Two Bayesian designs for first-in-human trials in cancer

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March 31, 2017

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Agenda

Two Bayesian designs for first-in-human trials in cancer

- Quick intro to first-in-human trials in cancer
- Continual Reassessment Method (CRM)
  - modified CRM (mCRM)
- Bayesian Optimal Interval Design (BOIN)

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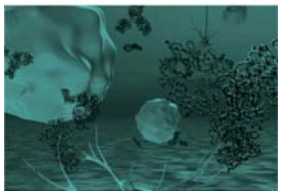
Credits & Thank You

CRM
Dr Ulf Forssmann, Sr Medical Director, Genmab A/S
- advocate of CRM + significant modifications

Kert Viele & *Anna McGlothlin*, Berry Consultants Inc.
- Implementation and advice

BOIN
Dr Ulf Forssmann

CRM + BOIN
Henning Friis Andersen, Genmab A/S



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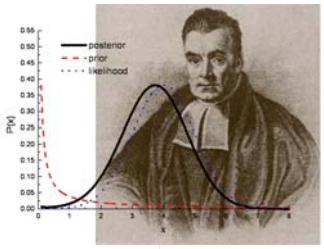
Thomas Bayes (1701?-April 7 1761)



- Nonconformist minister
  - Tunbridge wells, 70 km SE of London
- No mathematical/statistical publications
- Unknown/uninfluential on his contemporaries
- Made Fellow of the Royal Society 1741
- Richard Price read his work to the RS on Dec 23 1763
  - ”An assay towards solving a Problem in the Doctrine of Chances” (1764)
- One of the most widely known eponyms in Science today

$$p(\theta|y) = \frac{p(y|\theta)p(\theta)}{\int p(y|\theta)p(\theta)d\theta}$$

- Laplace, independently, developed same/similar ideas 1774

The History of Statistics, The Measurement of Uncertainty before 1900, Stephen M Stigler, 1986, Belknap Harvard University Press

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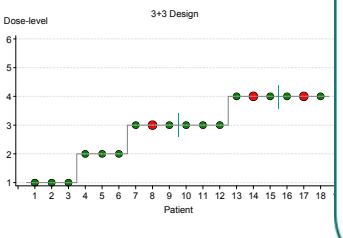
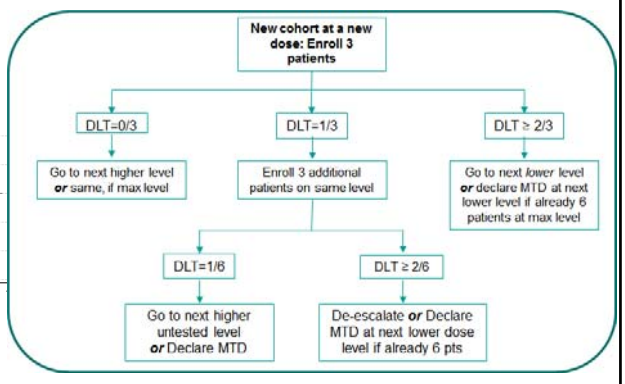
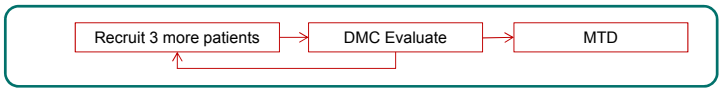
Standard Traditional 3+3







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Dose Limiting Toxicities (DLTs)

Table 5-2 Criteria for defining dose-limiting toxicities

Toxicity	Any of the following criteria:
Hematology	≥ CTCAE grade 3 neutropenia (ANC < 1.0 x 10^9/L)
	≥ CTCAE grade 3 thrombocytopenia (platelets < 50 x 10^9/L)
	≥ CTCAE grade 3 anemia (Hgb < 8.0 g/dL)
	Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.5°C)
Renal	Serum creatinine > 2 x ULN
Hepatic	≥ CTCAE grade 3 total bilirubin (> 3 x ULN)
	≥ CTCAE grade 2 total bilirubin and ≥ CTCAE grade 2 ALT
	≥ CTCAE grade 3 ALT
Pancreatic	≥ CTCAE grade 2 pancreatitis
	≥ CTCAE grade 3 amylase or lipase
Cardiac	≥ CTCAE grade 3
Dermatologic	≥ CTCAE grade 2 phototoxicity Any skin toxicity or rash resulting in interruption of LDK378 for >21 consecutive days
Ocular	Any ≥ CTCAE grade 3
Other adverse events	≥ CTCAE grade 3 vomiting or nausea despite optimal anti-emetic therapy
	≥ CTCAE grade 3 diarrhea despite optimal anti-diarrhea treatment
	Any ≥ CTCAE grade 3 AE, except for the exclusions noted below
	In view of the Investigators and Novartis any other unacceptable toxicity encountered
Exceptions to DLT criteria	CTCAE grade 3 or 4 elevations in alkaline phosphatase
	< 72 hours of CTCAE grade 3 fatigue
CTCAE version 4.0 will be used for all grading. Patients may receive supportive care (eg. PRBCs) as per local institutional guidelines. Optimal therapy for vomiting or diarrhea will be based in institutional guidelines, with consideration of the prohibited medications listed in this protocol.	
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; ANC, absolute neutrophil count; CTCAE, Common Terminology Criteria for Adverse Events; DLT, dose-limiting toxicity; PRBC, packed red blood cells; ULN, upper limit of normal,	

Shaw AT et al, Ceritinib in *ALK*-Rearranged Non–Small-Cell Lung Cancer, NEJM 370:13, pp1189-1197, protocol in appendix

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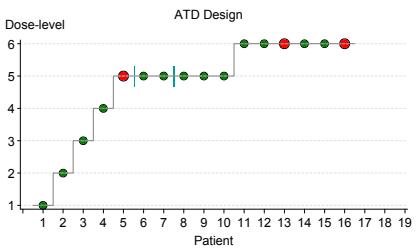
Accelerated Titration Design (ATD)

- Just like 3+3, but with one difference
- Initial cohorts: single-patient cohorts.
  - With or without intra-patient dose-escalation
- Continue with single-patient cohorts until:
  - DLT (or other relevant toxicity) seen, or
  - reached a ”high” dose-level
- Thereafter, continue as 3+3



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Trial designs in Phase I Cancer Trials

- Estimate from 2007[1]
  - **1991-2006**: 1235 abstracts from **Phase I Cancer Trials**
  - **98.4 % step-up-step-down designs**
  - 1.6% (n=20) Bayesian adaptive designs
- More recent estimate:
  - **49% 3+3**
  - **40% Accelerated Titration Design**
  - **10% Bayesian CRM**

[1] *Rogatko A et al,* Translation of Innovative Designs Into Phase I Trials, JCO, 25; 31, pp 4982-4986, 2007

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Use of CRM at Novartis

- Novartis:
  - Before 2000: the 3+3 design
  - In 2000
    - two trials with CRM
    - both failed (too aggressive dose-recommendations)
  - ~2004: another attempt (2-parameter Bayesian Logistic Regression)
    - Success
  - 2005: CRM is the new Novartis standard
    - Global phase I and Ib: 100%
    - > 60 trials, >30 compounds, >20 FIH

American Statistical Association Webinar, Bailey S, Neuenschwander B, April 27, 2011
FDA-Industry Workshop 2015, Roychoudhury, Neuenschwander, Wandel, Bayesian Adaptive Phase I Oncology Trials, September 2015

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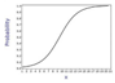
CRM 1/2

- Introduced in: O'Quigley J, Pepe M, Fisher L. Continual reassessment method: A practical design for Phase I clinical trials in cancer. Biometrics. 1990;46:33–48
- Start by assuming a functional relationship between Dose and DLT:
  - $\log\left(\frac{p_{DLT}}{1-p_{DLT}}\right) = \boldsymbol{\alpha} + \boldsymbol{\beta} \cdot dose$



  - Bayesian logistic regression:
    $\alpha\&\beta$ *are not fix parameters but have distributions*
  - Early: α fixed (e.g. *3)* ⇒ one-parameter logistic regression model
  - NB; not actual doses used in model: "dose labels" or "standardized doses" used
  - Define Target Toxixity Level (TTL): e.g. 17%-33%
    - The aim is to have *TTL* DLT-rate on MTD

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CRM 2/2

The Continual Re-assessment Method

Step	
1	Assume prior for θ
2	Treat 1 patient, at dose level closest to current estimate of the MTD
3	Observe DLT outcome
4	Compute posterior and update β: Treat the next patient at the level closest to the updated estimate of the MTD, based on posterior distribution of θ. Treat the next patient at model-based MTD-estimate: $d_{i+1} = \arg\min_{d_k} \lvert p(d_i, \hat{\beta}_i) - TTL \rvert,$ where $p(d_i, \beta)$= probability of DLT on dose-level *i,* $\hat{\beta}_i = \frac{\int_{-\infty}^{\infty} \beta L_i(\beta;\, \boldsymbol{d}, \boldsymbol{y}) dF(\beta)}{\int_{-\infty}^{\infty} L_i(\beta;\, \boldsymbol{d}, \boldsymbol{y}) dF(\beta)}$ as well as $L_i(\beta;\, \boldsymbol{d}, \boldsymbol{y}) = \prod_{j=1}^{i} p(d_j, \beta)^{DLT_j} \left[1 - p(d_j, \beta)\right]^{1-DLT_j},$ $F(\beta)$: a priori distribution for β, d_j: dose level for patient *j*, DLT_j: DLT outcome (0, 1) for patient *j*. Compute by numerical integration, *e.g.* MCMC.
5	Repeat Steps 1-5 until sufficient precision in estimate of θ, or N_{max} reached. MTD= the dose that would have been given to the *(N+1)*st patient.

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Safety concerns with the original CRM

Safety concerns:

- Starts at the expected MTD
- Goes straight for the MTD

Modifications proposed: modified CRM

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Escalation With Overdose Control (EWOC)

Limit the posterior probability of choosing a dose that exceeds the MTD

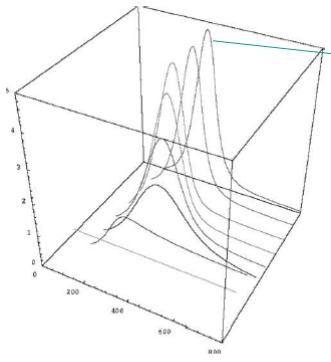

FIG. 1. *Posterior density of the MTD when the number of treated patients (from bottom to top) is* 1, 5, 10, 15, 20, 25, 30, 33.

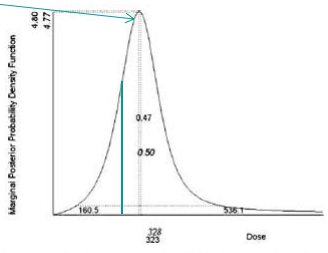

FIG. 2. *Posterior density of the MTD after* 33 *patients have been treated. The posterior mode is* 323 *(47th percentile) and the median and dose to be given to the* 34*th patient is* 328. *The* 95% *highest posterior density interval is* [160.5, 536.1].

Tighiouart M & Rogatko A, Dose Finding with Escalation with Overdose Control (EWOC) in Cancer Clinical Trials, Statistical Science 2010, Vol. 25, No. 2, 217–226

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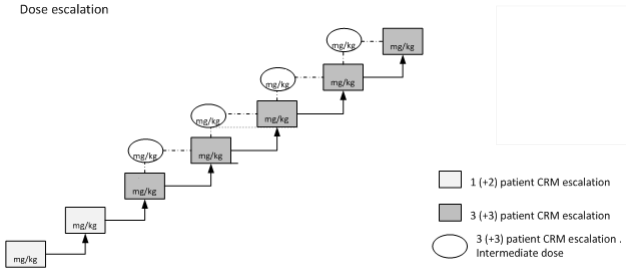
Modified CRM in GCT1021-01



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Modified CRM in GCT1021-01

- First-in-Human: Do not start at MTD, start low
- 3 patients per cohort
  - However, single-patient cohorts the first 2 dose-levels
- Main dose-levels and intermediate dose-levels
  - Escalate on main dose-levels until DLT observed, then intermediate dose-levels available
- Restricted dose-allocation: escalate one main dose-level at the time
- Escalation With Overdose Control

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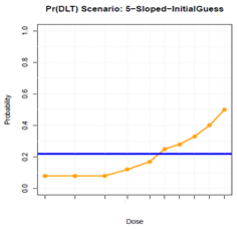
GCT1021-01 –before we start



- Assumed DLT-rates at dose-levels
  - 8 different scenarios
- Target Toxicity Level (on MTD): 22%
- Escalation with overdose control (EWOC)
  - Escalate to a "safe" dose level; level safe if $Pr(p_{DLT}(d) < 22\%) > 40\%$.
- Total N_{max}=41,
  - need 20-30 patients for CRM to work
- Prior distribution....

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mCRM in GCT1021-01 – historical data for the prior

Overview of start dose and MTD in some (MMAE-) ADC Phase 1 trials[1]

Drug						Dose		
Drug	Name	Company	Target	Linker	Indication	Ph1 Doses (mg/kg)	Ph1 Regimen	MTD (mg/kg)
Adcetris	Brentuximab vedotin	Seattle Genetics	CD30	vc	HL & ALCL	0.4-1.4 1.2-2.7*	Q1W Q3W	1.8
CDX-011	Glembatumumab vedotin	Celldex	GPNMB	vc	Breast	- - 0.03-2.63	Q1W Q2/3W Q3W	1.88
DCDT2980S	Pinatuzumab vedotin	Genentech/ Roche	CD22	MC-VC-PABC	NHL & DLBCL	0.1-3.2	Q3W	2.4
PSMA-ADC		Progenics	PSMA	vc	metCRPC	0.4-2.8	Q3W	2.5
DCDS4501A	Polatuzumab vedotin	Genentech/ Roche	CD79n	MC-VC-PABC	NHL & DLBCL	0.1-2.4	Q3W	In Ph2: '2.5 or 2.3'. Latter 'appropriate'[2]
ASG5E	-	Agensys (Astellas)	SLC44A4	Vc	Prost, gastr & pancr	0.3-1.5 0.3-3	Q1W Q3W	1.2 2.4
MLN0264	-	Millenium	Guanylyl cyclase C	ND	GI	0.3-1.8	Q3W	ND but >=1.8[3]
HuMax-TF-ADC[4]	Tisotumab vedotin	Genmab	TF	vc	Solid tumors	0.3-2.6	Q3W	2.0

Mean MTD ~ 2.1 mg/kg

ND- No Data
* 1 patient dosed at 3.6 mg/kg
[1] Deslandes, A., Comparative clinical pharmacokinetics of antibody-drug-conjugates in first-in-human Phase 1 studies, mAbs 6:4,1-12; July/August 2014
[2] Press Release http://ir.progenics.com/releasedetail.cfm?ReleaseID=898664
[3] No DLTs in doses up to 1.8 mg/kg in first 10 patients
[4] Genmab

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mCRM– Design Calibration

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mCRM in GCT1021-01

- Allows for flexibility in cohort sizes
  - In case of a drop-out: 2 patients, or 5 patients
  - In case of over-recruitment: 4 patients, 7 patients ...
- Better estimate of MTD
- More patients exposed to efficacious dose-levels
  - Efficacy information available earlier, before cohort-expansion

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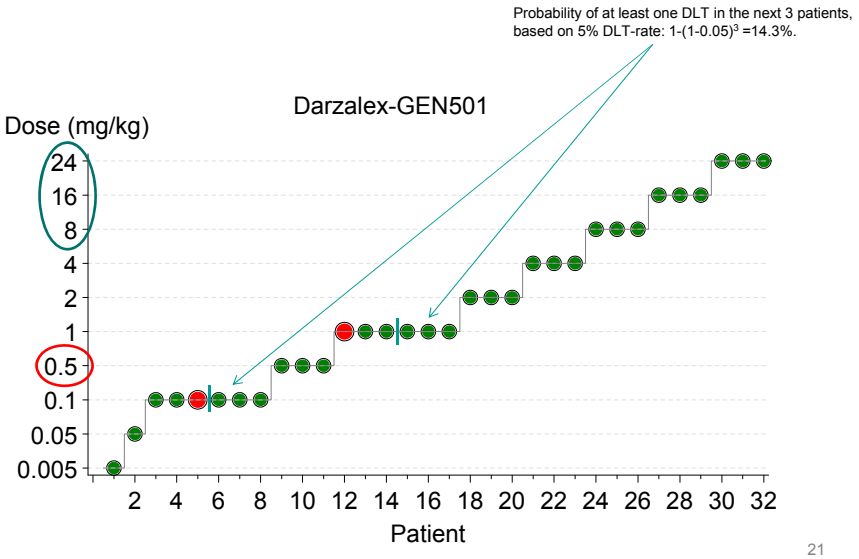
Example from GEN501



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Other version of the CRM

- Many modifications of CRM

- TITE-CRM (time to event CRM)
- Pharmacologically guided CRM
- Maximum Likelihood-versions of CRM
- ...

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Regulatory guidelines

- **Bayesian statistics**
  - **ICH E9**
    - Just mentions that it exists
  - **FDA**
    - ”Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials”.
      - ‘Non-medical-device’-divisions (CDER/CBER) refer to it.
  - **EMA**
    - No specific guidance
    - Mentioned in other guidances, e.g. ‘Guideline on clinical trials in small populations’ : ”Such [Bayesian] methods may be advantageous when faced with small datasets, although introducing prior beliefs is often a concern in drug regulation.”

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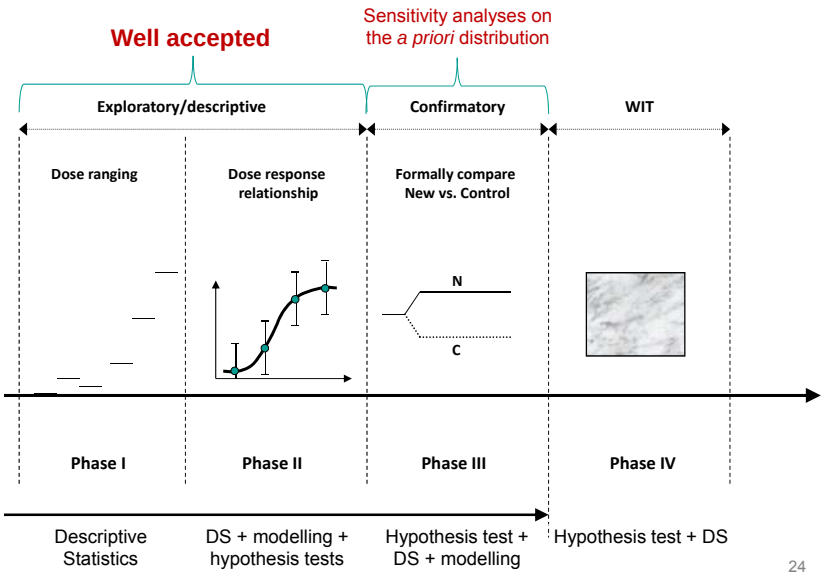
Bayesian methods



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Stakeholder interactions

- Internal
- External
  - KOLs
  - Regulatory authorities

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Software - CRM

SAS	Chang M, Adaptive Design Theory and Implementation Using SAS and R, *Second Edition*, CRC, Chapman and Hall, 2014	PROC IML 1-parameter power: $p_j^{e^\alpha}$
	Ed. Menon, SM & Zink RC, Modern Approaches to Clinical Trials Using SAS, Classical Adaptive and Bayesian Methods, , SAS Institute, 2015	PROC IML 1-parameter power: $p_j^{e^\alpha}$
	DIY	PROC MCMC Example 54.3 for inspiration
R	CRM	1-parameter hyperbolic or 1-parameter logistic CRM
	DFCRM	1-parameter logistic CRM
	BCRM	1-parameter hyperbolic or 1-parameter power or 1-parameter logistic or 2-parameter logistic CRM
	POCRM	Partial order CRM – for drug combination trials
	etc.	

+ several implementations found online

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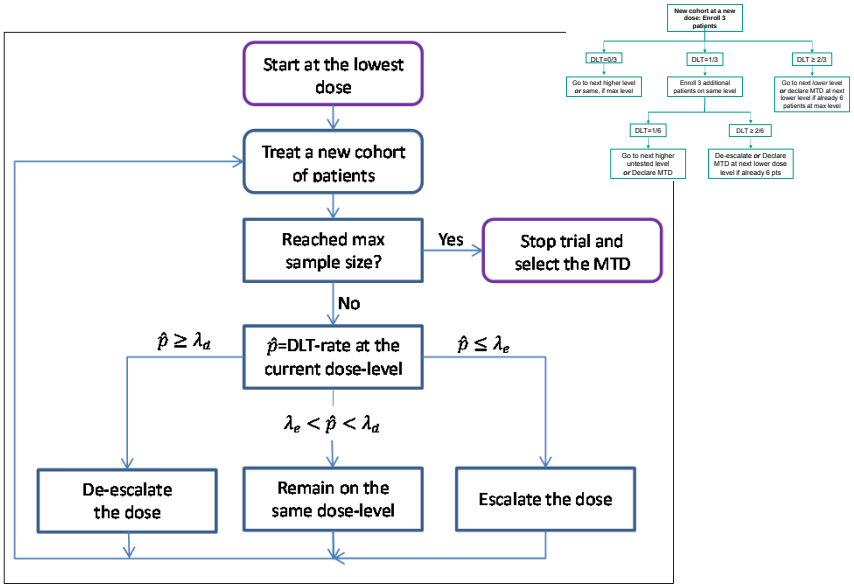
BOIN flow chart



Yuan Y, Hess KR, Hilsenbeck SG & Gilbert MR, Bayesian Optimal Interval Design: A Simple and Well-Performing Design for Phase I Oncology Trials, Clinical Cancer Research, 22 (17); 4291-4301, 2016

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Boundaries

Table 1. Dose escalation and de-escalation boundaries

	Target toxicity rate for the MTD						
Boundary	**0.1**	**0.15**	**0.2**	**0.25**	**0.3**	**0.35**	**0.4**
λ_e (escalation)	0.078	0.118	0.157	0.197	0.236	0.276	0.316
λ_d (de-escalation)	0.119	0.179	0.238	0.298	0.358	0.419	0.479

Table 2. Dose escalation and de-escalation boundaries for target toxicity rate = 30%

	The number of patients treated at the current dose																	
Action	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
Escalate if no. of DLTs ≤	0	0	0	0	1	1	1	1	2	2	2	2	3	3	3	3	4	4
De-escalate if no. of DLTs ≥	1	1	2	2	2	3	3	3	4	4	4	5	5	6	6	6	7	7

Yuan Y, Hess KR, Hilsenbeck SG & Gilbert MR, Bayesian Optimal Interval Design: A Simple and Well-Performing Design for Phase I Oncology Trials, Clinical Cancer Research, 22 (17); 4291-4301, 2016

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Bayesian Optimal Interval Design - BOIN

- Similar to 3+3, but
- Allows flexible cohort sizes
- May allow re-escalation

Yuan Y, Hess KR, Hilsenbeck SG & Gilbert MR, Bayesian Optimal Interval Design: A Simple and Well-Performing Design for Phase I Oncology Trials, Clinical Cancer Research, 22 (17); 4291-4301, 2016

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BOIN(9,48) boundaries - example

Decision, based on the number of patients with DLTs (N_{DLT})	**Number of patients evaluable for DLT at the current dose-level**								
	1	2	3	4	5	6	7	8	9
Escalate if $N_{DLT} \leq$	0	0	0	0	0	1	1	1	1
Remain on dose-level if $N_{DLT} =$	-	-	1	1	1	2	2	2	2,3*
De-escalate if $N_{DLT} \geq$	1	1	2	2	2	3	3	3	4
Disallow dose-level if $N_{DLT} \geq$	NA	NA	≥3	≥3	≥3	≥4	≥4	≥5	≥5

- Trial stops when:
  - the maximum sample size has been reached (*e.g.* N_{max}=48), or
  - there are *n* (*e.g. n*=9) patients evaluable for DLTs on a dose-level, or
  - the lowest dose has been disallowed
- Allows for flexibility in cohort sizes
  - In case of a drop-out: 2 patients, or 5 patients
  - In case of over-recruitment: 4 patients, 7 patients ...

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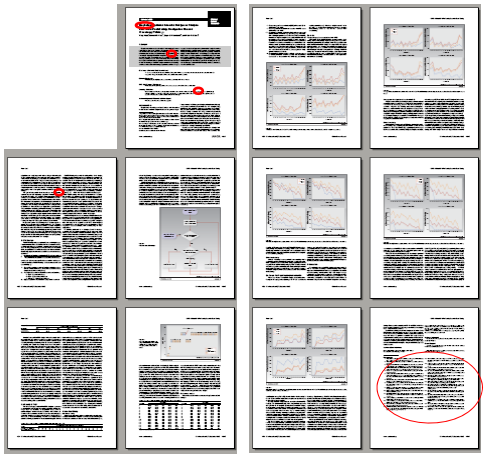
BOIN – Where's the "Bayes"?

Yuan Y, Hess KR, Hilsenbeck SG & Gilbert MR, Bayesian Optimal Interval Design: A Simple and Well-Performing Design for Phase I Oncology Trials, Clinical Cancer Research, 22 (17); 4291-4301, 2016



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Closer look at the BOIN lambdas

- θ=target toxicity level, θ_1= lower boundary, θ_2=upper boundary
- Authors propose, as default, θ_1 =0.6·θ and θ_2=1.4·θ (*e.g.* θ=0.3, θ_1=0.18, θ_2=0.42)
- $\lambda_{e,j} = \frac{log\left(\frac{1-\theta_1}{1-\theta}\right)+n_j^{-1}log\left(\frac{\pi_{1j}}{\pi_{0j}}\right)}{log\left(\frac{\theta(1-\theta_1)}{\theta_1(1-\theta)}\right)}$, $\lambda_{d,j} = \frac{log\left(\frac{1-\theta}{1-\theta_2}\right)+n_j^{-1}log\left(\frac{\pi_{0j}}{\pi_{2j}}\right)}{log\left(\frac{\theta_2(1-\theta)}{\theta(1-\theta_2)}\right)}$
- Let p_j = true toxicity probability for dose-level *j*.
- Formulate 3 hypotheses: H_{0j}: $p_j = \theta$, H_{1j}: $p_j = \theta_1$, H_{2j}: $p_j = \theta_2$, π_{kj}= $Pr(H_{kj})$ *i.e.* the *a priori* probability of hyptothesis *k* being true
- Assign equal *a priori* probabilities: $\pi_{0j} = \pi_{1j} = \pi_{2j} = 1/3$
  - Renders $\lambda_{e,j}$ and $\lambda_{d,j}$ invariant to *j* (the dose level)
  - Renders $\lambda_{e,j}$ and $\lambda_{d,j}$ invariant to n_j (sample size on dose level *j*)

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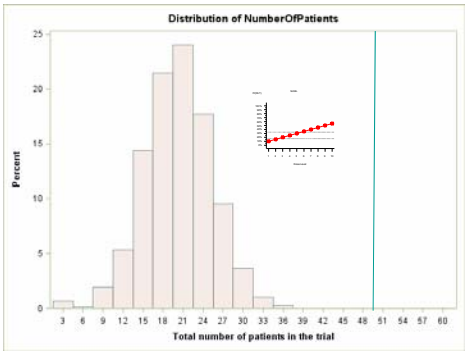
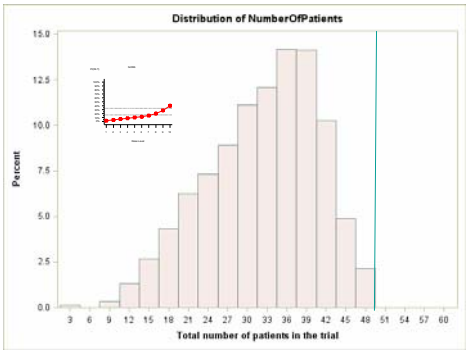
BOIN something about Nmax

- Stopping criterion for the trial
- Allocate enough patients to allow the trial to find MTD





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Software - BOIN

R	BOIN	Developed by authors et al. Implementation includes features not included in the paper, and vice versa. + can handle combination trials.

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Operational characteristics

- Expected total number of patients
- Expected number of cohorts
- Expected Number of DLTs per dose-level
- Estimated MTD

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Some Trial Designs for Next Trial

- 3+3: the standard traditional 3+3 design.
- ATD (accelerated titration design): a version of 3+3
  - Stage 1: Single patient cohorts in first 2 dose levels or until relevant toxicity observed, thereafter Stage 2
  - Stage 2: Standard traditional 3+3
- aBOIN(9,48): Same as BOIN(9,48) except for single patient cohorts in first 2 dose levels
- BOIN(9,48): BOIN that stops after 9 patients on dose-level or 48 patients in Total. Patients allocated in cohorts of 3 patients

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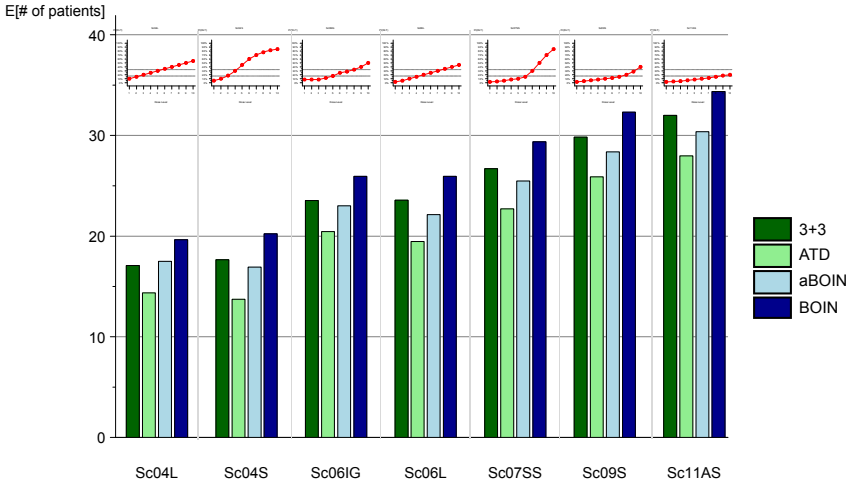
Number of Patients



- "Standard" vs. "accelerated": standard designs (3+3 and BOIN) require 3-4 patients more than accelerated designs (ATD & aBOIN)
- "BOIN" vs. "3+3" : BOIN / aBOIN designs require 2-4 patients more than 3+3 / ATD

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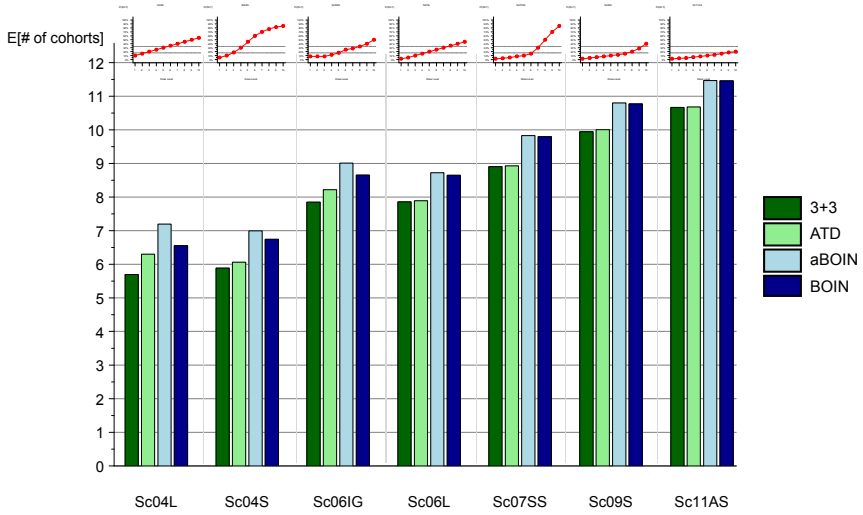
Number of Cohorts

BOIN / aBOIN designs require 0.5-1 cohort more than 3+3 / ATD



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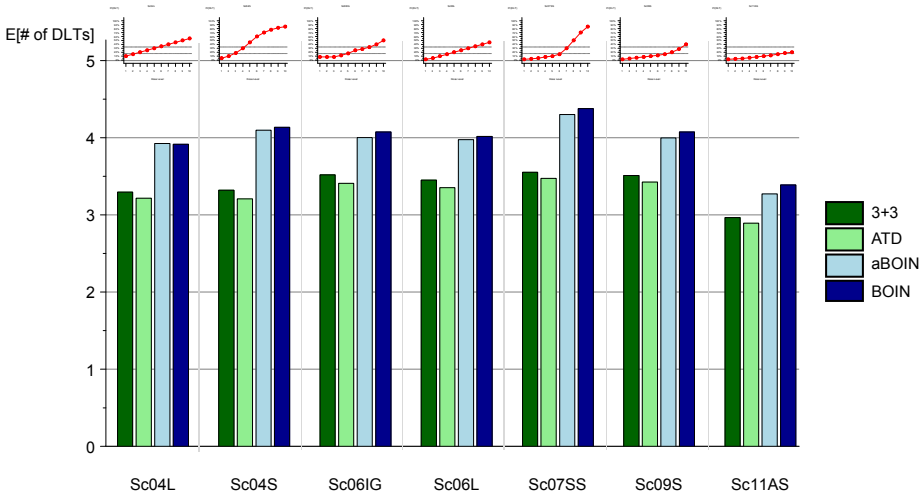
Number of DLTs

0.5-1 more DLTs on BOIN / aBOIN



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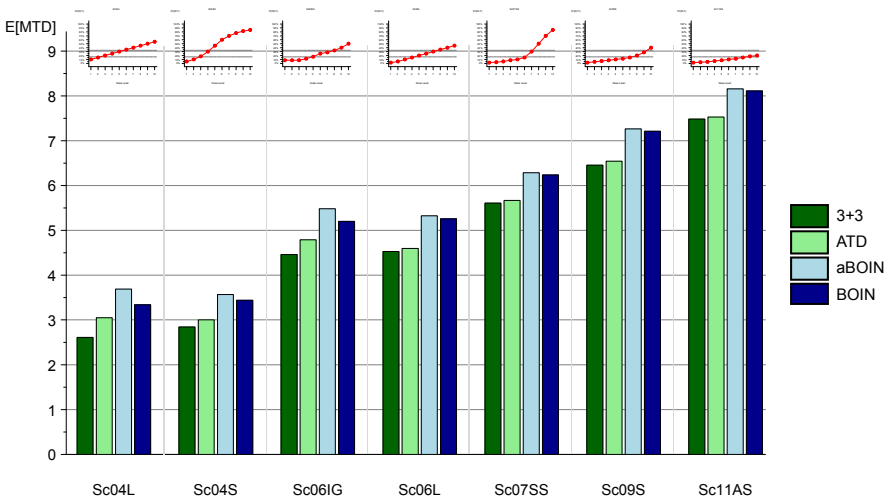
Expected MTD

The MTD on the 3+3s are ~1/2 dose-level lower than the BOINs



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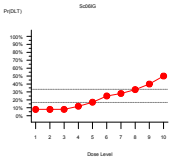
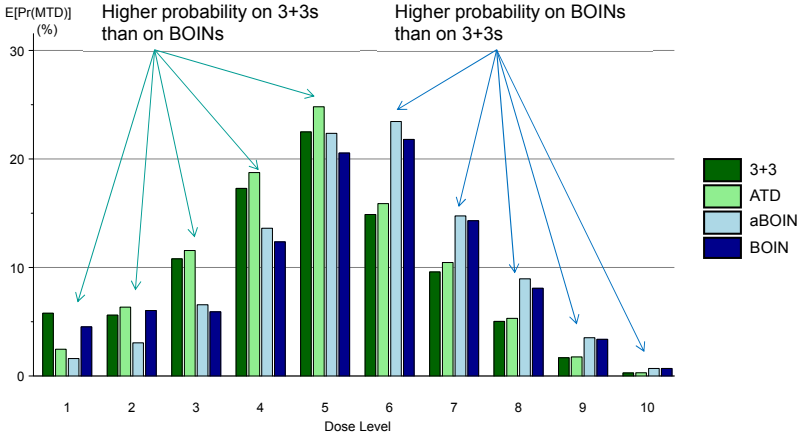
Expected MTD



The 3+3s find MTD earlier than the BOINs



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Comparison of a mCRM, aBOIN(9,48) and ATD: mean number of patients

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In summary

	mCRM	ATD	aBOIN
Estimate of MTD	Estimates *at* or *near* actual MTD.	Under-estimation of MTD by design, not as bad as 3+3.	Estimates *at* or *near* actual MTD.
Number of patients	In line with aBOIN	Smallest sample size, 1-5 patients less than the others	In line with mCRM
Number of patients on different dose levels	More patients on higher (near MTD) dose levels	Stop earlier: more patients on lower dose levels	More patients on higher dose levels
Number of patients with DLT	More patients with DLTs (~1)	Less patients with DLTs	More patients with DLTs (~1)
Pros	Better estimate of MTD (accuracy & precision) Flexibility (cohort sizes may vary) Uses information available before and during trial	Straightforward Nearly memoryless	Better estimate of MTD (accuracy & precision) Flexibility (cohort sizes may vary)
Cons	Can "go wrong"* if not set-up correctly	Rigid "3+3" & more biased and uncertain	

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Thank you!
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