Modified Toxicity Probability Intervals (mTPI), Bayesian Logistic Regression Modeling (BLRM), Continual Reassessment Method (CRM) via EAST6.3.1 vs. T-statistic (Tstat) Design via COMPASS for finding MTD

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Motivation

- mTPI is appealing and popular for adaptive dose-finding of Maximum Toxicity Dose (MTD)
  - Easy to implement (fixed pre-stated algorithm; DR-model-independent)
  - Efficient as competitor DR-model-based designs (CRM, BLRM)
  - Better than traditional 3+3 design
- T-statistic design is appealing and popular with some for adaptive dose-finding of Target Dose
  - Easy to implement (requires simple calculation after each cohort; based on isotonic DR-model)
  - Efficient as competitor designs (Bayesian 4PL, Emax, NDLM)
  - Better than fixed-randomized designs

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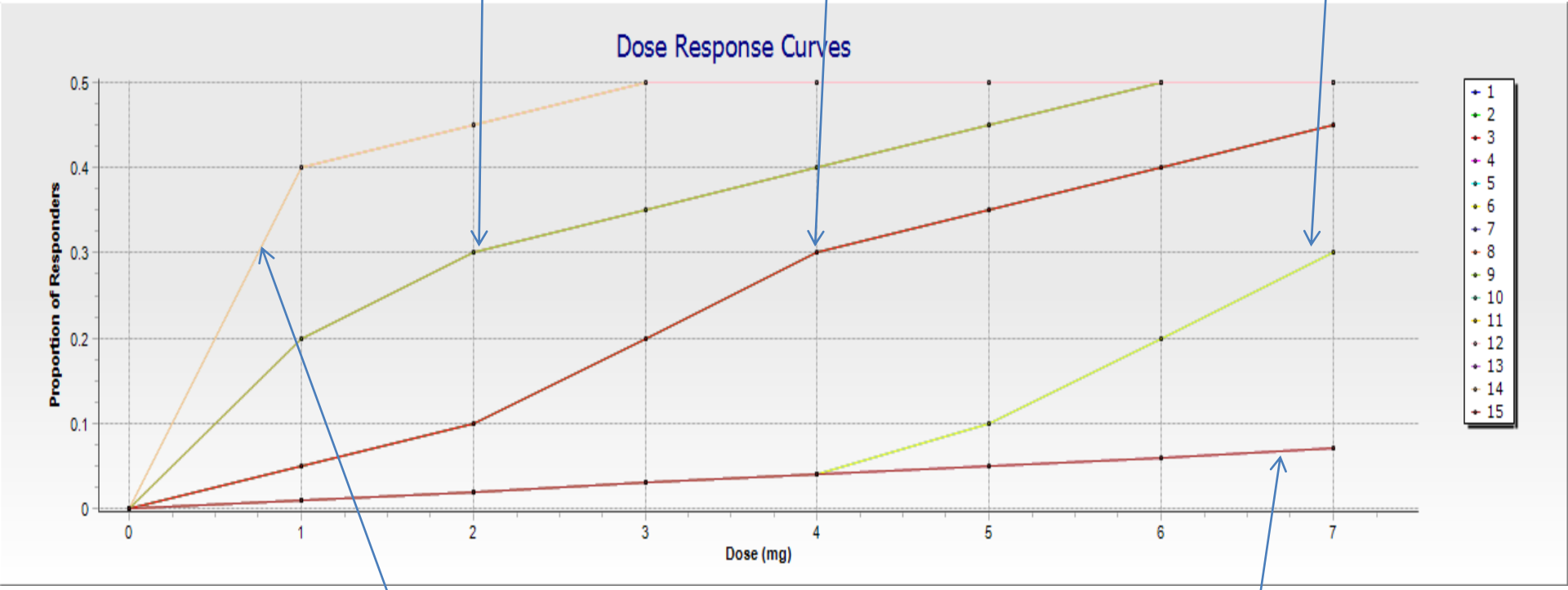
Dose-Response Curves Simulated

(MTD = dose with probability of response = 0.3)

DR1 EAST6.1.3 default linear

DR3 left-shifted

DR2 right-shifted



DR4 extreme high

DR5 extreme low

Design Parameters

- 7 doses (1,2,3,4,5,6,7)
- Total N=30 subjects
  - 10 sequential cohorts of 3 subjects each
- 1st cohort at Dose1
- Each subsequent cohort assigned a single dose per adaptive design
- Target Toxicity Level 0.3
- 10K simulations of each DR curve scenario

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mTPI method

- Bayesian Posterior Probability that TRUE DLT rate lies in each of 3 Toxicity Intervals
  - Under dosing: <0.25
  - On-Target dosing: 0.25-0.35
  - Over dosing: >0.35
- Prior on TRUE toxicity probability at each dose ~ Beta(1,1)
- Applies up/down/stay rules for next dose based on posterior probabilities of being in each toxicity interval at current dose
- Over-Dosing Exclusion Rule
  - Prob(Pi>Pt|data) > 0.9999 [to yield full sample size]
    - Pi = Prob(toxicity at dose i)
    - Pt = Target probability of toxicity = 0.3
    - Similar results for EAST default Prob > 0.95 (not shown)
    - Prob>0.6 also assessed
- No Under-dosing exclusion rule used

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mTPI “optimization”

- 2 levels of early stopping
  - posterior probability required (0.95 and 0.80).

- 2 toxicity probability ranges:

	+/-"05" range	+/-"20" range
under dosing	0 to 0.25	0 to 0.10
target dosing	0.25 to 0.35	0.10 to 0.50
over dosing	0.35 to 1.00	0.50 to 1.00

- beta(1,2) prior to yield estimate of ~0.3 for probability of toxicity at each dose since the target toxicity level is 0.3
  - beta(1,1) also run; it yields estimate 0.5

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T-stat Parameters (1)

- T = (Pi-0.3)/sqrt((Pi*(1-Pi)/n)
  - Pi = isotonic estimated proportion of toxicity at Dose i
- Dose escalation / de-escalation rules:

$T < -2$	➔ up 2 dose increments
$-2 \leq T < -0.1$	➔ up 1 dose increment
$-0.1 \leq T < 0.1$	➔ repeat dose
$0.1 \leq T < 2$	➔ down 1 dose increment
$2 \leq T$	➔ down 2 dose increments

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T-stat Parameters (2)

- T = (Pi-0.3)/sqrt((Pi*(1-Pi)/n)
  - Pi = isotonic estimated proportion of toxicity at Dose i
- Dose escalation / de-escalation rules:

  $T < -2$ ➔ up 2 dose increments

  $-2 \le T < -1$ ➔ up 1 dose increment

  $-1 \le T < 1$ ➔ repeat dose

  $1 \le T < 2$ ➔ down 1 dose increment

  $2 \le T$ ➔ down 2 dose increments

- Early Stopping Via Post.Prob.(toxicity rate > 0.35)
  - Three cutoffs (0.5, 0.65, and 0.8)

NOTE: T-stat may have unfair advantage over dose esc. designs since it can skip a dose in extreme cases (i.e., $|T|>2$)

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BLRM Parameters
(Bayesian Logistic Regression Modeling)

- Toxicity Intervals

  Under dosing: <0.25

  Target toxicity: 0.25-0.35

  Excessive toxicity: 0.35-0.45

  Unacceptable toxicity: >0.45

- Prior Distribution: Bivariate Lognormal for the 2 logistic parameters
- Prior on Lowest Dose and MTD
  - Prob.(DLT) at D1 = 0.05
  - Estimated MTD = 4
  - # Beta Samples = 1000 (Direct Sampling; default settings)
- Probability(Overdosing) < 0.25
- No Early Stopping

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BLRM “Optimization”

- 3 priors for logistic regression model, per Neuenschwander(2008)
- Doses with EWOC OD post.prob > 0.25,0.5, 0.8 evaluated

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CRM Parameters
(Continual Reassessment Method)

- Target Probability of Toxicity = 0.3
- Toxicity Probability Upper Limit = 0.3
- Model Type = 1-parameter power and logistic
  - Gamma(1,1) prior
- Default prior

Doses:	D1	D2	D3	D4	D5	D6	D7
Prob(tox):	0.05	0.1	0.2	0.3	0.35	.4	0.45

- No EWOC, but early stopping if Prob(lowest dose toxicity rate > 0.3)>0.9

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CRM “Optimization”

- Permit skipping doses since Tstat dose so
- Permit dose escalation if a prior subject experienced a toxicity
- Three priors (CRM1,2,3) chosen for similarity to the priors for BLRM plus a very-close-to-flat prior (CRM4) for one-parameter power model:
  - all use gamma(1,1) as prior for the power parameter
- 2 upper toxicity probability limits for the EAST default one-parameter logistic model

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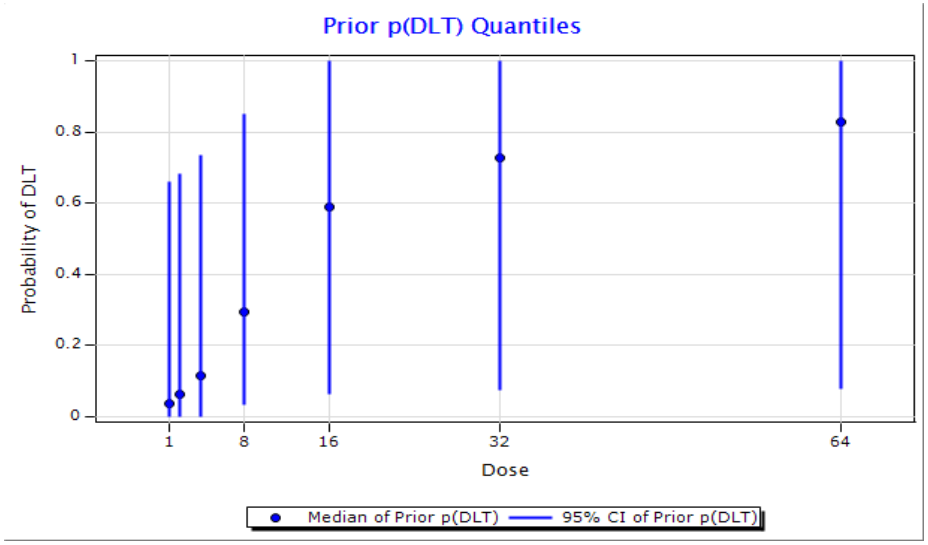
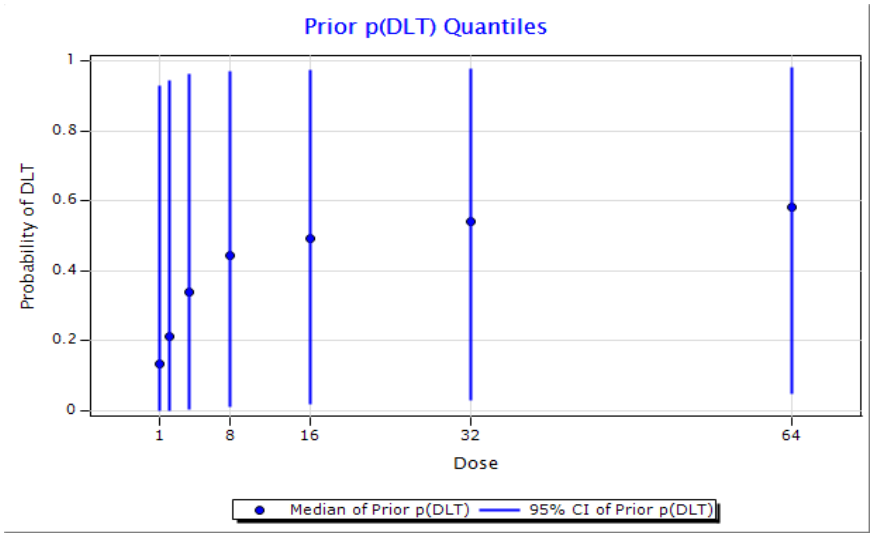
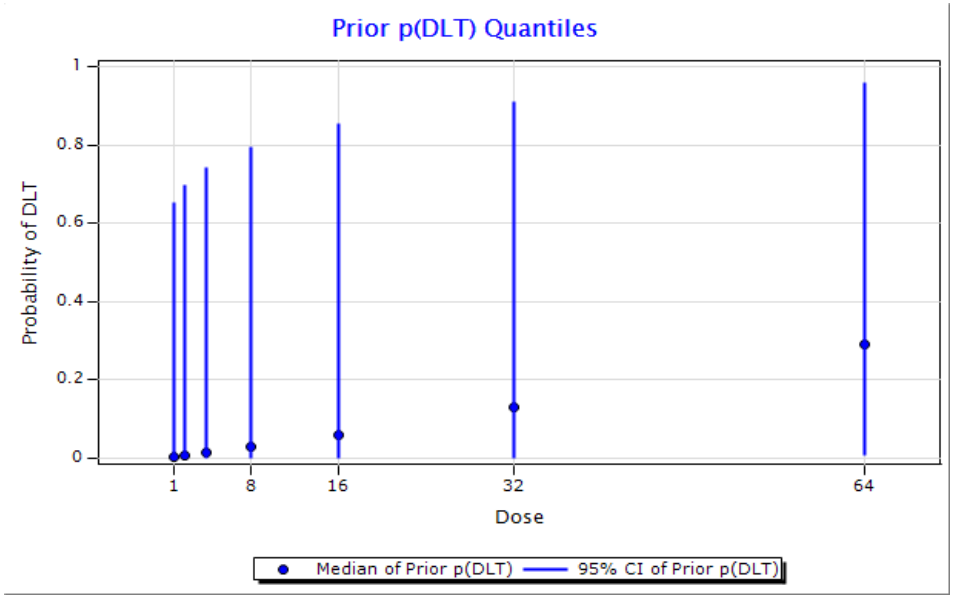
BLRM default prior



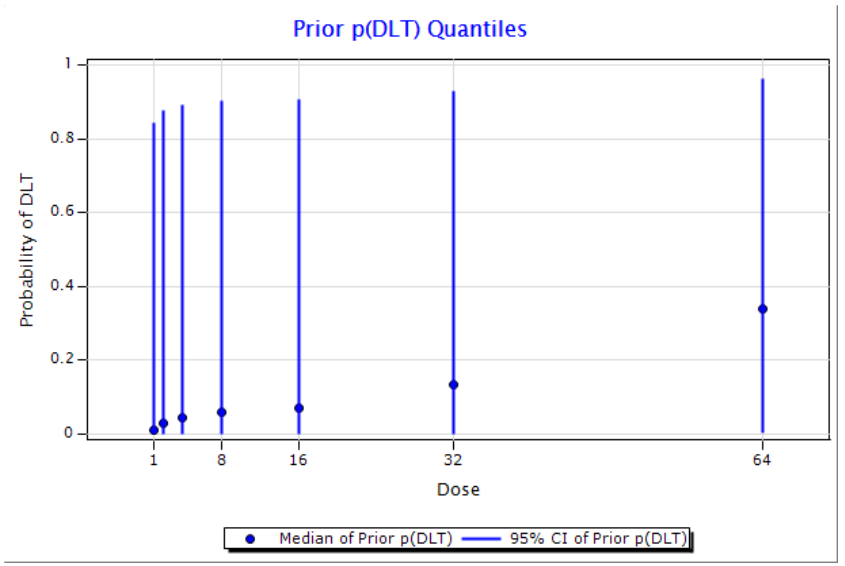
CRM default prior



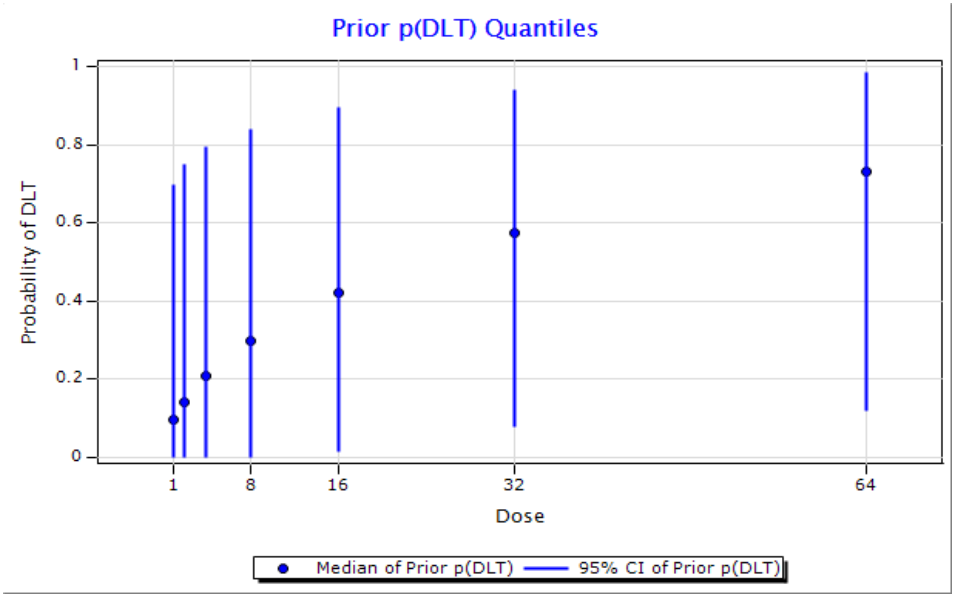
BLRM(prior1 “low”)



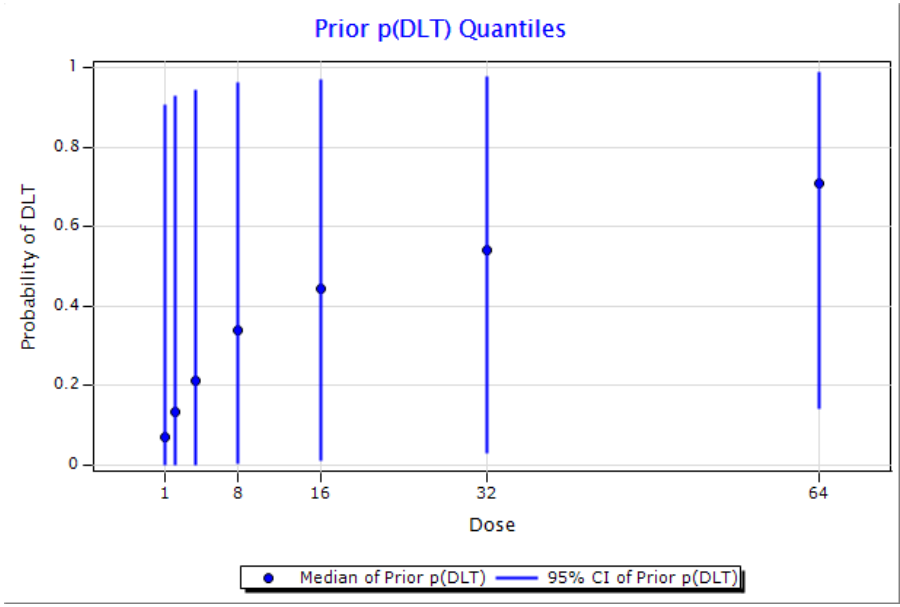
CRM(prior1 “low”)



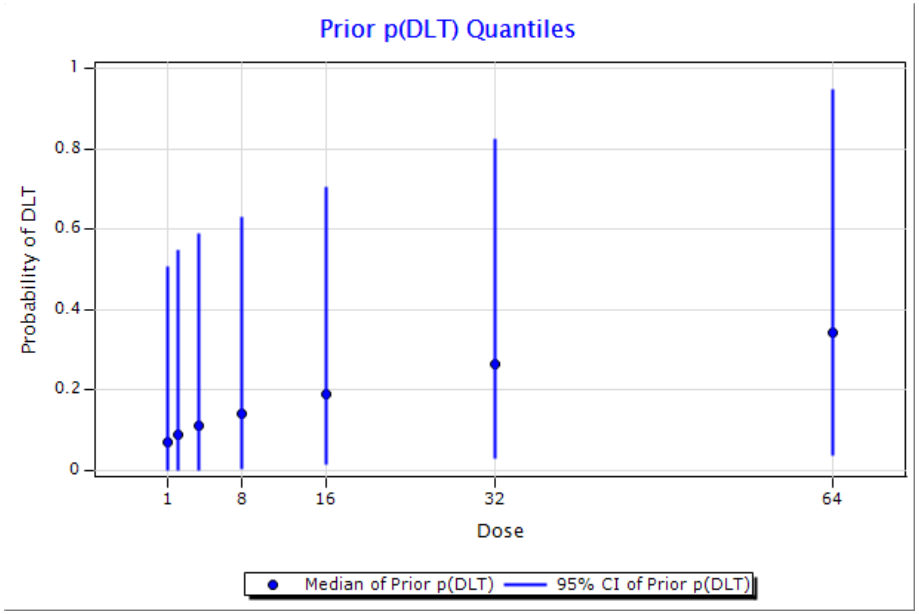
BLRM(prior2 “high”)



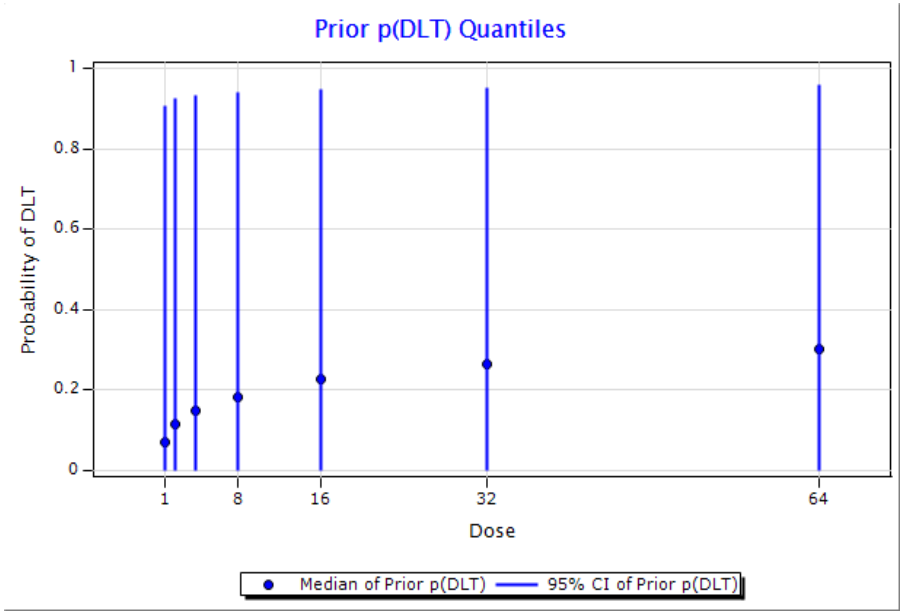
CRM(prior2 “high”)



BLRM(prior3 “mid”)



CRM(prior3 “mid”)



Remarks on mTPI vs BLMR vs CRM vs Tstat from simulations

- Tstat design looks like a competitor to mTPI, BLRM, CRM for toxicity dose-finding trials
  - Based on 4 Performance Criteria:
    - Probability of identifying correct target ID,
    - Probability of estimating MTD at or adjacent to correct MTD
    - probability of assigning subjects to doses > target (OD's),
    - # dose-limiting toxicities (DLT's) observed
  - Each of the 4 designs could be optimized better than the others ***for particular individual*** DR curves and/or ***particular performance criteria***
- Indications are that Tstat is competitive with mTPI, BLRM, CRM in consideration of the spectrum of TRUE underlying DR curves simulated when the 4 performance criteria are combined with equal weights

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One Way to Rank the Designs Across the Five DR Curves & 3 Performance Criteria

- Weight each of 4 performance criteria 1:1:1:1 since 2 assess MTD estimation and 2 assess safety
- Compute "relative difference from optimal over all design scenarios" for each DR curve for each design:
  - (Max.%correct – %correct)/(Max. – Min.%correct)
  - (Max.%at_near – %at_near)/(Max. – Min.%at_near)
  - 100 – (Prob.Assgn>Tgt – Min.Prob.)/(Max. – Min.Prob.Assgn>Tgt)
  - 100 – (Avg#tox – Min.Avg#tox)/(Max. – Min.Avg#tox)
- Then compute average across all DR curves & multiply by 100
- Values closer to 100 indicate closer to optimal design
- Values closer to 0 indicate closer to worst design
- Values = 50 indicate mid-way between optimal and worst designs

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Summary Scores Limited to Best 2 Designs of each type

- Wide range of values for each performance characteristic could unduly inflate / deflate summary scores
- Hence, choose best 2 designs of each type and re-compute summary scores based on only those 8 designs
- Each of the designs out-performs the other 3 designs for at least one performance criteria across all 5 DR curves or for at least one DR curve across all 4 performance criteria (next slide)
- Tstat Design performed best overall, but not by much, across ALL DR curves for average of all 4 performance criteria scores (next slide)

Summary Scores Limited to Best 2 Designs of each type

	over all DR curves				over all 4 perf.char.					
design	%at	%at/ nexto	#OD	#DLTs	DR1	DR2	DR3	DR4	DR5	DR1-5
Tstat2s3550_f	62	50	85	65	45	69	54	**93**	50	**[65]**
Tstat1s3550_f	65	52	77	60	44	**72**	54	86	50	64
mTPIr2s9p11_m	40	40	**100**	60	**100**	50	33	25	67	60
BLRMpr2-s25_f	51	**65**	41	53	73	55	61	50	24	53
BLRMdefault_f	20	40	53	**92**	90	53	33	37	33	51
CRM_defltPW_m	60	60	0	40	0	50	**67**	75	33	40
mTPIr5s7p11_f	**71**	47	17	20	19	18	59	36	**89**	38
CRM_defltPW_f	61	57	14	14	23	28	17	63	67	37

- Each of the design type out-performed the other 3 design types for at least one performance criteria across all 5 DR curves or for at least one DR curve across all 4 performance criteria (**bold underlined results above**)
- Tstat Design performed best, but not by much, across ALL DR curves for average of all 4 performance criteria scores **[above]**

Remarks on mTPI vs BLMR vs CRM vs Tstat

- Tstat design looks like a competitor to mTPI, BLRM, CRM for toxicity dose-finding trials
  - Based on Performance criteria:
    - Probability of identifying correct target ID,
    - Probability of estimating MTD at or adjacent to correct MTD
    - probability of assigning subjects to doses > target (OD's),
    - # dose-limiting toxicities (DLT's) observed
  - Each of the 4 designs could be optimized better than the others ***for particular individual*** DR curves and/or ***particular performance criteria***
- Indications are that Tstat is competitive with mTPI, BLRM, CRM in consideration of the spectrum of TRUE underlying DR curves simulated when the 4 performance criteria are combined with equal weights

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Next Steps re: Tstat for toxicity dose-finding

- Consider Tstat in addition to traditional adaptive escalation designs as in EAST
- Consider other ranking mechanisms to compare the design performance characteristics
- Evaluate additional design configurations to optimize, e.g., enhancements in EAST6.4
- Consider Ivanova(2012) Bayesian Isotonic Adaptive Dose-Finding design vs mTPI, CRM, BLRM, Tstat

- Other ?? [DISCUSSION: bolognese@cytel.com]

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REFERENCES

- Ivanova A, Bolognese J, Perevozskaya I. Adaptive design based on T-statistic for dose-response trials. *Statistics in Medicine*, 2008 May 10;27(10):1581-92
- EAST6.3.1 User Manual, Cytel Inc., Cambridge, MA 2014
- COMPASS User Manual, Cytel Inc., Cambridge, MA, 2012
- Ivanova A, Xiao C, Tymofyeyev Y. Two-stage designs for Phase 2 dose-finding trials. *Statist. Med.* 2012; **31:**2872–2881
- Ji Y, Liu P, Li Y, and Bekele N (2010). A modified toxicity probability interval method for dose finding trials. Clinical Trials, 7:653-656.
- Neuenschwander B, Branson M, and Gsponer T (2008). Clinical aspects of the Bayesian approach to phase I cancer trials. Statistics in Medicine, 27:2420-2439.
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- Bolognese JA, Patel N, Tymofyeyev Y, Perevozskaya I, Palmer J. T-Statistic-based Up&Down Design for Dose-Finding Competes Favorably with Bayesian 4-parameter Logistic Design. Joint Statistics Meetings, Washington, DC, August 5, 2009. (invited presentation)

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SUPPLEMENTAL INFO

FOLLOWS THIS SLIDE

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mTPI cases simulated

mTPIdefault_f	**mTPIr2s9p11_m**
mTPIdefault_m	mTPIr2s9p37_f
mTPIdeflt37_f	mTPIr2s9p37_m
mTPIdeflt37_m	mTPIr5s7p11_f
mTPIr2s7p11_f	mTPIr5s7p11_m
mTPIr2s7p11_m	mTPIr5s7p37_f
mTPIr2s7p37_f	mTPIr5s7p37_m
mTPIr2s7p37_m	mTPIr5s9p37_f
mTPIr2s9p11_f	mTPIr5s9p37_m

("m" indicates MTD estimate via the method description in the reference; "f" indicates via isotonic regression fit)

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Tstat cases simulated

Tstat1_____f	Tstat2_____f
Tstat1_____m	Tstat2_____m
Tstat1s3550_f	Tstat2s3550_f
Tstat1s3550_m	Tstat2s3550_m
Tstat1s3565_f	Tstat2s3565_f
Tstat1s3565_m	Tstat2s3565_m
Tstat1s3580_f	Tstat2s3580_f
Tstat1s3580_m	Tstat2s3580_m
Tstat1s5080_f	Tstat2s5080_f
Tstat1s5080_m	Tstat2s5080_m

BLRM cases simulated

BLRMdefault_f	**BLRMpr2-s50_f**
BLRMdefault_m	BLRMpr2-s50_m
BLRMpr1-s25_f	BLRMpr2-s80_f
BLRMpr1-s25_m	BLRMpr2-s80_m
BLRMpr1-s50_f	BLRMpr3-s25_f
BLRMpr1-s50_m	BLRMpr3-s25_m
BLRMpr1-s80_f	BLRMpr3-s50_f
BLRMpr1-s80_m	BLRMpr3-s50_m
BLRMpr2-s25_f	BLRMpr3-s80_f
BLRMpr2-s25_m	BLRMpr3-s80_m

CRM Cases simulated

CRM_defltLG_f	**CRM_p2modLG_f**
CRM_defltLG_m	CRM_p2modLG_m
CRM_defltPW_f	CRM_p2modPW_f
CRM_defltPW_m	CRM_p2modPW_m
CRM_p1modLG_f	CRM_p3modLG_f
CRM_p1modLG_m	CRM_p3modLG_m
CRM_p1modPW_f	CRM_p3modPW_f
CRM_p1modPW_m	CRM_p3modPW_m

BLRM Priors (Neuenschwander, 2008)

- bivariate normal prior for means of log(alpha) and log(beta) in the Bayesian logistic linear regression model:
  - mean(alpha) = logit(p-star)=log(0.3/0.7)=-0.847, where p-star is the target toxicity level

    mean(beta) = 0, SD(alpha) = 2, SD(beta) = 1, correlation = 0
- setting prior probabilities of
  - (1) exceeding the minimum unacceptable toxicity proportion at the lowest dose, and
  - (2) falling below the maximum under-dosing toxicity proportion at the highest dose at, e.g., 0.05.
  - then deriving corresponding multivariate normal parameters.
  - For Prob(p1>0.6)=0.05 and Prob(pK<0.2=0.05), the corresponding 5 multivariate normal parameters (m1,m2,s1,s2,rho) are (-0.376, -0.466, 0.853, 0.931, -0.119).
- Flatter prior: mean(alpha)=-1.025, mean(beta)=-1.091, SD(alpha)=0.893, SD(beta)=1.147, corr=-0.084.

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T-stat Dose-Stopping Rules

- Posterior probability (with beta(1,1) prior) that estimated toxicity at a dose > unacceptable toxicity level exceeds cutoff, then that dose and all higher doses no longer assigned
- Three cutoffs (0.5, 0.65, and 0.8) simulated for unacceptable toxicity level 0.35
- As a liberal criteria, cutoff 0.8 simulated for unacceptable toxicity level 0.5.

- Simulated for each of Tstat(1) and Tstat(2)
- Also considered NO dose-stopping

- MANY THANKS to Jaydeep Bhattacharyya for programming the early stopping into CytelSim

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CRM "Optimization"

- Permit skipping doses since Tstat dose so
- Permit dose escalation if a prior subject experienced a toxicity
- Three priors (CRM1,2,3) chosen for similarity to the priors for BLRM plus a very-close-to-flat prior (CRM4) for one-parameter power model:
  - all use gamma(1,1) as prior for the power parameter
  - D1 D2 D3 D4 D5 D6 D7
- Default prior 0.05, 0.1, 0.2, 0.3, 0.35, 0.4, 0.45
- Prior1 0.001, 0.005, 0.01, 0.015, 0.02, 0.05, 0.2
- Prior2 0.02, 0.05, 0.1, 0.2, 0.3, 0.4, 0.6
- Prior3 0.02, 0.04, 0.06, 0.08, 0.11, 0.14, 0.17
- 2 upper toxicity probability limits for the EAST default one-parameter logistic model
- 6 CRM configurations in all

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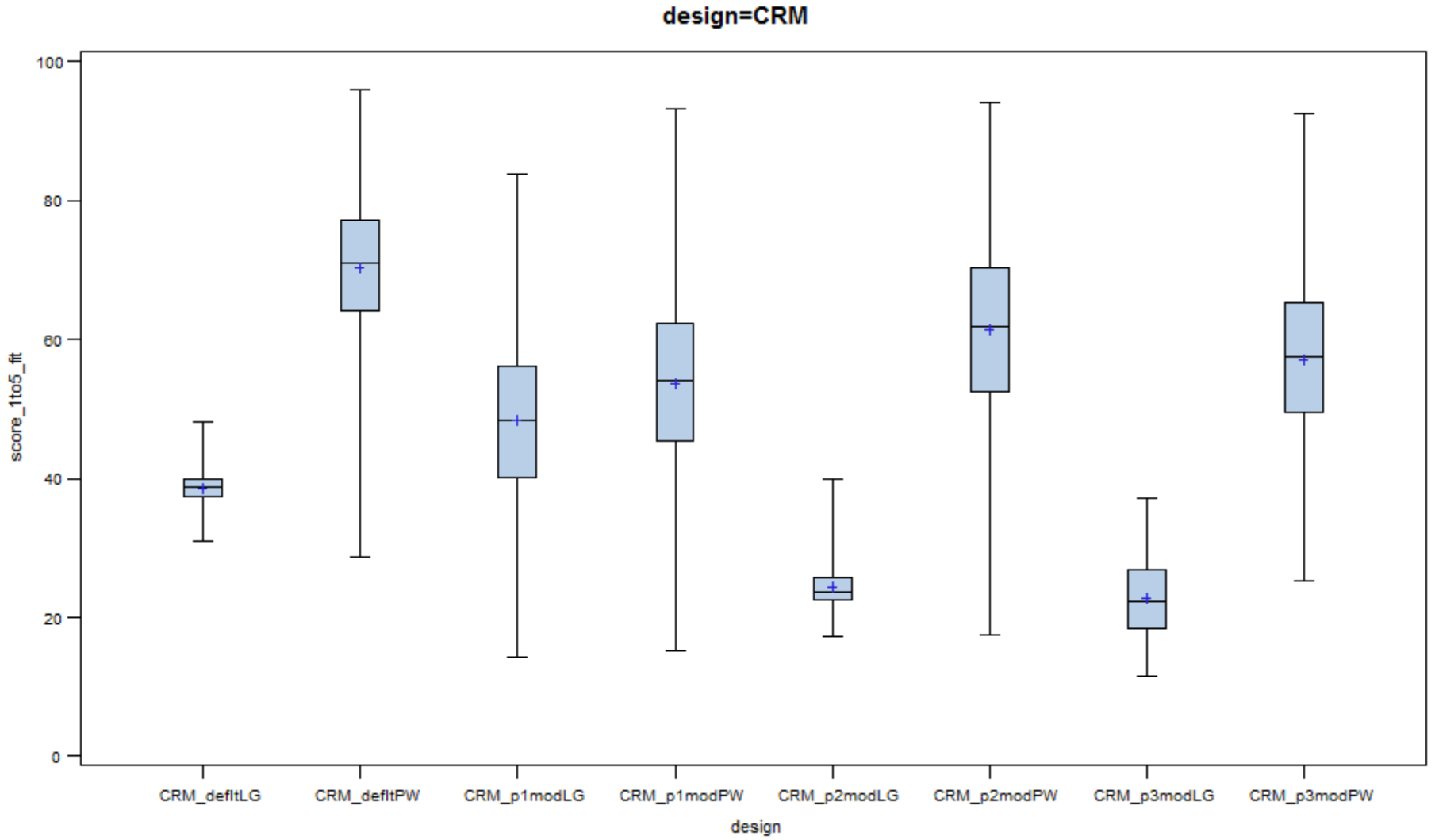
Distribution of summary scores across all DR curves and performance criteria



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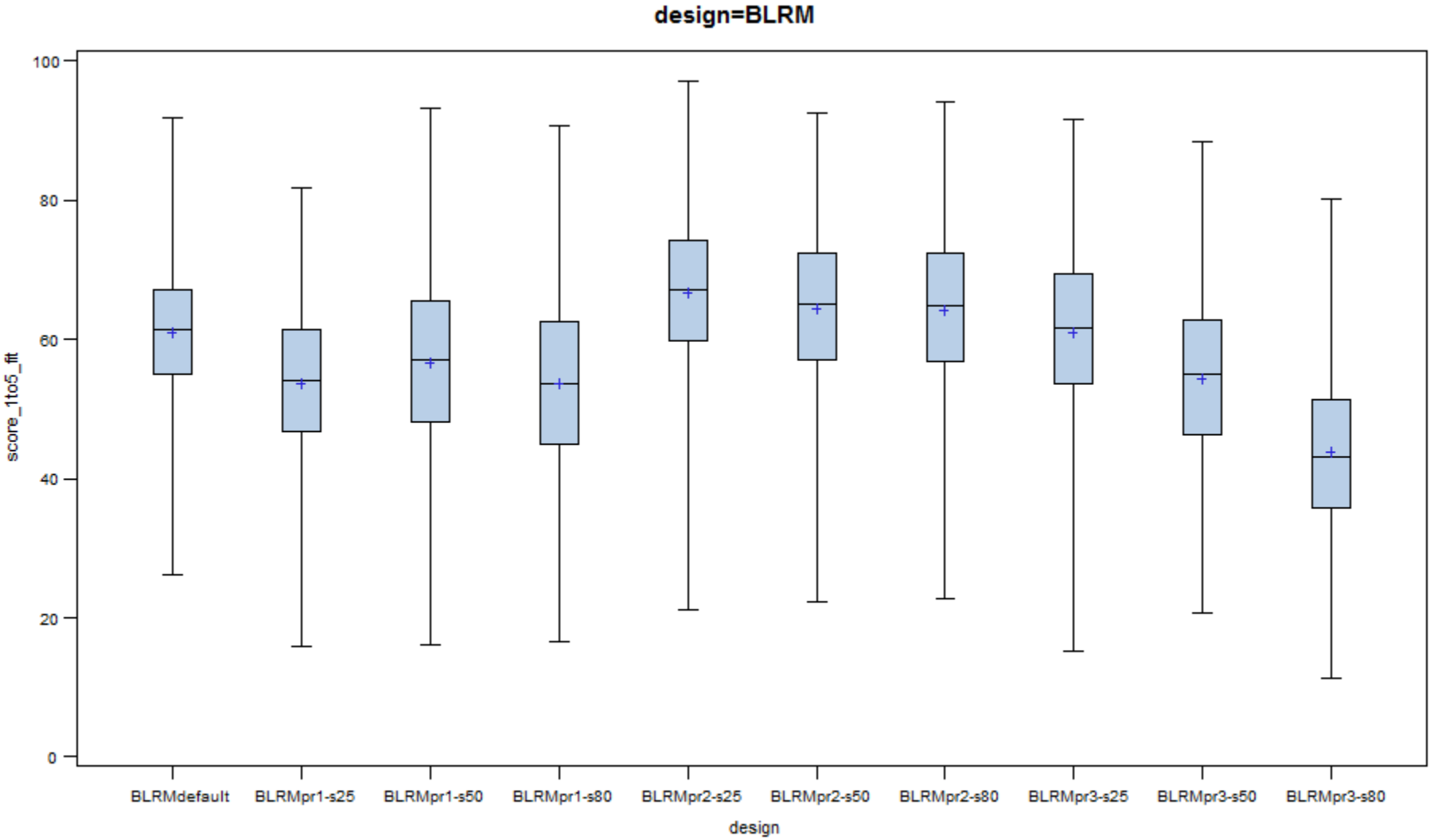
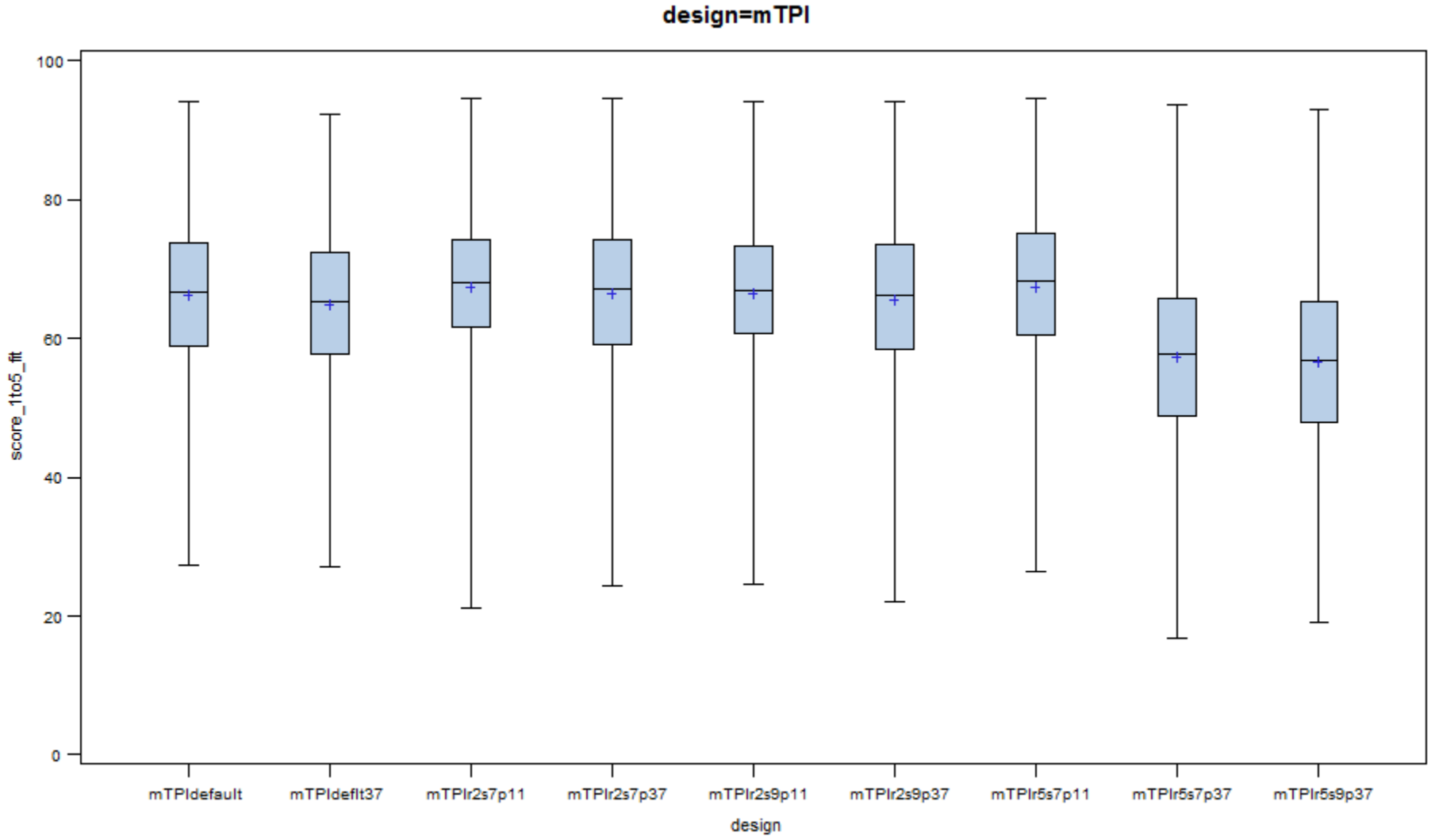
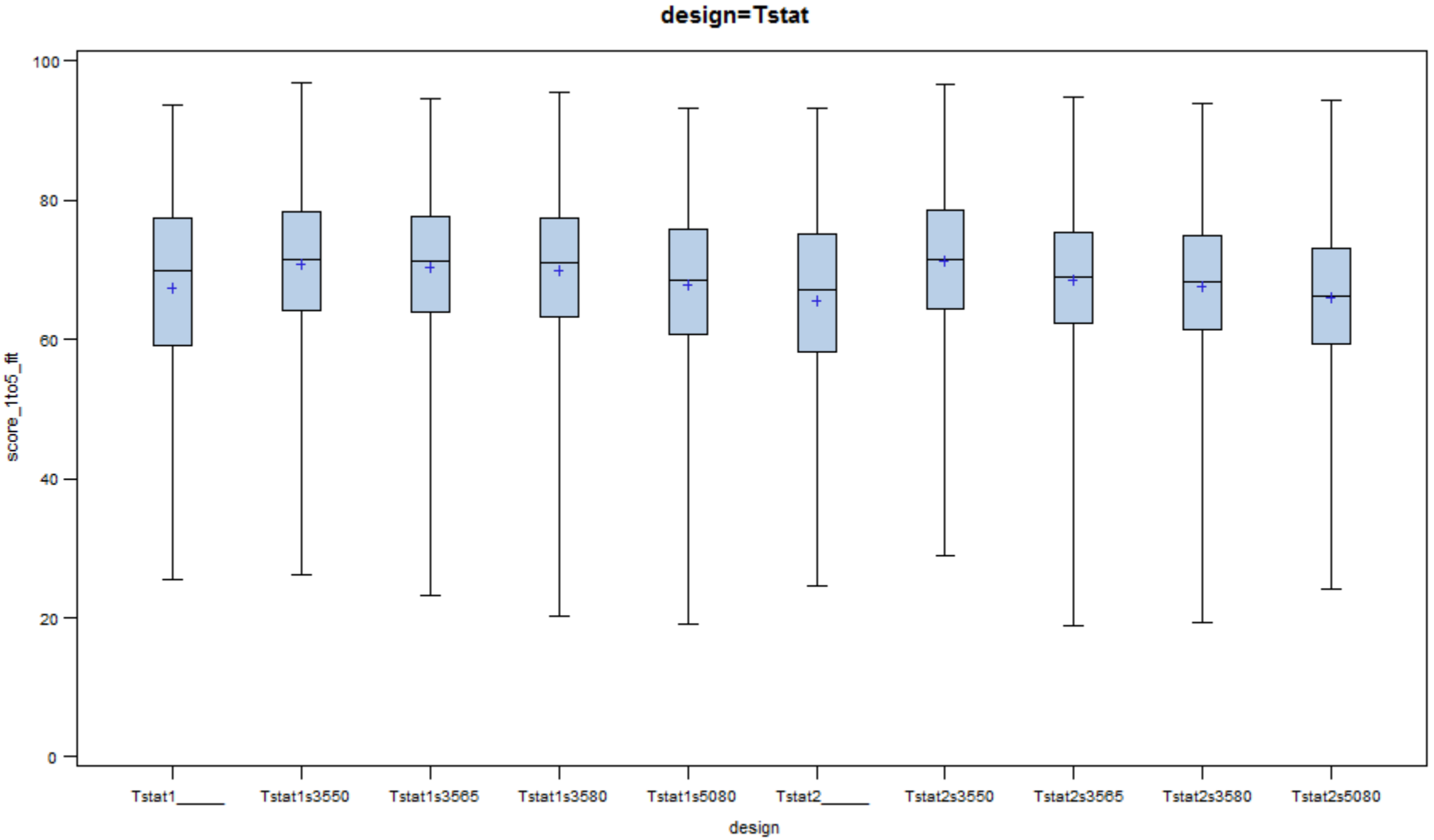


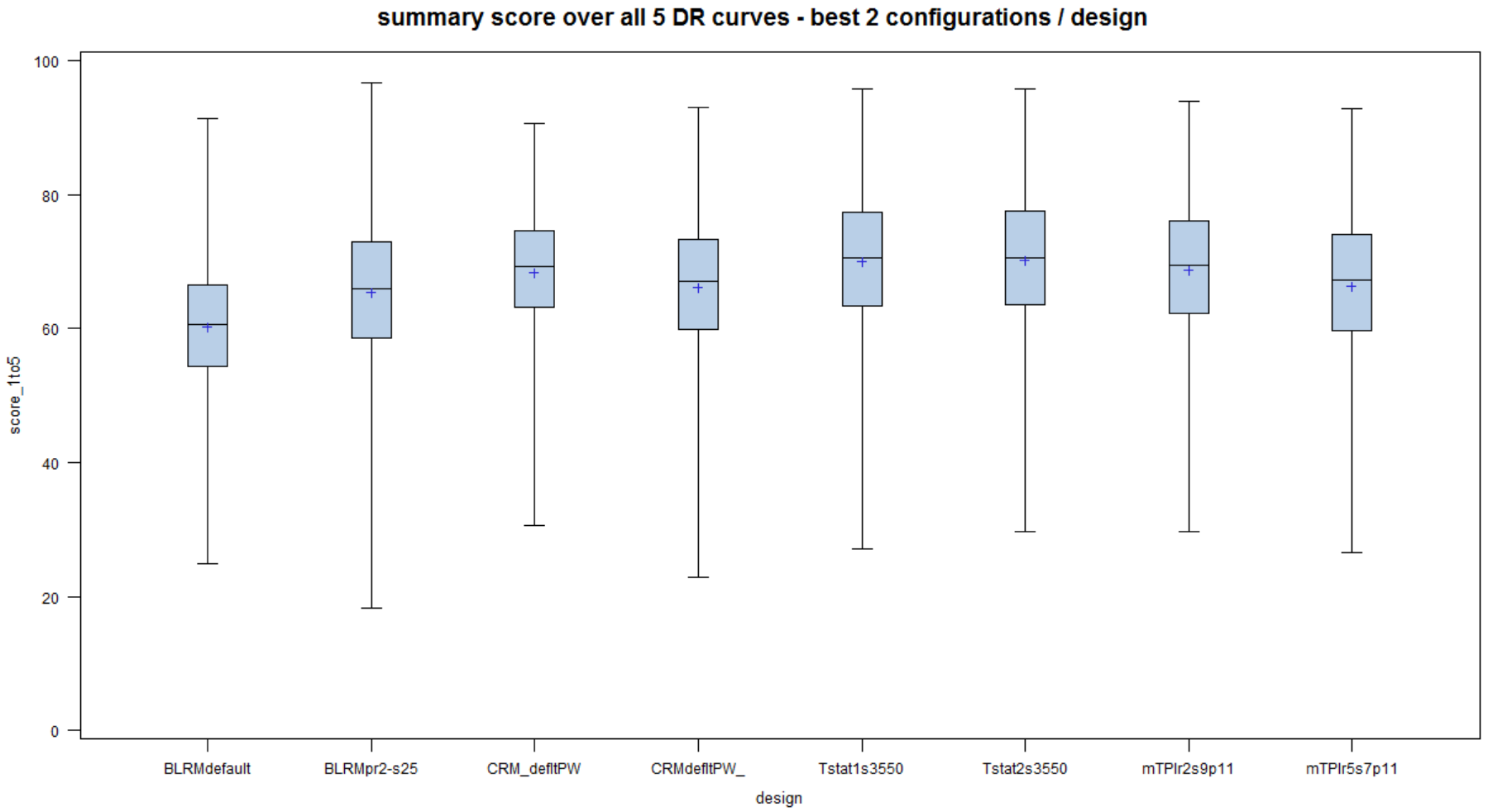
Distribution of summary scores across all DR curves and performance criteria



Distribution of summary scores across all DR curves and performance criteria



Distribution of summary scores across all DR curves and performance criteria



Tstat as easy as mTPI to implement

Number of Toxicities	T-Statistic Design for Target Toxicity Level = 0.3 — Number of Subjects Observed																											
	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
1	0	0	0	0	1	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
2	-1	0	0	0	0	0	0	0	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
3	-2	-2	-1	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2
4		-2	-2	-1	-1	-1	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	2	2	2	2	2
5			-2	-2	-2	-1	-1	-1	-1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1
6				-2	-2	-2	-2	-1	-1	-1	-1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
7					-2	-2	-2	-2	-2	-1	-1	-1	-1	-1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
8						-2	-2	-2	-2	-2	-2	-2	-1	-1	-1	-1	-1	0	0	0	0	0	0	0	0	0	0	0
9							-2	-2	-2	-2	-2	-2	-2	-2	-1	-1	-1	-1	-1	-1	0	0	0	0	0	0	0	0
10								-2	-2	-2	-2	-2	-2	-2	-2	-2	-1	-1	-1	-1	-1	-1	-1	0	0	0	0	0
11									-2	-2	-2	-2	-2	-2	-2	-2	-2	-2	-2	-1	-1	-1	-1	-1	-1	-1	0	0
12										-2	-2	-2	-2	-2	-2	-2	-2	-2	-2	-2	-2	-1	-1	-1	-1	-1	-1	-1
13											-2	-2	-2	-2	-2	-2	-2	-2	-2	-2	-2	-2	-2	-2	-1	-1	-1	-1
14												-2	-2	-2	-2	-2	-2	-2	-2	-2	-2	-2	-2	-2	-2	-2	-1	-1
15													-2	-2	-2	-2	-2	-2	-2	-2	-2	-2	-2	-2	-2	-2	-2	-2
16														-2	-2	-2	-2	-2	-2	-2	-2	-2	-2	-2	-2	-2	-2	-2
17															-2	-2	-2	-2	-2	-2	-2	-2	-2	-2	-2	-2	-2	-2
18																-2	-2	-2	-2	-2	-2	-2	-2	-2	-2	-2	-2	-2
19																	-2	-2	-2	-2	-2	-2	-2	-2	-2	-2	-2	-2
20																		-2	-2	-2	-2	-2	-2	-2	-2	-2	-2	-2
21																			-2	-2	-2	-2	-2	-2	-2	-2	-2	-2
22																				-2	-2	-2	-2	-2	-2	-2	-2	-2
23																					-2	-2	-2	-2	-2	-2	-2	-2
24																						-2	-2	-2	-2	-2	-2	-2
25																							-2	-2	-2	-2	-2	-2
26																								-2	-2	-2	-2	-2
27																									-2	-2	-2	-2
28																										-2	-2	-2
29																											-2	-2

modify yellow-highlighted cells to modify design spec's

Tstat as easy as mTPI to implement (spreadsheet computes table in previous slide)

Dose Selection Rules		
Values of T		Dose Increment
from	to	
-infinity	-2	2
-2	-1	1
-1	1	0
1	2	-1
2	+infinity	-2