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- Two group problem (patient heterogeneity)

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- Graded toxicities

Extended models / Bayesian model selection

Bayesian model choice/model selection/model adaptive/assessment/diagnostic Refs: Kass and Raftery, Gelfand, Gelfand and Ghosh, others

- Model averaging (Yin and Yuan 2009)
- Patient heterogeneity
- Bridging studies
- Multi-drug problem, partial ordering
- Biologics and targeted agents
- Graded toxicities

Simple extended model for 2-group problem

1. Model 1: $m = 1$

$$\Pr(Y = 1 \mid d_i, z = 0) = \psi(d_i, a)$$
$$\Pr(Y = 1 \mid d_i, z = 1) = \psi(d_i, a)$$

2. Model 2: $m = 2$

$$\Pr(Y = 1 \mid d_i, z = 0) = \psi(d_i, a)$$
$$\Pr(Y = 1 \mid d_i, z = 1) = \psi(d_{i+1}, a)$$

3. Model 3: $m = 3$

$$\Pr(Y = 1 \mid d_i, z = 0) = \psi(d_i, a)$$
$$\Pr(Y = 1 \mid d_i, z = 1) = \psi(d_{i-1}, a)$$

Extended model based designs

- Instead of one working model $\psi(x_j, a)$ we have small family of models; $\psi_m(x_j, a)$ for $m = 1$ to M.
- We might consider

$$\psi_m(d_i, a) = \alpha_{mi}^{\exp(a)}, \quad (i = 1, ..., k; \ m = 1, ..., M)$$

where $0 < \alpha_{m1} < \ldots < \alpha_{mk} < 1$ and $-\infty < a < \infty$, as an immediate generalization of the single model

- $\pi(m), m = 1, \ldots, M$, where $\pi(m) \geq 0$ and where $\sum_m \pi(m) = 1$ could provide priors for the models.

- Likelihood $\mathcal{L}_{mj}(a)$ for model m after j patients is (proportional);

$$\sum_{\ell=1}^{j} y_\ell \log \psi_m(x_\ell, a) + \sum_{\ell=1}^{j} (1 - y_\ell) \log(1 - \psi_m(x_\ell, a))$$

- Obtain $\hat{a}_{mj}$
- Estimate probability of toxicity d_i via:
  $\hat{R}(d_i) = \psi_m(d_i, \hat{a}_{mj}), \quad (i = 1, \ldots, k).$
- Given m, the dose to be given to the $(j+1)$ th patient, x_{j+1} is determined.
- Given Ω_j, posterior model probabilities are:

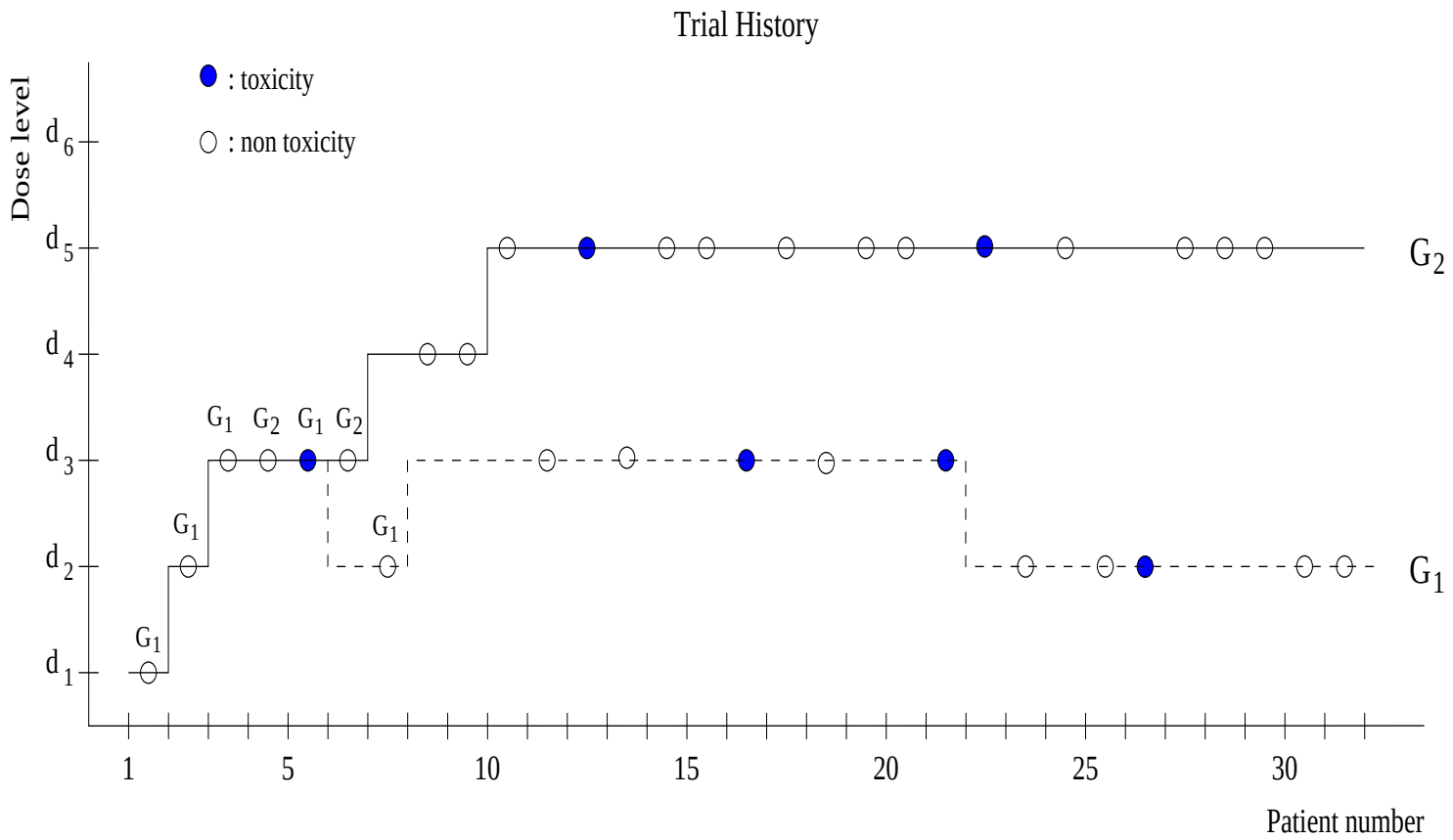
$$\pi(m|\Omega_j) = \frac{\pi(m) \int_{-\infty}^{\infty} \exp\{\mathcal{L}_{mj}(u)\} g(u)\, du}{\sum_{m=1}^{M} \pi(m) \int_{-\infty}^{\infty} \exp\{\mathcal{L}_{mj}(u)\} g(u)\, du}$$

Simple patient heterogeneity: 2 groups

- A dose finding study for breast cancer treatment at UVA CC. to determine the MTD of dasatinib.
- Two groups of patients
  - Dasatinib plus capecitabine for paclitaxel-refractory metastatic breast cancer patients (G1)
  - Dasatinib plus fulvestrant for hormone-sensitive, progressive metastatic breast cancer patients (G2)
- G1 patients are more sensitive to dasatinib and may have a higher probability of toxicity.
- G2 patients may have higher MTD than G1 patients.

Two groups in a single trial, bridging studies

R_1	.02	.19	.31	.45	.51	.63
R_2	.03	.05	.11	.21	.39	.50



Four schemes

1. Two-sample CRM shift design
2. Two-group two-parameter CRM design
3. Two separate studies design
4. One single study design, ignoring the group difference

Target rate =0.20
Δ = 0, 1, or 2

Table: Scenarios of probability of toxicity

Scenario	Gr.i	Probability of toxicity $R_i(d_k)$					
A	1	.07	**.23**	.31	.35	.45	.57
	2	.07	**.23**	.31	.35	.45	.57
B	1	.08	**.20**	.35	.50	.70	.80
	2	.01	.05	**.18**	.40	.55	.70
C	1	.02	**.19**	.31	.45	.51	.63
	2	.03	.05	.11	**.21**	.39	.50

Table: MTD recommendation and in-trial allocation for scenario A

	Group 1						Group 2					
	$d1$	$d2$	$d3$	$d4$	$d5$	$d6$	$d1$	$d2$	$d3$	$d4$	$d5$	$d6$
$R_i(d_k)$	.07	**.23**	.31	.35	.45	.57	.07	**.23**	.31	.35	.45	.57
Proportion of MTD												
Scheme I	.27	**.49**	.19	.04	.00	.00	.12	**.45**	.28	.13	.02	.00
Scheme II	.27	**.47**	.19	.05	.00	.00	.09	**.40**	.29	.16	.04	.00
Scheme III	.22	**.38**	.23	.11	.04	.01	.22	**.39**	.22	.12	.04	.01
Scheme IV	.17	**.51**	.23	.09	.01	.00	.17	**.51**	.23	.09	.01	.00
Proportion of Patients												
Scheme I	.35	**.38**	.19	.06	.02	.00	.19	**.33**	.25	.15	.06	.02
Scheme II	.35	**.33**	.19	.07	.03	.02	.17	**.29**	.26	.15	.08	.03
Scheme III	.31	**.29**	.20	.11	.06	.03	.31	**.29**	.20	.11	.06	.03
Scheme IV	.25	**.37**	.22	.11	.04	.01	.25	**.37**	.22	.11	.04	.01

Table: Recommendation and in-trial allocation for scenario B

	Group 1						Group 2					
	$d1$	$d2$	$d3$	$d4$	$d5$	$d6$	$d1$	$d2$	$d3$	$d4$	$d5$	$d6$
$R_i(d_k)$	.08	**.20**	.35	.50	.70	.80	.01	.05	**.18**	.40	.55	.70
Proportion of MTD												
Scheme I	.18	**.54**	.27	.01	.00	.00	.00	.19	**.61**	.19	.01	.00
Scheme II	.23	**.49**	.26	.01	.00	.00	.00	.12	**.63**	.21	.03	.00
Scheme III	.22	**.47**	.26	.04	.00	.00	.00	.15	**.62**	.21	.02	.00
Scheme IV	.02	**.43**	.53	.03	.00	.00	.02	.43	**.53**	.03	.00	.00
Proportion of Patients												
Scheme I	.24	**.40**	.29	.06	.01	.00	.07	.22	**.43**	.22	.05	.01
Scheme III	.32	**.35**	.25	.05	.02	.01	.06	.17	**.44**	.23	.08	.03
Scheme II	.30	**.33**	.24	.09	.03	.01	.10	.20	**.41**	.20	.07	.02
Scheme IV	.11	**.35**	.42	.09	.02	.01	.11	.35	**.42**	.09	.02	.01

Table: Recommendation and in-trial allocation for scenario C

	Group 1						Group 2					
	$d1$	$d2$	$d3$	$d4$	$d5$	$d6$	$d1$	$d2$	$d3$	$d4$	$d5$	$d6$
$R_i(d_k)$	.02	**.19**	.31	.45	.51	.63	.03	.05	.11	**.21**	.39	.50
Proportion of MTD												
Scheme I	.07	**.47**	.39	.07	.01	.00	.00	.07	.32	**.48**	.12	.01
Scheme II	.11	**.47**	.32	.08	.02	.00	.01	.06	.32	**.38**	.20	.03
Scheme III	.11	**.46**	.34	.07	.01	.00	.00	.04	.30	**.43**	.20	.03
Scheme IV	.01	**.23**	.55	.19	.02	.00	.01	.23	.55	**.19**	.02	.00
Proportion of Patients												
Scheme I	.16	**.38**	.34	.09	.03	.00	.05	.13	.29	**.35**	.15	.03
Scheme II	.23	**.34**	.28	.10	.03	.02	.06	.11	.27	**.30**	.18	.08
Scheme II	.24	**.34**	.25	.10	.05	.02	.10	.14	.26	**.26**	.16	.08
Scheme IV	.08	**.24**	.39	.20	.06	.02	.08	.24	.39	**.20**	.06	.02

Related applications

- Bridging studies
- Several prognostic groups: $\Delta_1, \Delta_2, \Delta_3, \ldots,$
- Several groups, some having known orderings
- Continous prognostic variable broken into classes
- Different treatment schedules
- Schedules $\times$ prognostic groups

Biologics and targeted agents

Suppose that the monotonicity does not hold. In particular suppose that we reach a plateau. Consider 6 dose levels and the following skeletons:

1. $M_1 : \alpha_1 = (0.1,\ 0.2,\ 0.3,\ 0.4,\ 0.5,\ 0.6)$
2. $M_2 : \alpha_2 = (0.1,\ 0.2,\ 0.3,\ 0.4,\ 0.5,\ 0.5)$
3. $M_3 : \alpha_3 = (0.1,\ 0.2,\ 0.3,\ 0.4,\ 0.4,\ 0.4)$
4. $M_4 : \alpha_4 = (0.1,\ 0.2,\ 0.3,\ 0.3,\ 0.3,\ 0.3)$
5. $M_5 : \alpha_5 = (0.1,\ 0.2,\ 0.2,\ 0.2,\ 0.2,\ 0.2)$

noindent Multiple skeletons and model choice solve problem.

Phase I study of a combination

Table: Drug combinations used in Phase 1 trial of Samarium Lexidronam and Bortezomib DLT defined by as a grade 3+ neutropenia (Berenson et al. 2009)

	Drug Combination					
Agent	d_1	d_2	d_3	d_4	d_5	d_6
Sm (mCi/kg)	0.25	0.5	1.0	0.25	0.5	1.0
Bortezomib (mg/m^2)	1.0	1.0	1.0	1.3	1.3	1.3

- We index the models by M where M takes value M_h under the h^{th} possible ordering

$$M_1 : d_1 \to d_2 \to d_3 \to d_4 \to d_5 \to d_6$$
$$M_2 : d_1 \to d_2 \to d_4 \to d_3 \to d_5 \to d_6$$

Set of possible orders of toxicity probabilities

M	Simple Order											
M_1	$R(d_1)$	$\leq$	$R(d_2)$	$\leq$	$R(d_3)$	$\leq$	$R(d_4)$	$\leq$	$R(d_5)$	$\leq$	$R(d_6)$
M_2	$R(d_1)$	$\leq$	$R(d_2)$	$\leq$	$R(d_4)$	$\leq$	$R(d_3)$	$\leq$	$R(d_5)$	$\leq$	$R(d_6)$
M_3	$R(d_1)$	$\leq$	$R(d_2)$	$\leq$	$R(d_4)$	$\leq$	$R(d_5)$	$\leq$	$R(d_3)$	$\leq$	$R(d_6)$
M_4	$R(d_1)$	$\leq$	$R(d_4)$	$\leq$	$R(d_2)$	$\leq$	$R(d_3)$	$\leq$	$R(d_5)$	$\leq$	$R(d_6)$
M_5	$R(d_1)$	$\leq$	$R(d_4)$	$\leq$	$R(d_2)$	$\leq$	$R(d_5)$	$\leq$	$R(d_3)$	$\leq$	$R(d_6)$

Illustration

- $R = (0.04, 0.07, 0.20, 0.35, 0.55, 0.70)$.
- Target toxicity rate $\theta = 0.20$.
- The trial will treat $n = 24$ patients.
- For each ordering, we used the power model,

$$\psi_m(d_i, a) = \alpha_{mi}^{a}; \quad m = 1, \ldots, 5\,; \quad i = 1, \ldots, 6$$

Working Models

Table: Working model for five simple orders

M		Combinations					
		1	2	3	4	5	6
$m = 1$	1-2-3-4-5-6	0.01	0.07	0.20	0.38	0.56	0.71
$m = 2$	1-2-4-3-5-6	0.01	0.07	0.38	0.20	0.56	0.71
$m = 3$	1-2-4-5-3-6	0.01	0.07	0.56	0.20	0.38	0.71
$m = 4$	1-4-2-3-5-6	0.01	0.20	0.38	0.07	0.56	0.71
$m = 5$	1-4-2-5-3-6	0.01	0.20	0.56	0.07	0.38	0.71

Simulation results

Dose	d_1	d_2	d_3	d_4	d_5	d_6	n	tox
$R(d_i)$	0.26	**0.33**	0.51	0.62	0.78	0.86	-	-
Conaway et al.	0.35	**0.52**	0.11	0.02	0.00	0.00	21.3	8.5
POCRM	0.29	**0.50**	0.16	0.04	0.01	0.00	22.0	8.4
CRM	0.27	**0.49**	0.23	0.01	0.00	0.00	22.0	7.9
$R(d_i)$	0.12	0.21	**0.34**	0.50	0.66	0.79	-	-
Conaway et al.	0.07	0.29	**0.42**	0.21	0.01	0.00	25.6	9.0
POCRM	0.02	0.23	**0.55**	0.11	0.10	0.00	26.0	10.0
CRM	0.01	0.18	**0.63**	0.17	0.01	0.00	25.0	7.5
$R(d_i)$	0.04	0.07	0.20	**0.33**	0.55	0.70		-
Conaway et al.	0.00	0.02	0.38	**0.51**	0.08	0.02	28.5	8.8
POCRM	0.00	0.00	0.26	**0.50**	0.23	0.01	29.0	10.8
CRM	0.00	0.01	0.19	**0.67**	0.13	0.00	28.0	8.0
$R(d_i)$	0.01	0.04	0.05	0.17	**0.33**	0.67		-
Conaway et al.	0.00	0.00	0.06	0.25	**0.64**	0.05	29.0	7.8
POCRM	0.00	0.00	0.01	0.29	**0.61**	0.09	29.0	9.4
CRM	0.00	0.00	0.00	0.18	**0.76**	0.06	28.0	6.3
$R(d_i)$	0.01	0.02	0.05	0.15	0.20	**0.33**		-
Conaway et al.	0.00	0.00	0.01	0.04	0.37	**0.59**	26.2	5.8
POCRM	0.00	0.00	0.00	0.20	0.12	**0.68**	27.0	6.4
CRM	0.00	0.00	0.00	0.05	0.26	**0.69**	27.0	4.3

Most successful dose (MSD)

Example in HIV;

1. Treatment over long period.
2. Toxicity is inability to take treatment.
3. Observation window for efficacy comparable to toxicity.
4. Lack of efficacy as bad, possibly worse, than toxicity.

Introduce the following definitions;

1. $R(x_j) = \Pr(Y_j = 1 | X_j = x_j)$
2. $Q(x_j) = \Pr(V_j = 1 | X_j = x_j, Y_j = 0)$
3. $P(d_i) = Q(d_i)\{1 - R(d_i)\}$.

Models

Let; $R(x_j) = E(Y_j|x_j) = \psi(x_j, a)$;
$Q(x_j) = E(V_j|x_j, Y_j = 0) = \phi(x_j, b)$

$P(x_j) = \phi(x_j, b)\{1 - \psi(x_j, a)\}$ and $Q(x) = H\{R(x)\}$

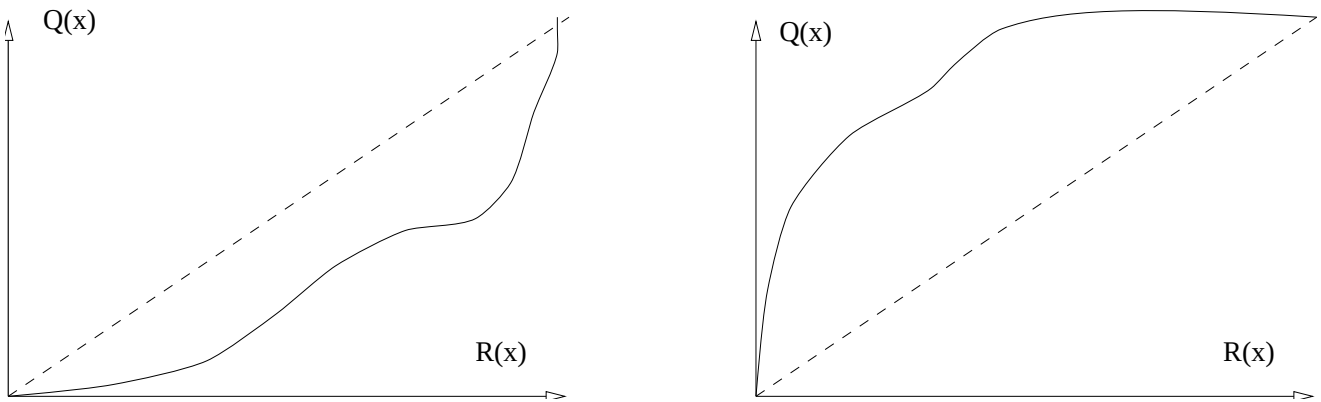


Figure: Possible relationships for $Q(x) = H\{R(x)\}$

Compromise structure

O'Quigley, Hughes and Fenton (*Biometrics* **57**, 1018-29) suggest;

1. Choose, say, $\theta = 0.1$
2. Use SPRT to test $H_0 : P \in (0, 0.7)$ versus $H_1 : P \in (0.7, 1.0)$
3. If SPRT chooses H_0 at d_i then remove levels $d_1, ..., d_i$, and, modify θ to $\theta + \Delta$.

Some simulated situations

	d_1	d_2	d_3	d_4	
R_k	0.06	0.15	0.25	0.30	
Q_k	0.21	0.82	0.80	0.71	Scheme 1
P_k	0.20	0.70	0.60	0.50	
R_k	0.15	0.30	0.40	0.50	
Q_k	0.82	0.71	0.83	0.80	Scheme 2
P_k	0.70	0.50	0.50	0.40	
R_k	0.00	0.05	0.15	0.30	
Q_k	0.10	0.32	0.82	0.71	Scheme 3
P_k	0.10	0.30	0.70	0.50	
R_k	0.00	0.00	0.10	0.15	
Q_k	0.20	0.30	0.56	0.82	Scheme 4
P_k	0.20	0.30	0.50	0.70	

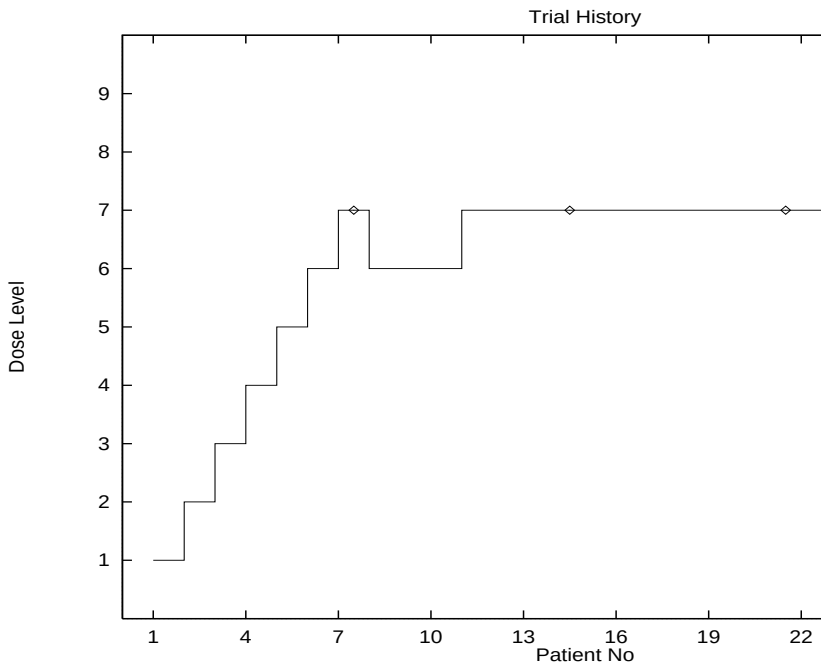
Some simulated situations

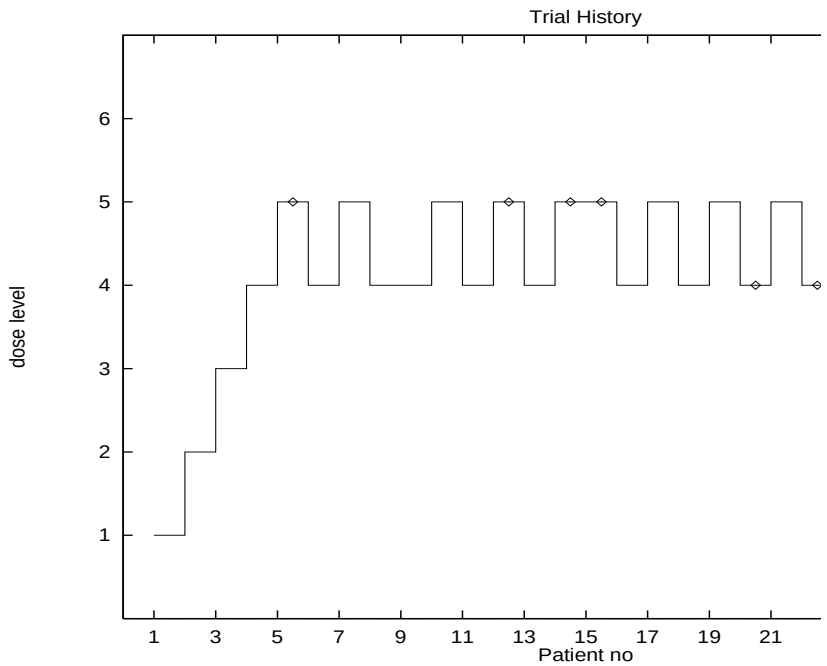
	d_1	d_2	d_3	d_4	
% rec	0.00	0.97	0.03	0.00	Scheme 1
% alloc	0.23	0.75	0.02	0.00	$\bar{n} = 24.9$
% rec	0.96	0.04	0.00	0.00	Scheme 2
% alloc	0.76	0.24	0.00	0.00	$\bar{n} = 21.7$
% rec	0.00	0.01	0.93	0.06	Scheme 3
% alloc	0.06	0.44	0.44	0.06	$\bar{n} = 37.6$
% rec	0.00	0.00	0.12	0.87	Scheme 4
% alloc	0.00	0.37	0.32	0.31	$\bar{n} = 48.5$

Table: Recommendation and in-trial allocation for the 4 schemes

Modification of algorithm

1. Choose level d_j closest to target.
2. Choose level d_j according to some probability mechanism.





Within patient escalation

Patient	level 1	level 2	level 3	level 4	level 5
1	0	1	1		
2		0	1		
3			2		
4				2	3
5				1	4 (DLT)
6				?	

Table: *Acceleration information from graded toxicities. Entries are the grades.*

Some initial escalation schemes

# pats	1	2	3	4	5	6	7	8	9	etc.
3+3	d_1	d_1	d_1	d_2	d_2	d_2	d_3	d_3	d_3	etc.
CRM(2S)	d_1	d_2	d_2	d_3	d_3	d_3	d_4	d_4	d_4	etc.
CRM(G)	d_1	d_2	d_3	d_3	d_4	d_4	d_5	d_5	d_5	etc.

Table: Example of initial escalation stage using acceleration.

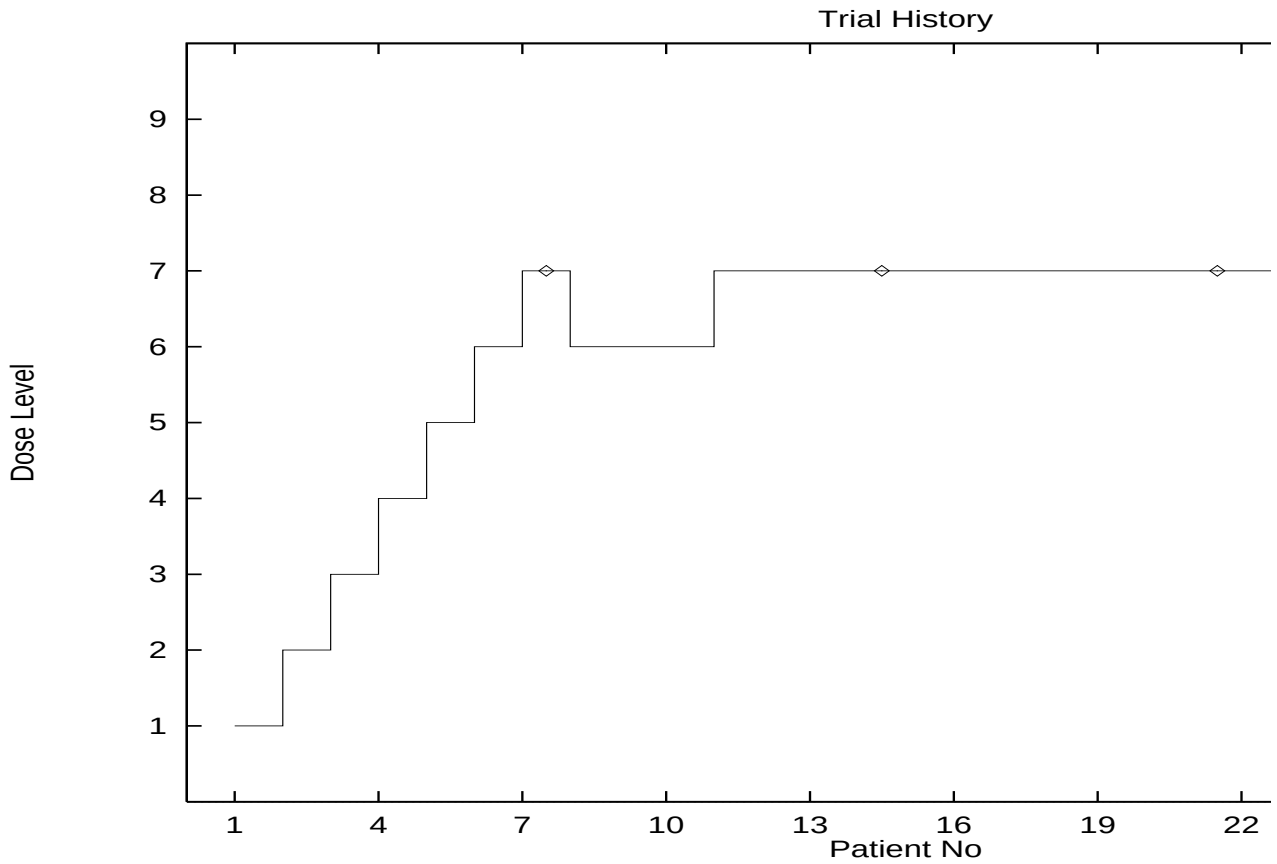
Rapid early escalation using grades

Severity	Degree of Toxicity
0	No toxicity
1	Mild toxicity (non dose-limiting)
2	Non-mild toxicity (non dose-limiting)
3	Severe toxicity (non dose-limiting)
4	Dose limiting toxicity

Table: Toxicity “grades” (severities) for trial.

The rule is to escalate providing $S(i)$ is less than 2. Furthermore, once we have included 3 patients at some level then escalation to higher levels only occurs if each cohort of 3 patients does not experience dose limiting toxicity.

Rapid escalation based on grades



Probability model for grades

- Model $R(d_i)$, the true probability of dose-limiting toxic response for the j^{th} patient via:

$$R(d_i) = \Pr(Y_j = 3|d_i) = \psi(d_i, a) = \alpha_i^a$$

- Model the probability of a grade 2 or grade 3 response by implementing the parameter b:

$$\Pr(Y_j = 2 \text{ or } Y_j = 3|d_i) = \xi(d_i, a, b) = [\alpha_i^a]^b$$

- From which the probability of a grade 2 toxicity is obtained

$$\Pr(Y_j = 2|d_i) = \xi(d_i, a, b) - \psi(d_i, a) = [\alpha_i^a]^b - \alpha_i^a$$

- The probability of a grade 1 toxicity follows:

$$\Pr(Y_j = 1|d_i) = 1 - \xi(d_i, a, b) = 1 - [\alpha_i^a]^b$$

Simulation Results

Table: Compared Frequency of Final Recommendation of a Standard CRM and a Design Using Known Information on Graded Toxicities (θ=0.25, n=25)

	d_1	d_2	d_3	d_4	d_5	d_6
R_k	0.05	0.11	**0.22**	0.35	0.45	0.60
Standard CRM	0.00	0.13	**0.53**	0.30	0.04	0.00
CRM using grades	0.00	0.09	**0.60**	0.29	0.02	0.00

Retrospective analysis

1. What would be estimated MTD had CRM being used instead of 3+3?
2. What happens if we change design half way through study.
3. Bridging designs.
4. Meta-analysis
5. How robust are results to initial choice of model?

Estimating equation in terms of patients

$$U_j(a) = \frac{1}{j}\sum_{\ell=1}^{j}\left\{y_\ell \frac{\psi'}{\psi}(x_\ell, a) + (1 - y_l)\frac{-\psi'}{1-\psi}(x_\ell, a)\right\}.$$

Estimating equation in terms of dose levels

$$U_j(a) = \sum_{i=1}^{k} H\{n_i(j)\}\hat{\pi}_j(d_i)\left[\frac{t_i(j)}{n_i(j)}\frac{\psi'}{\psi}(d_i, a) + \left\{1 - \frac{t_i(j)}{n_i(j)}\right\}\frac{-\psi'}{1-\psi}(d_i, a)\right],$$

- View above as weighted estimating equation.
- Modify estimating equation using inverse probability weighting