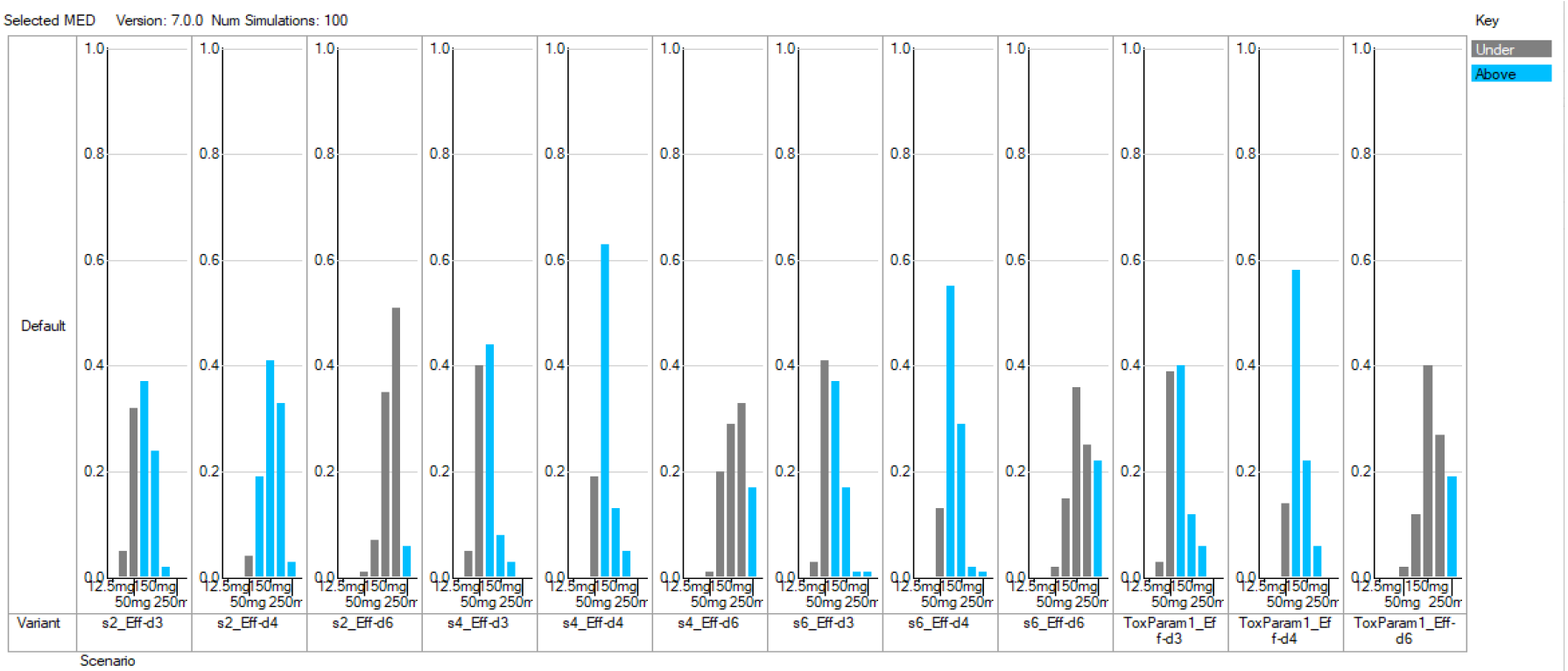
MED



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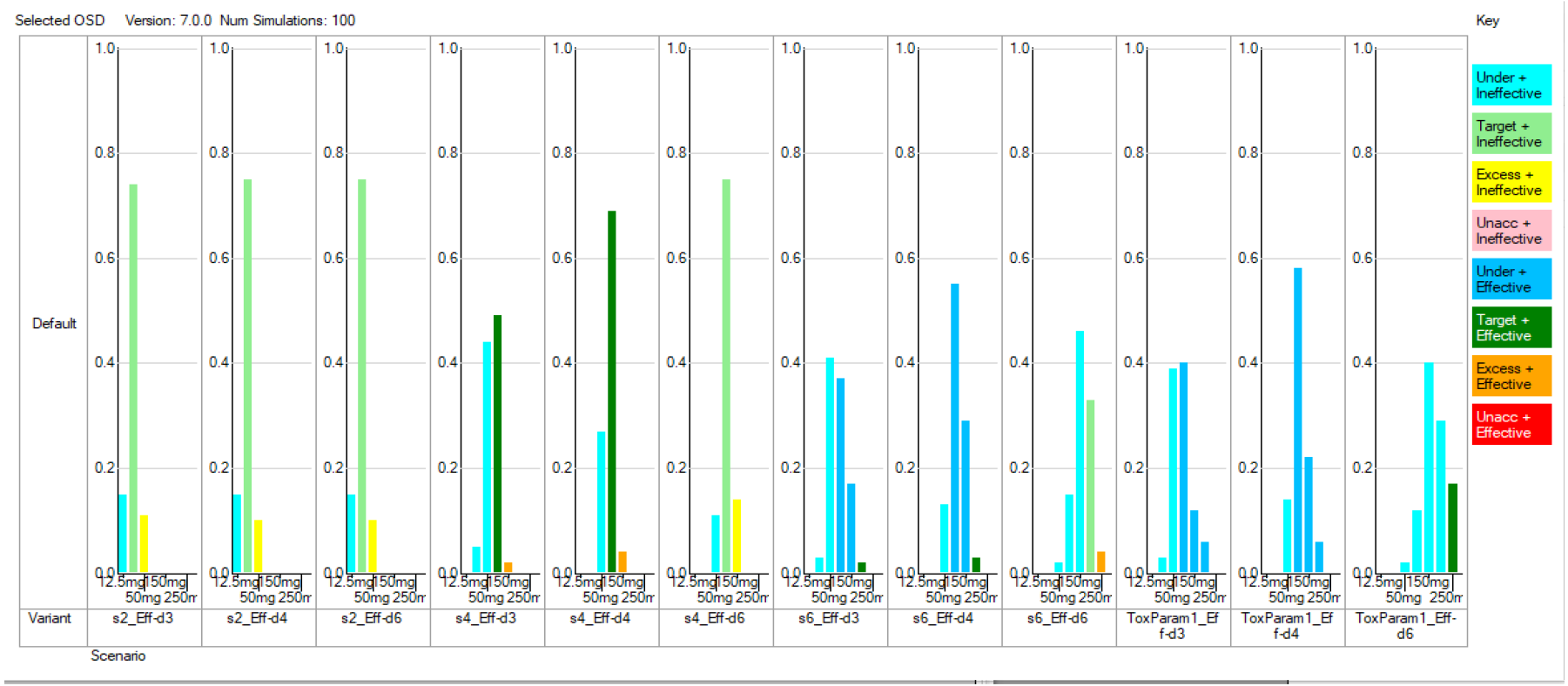
OSD = if (MED<MTD) MED else MTD



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Sample size

- Mean subj ranges from 26.7 to 31.7 depending on scenario.
- Ppn tox ranges from 0.02 (MTD dose 7) to 0.27 (MTD dose 2)
- If MED < MTD Ppn efficacy 0.4-0.5.

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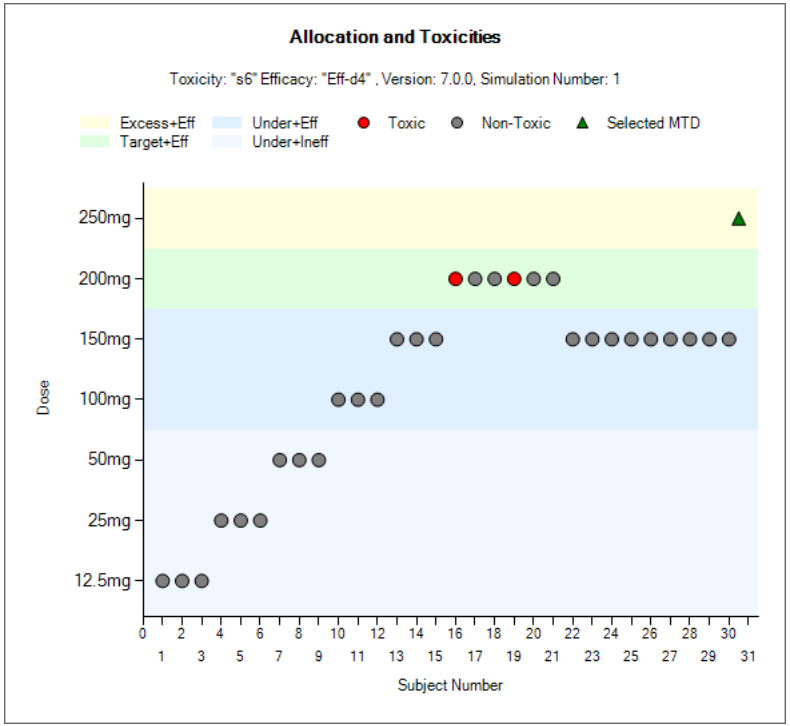
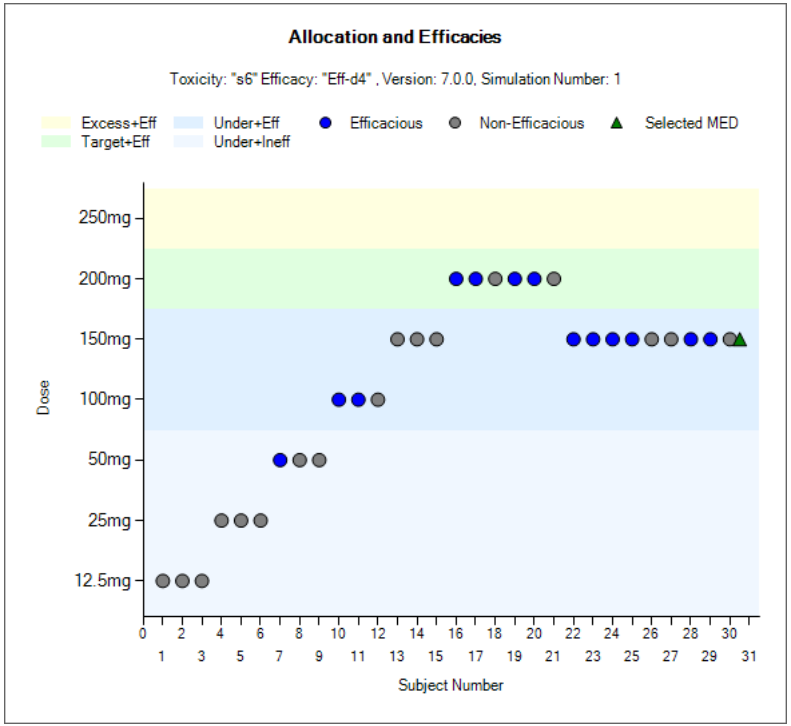
Example histories





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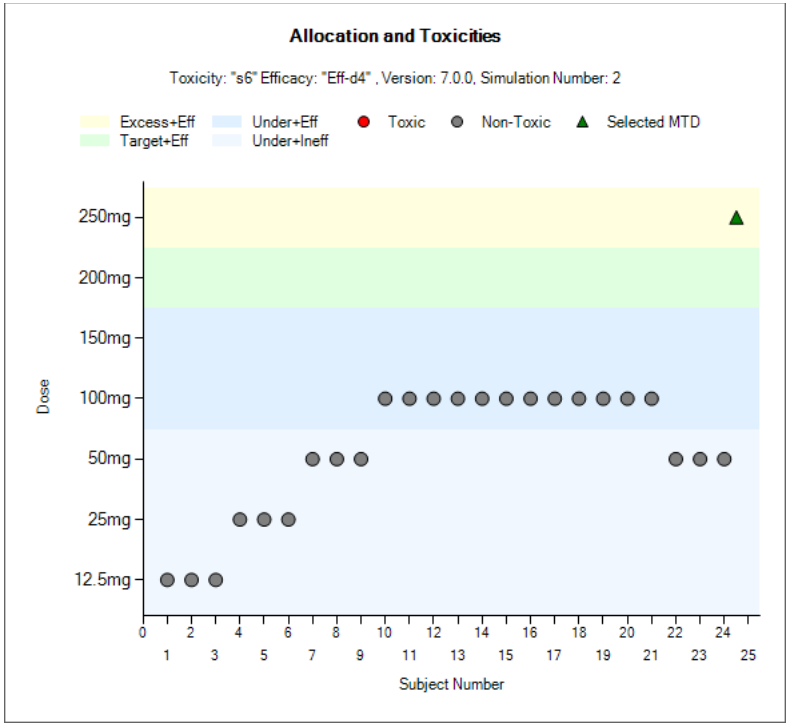
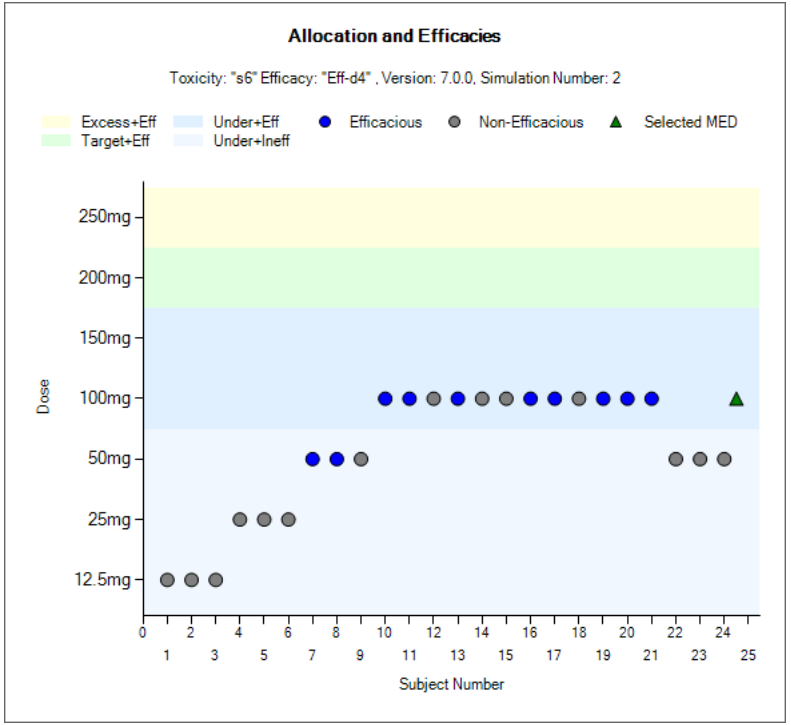
Example history #2





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FACTS Dose Escalation 2024

- Enhance mTPI to mTPI-2
- Add BOIN
- Add i3+3
- Add backfill to N-CRM cohort enrolment
- Add different end times for efficacy and toxicity
- Allow tox MTD to target lower grade tox

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