Some recent work in dose finding designs

John O'Quigley

Dept of Medical Informatics; Ljubljana, 6 November 2006

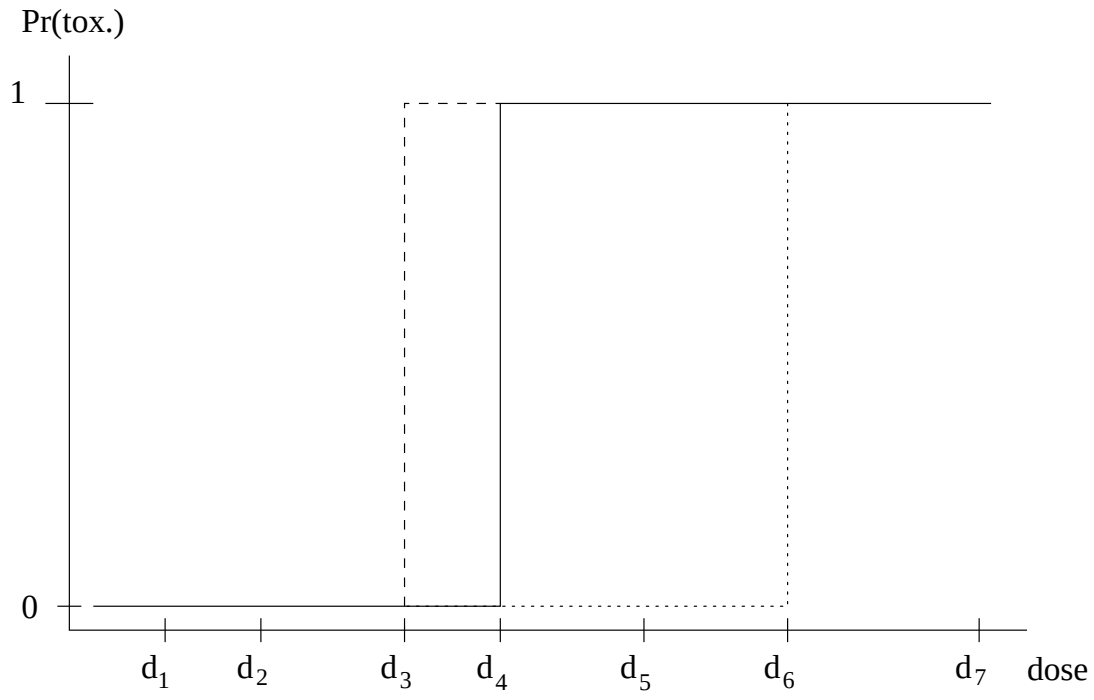


Figure 1: Dose toxicity curve for 3 patients

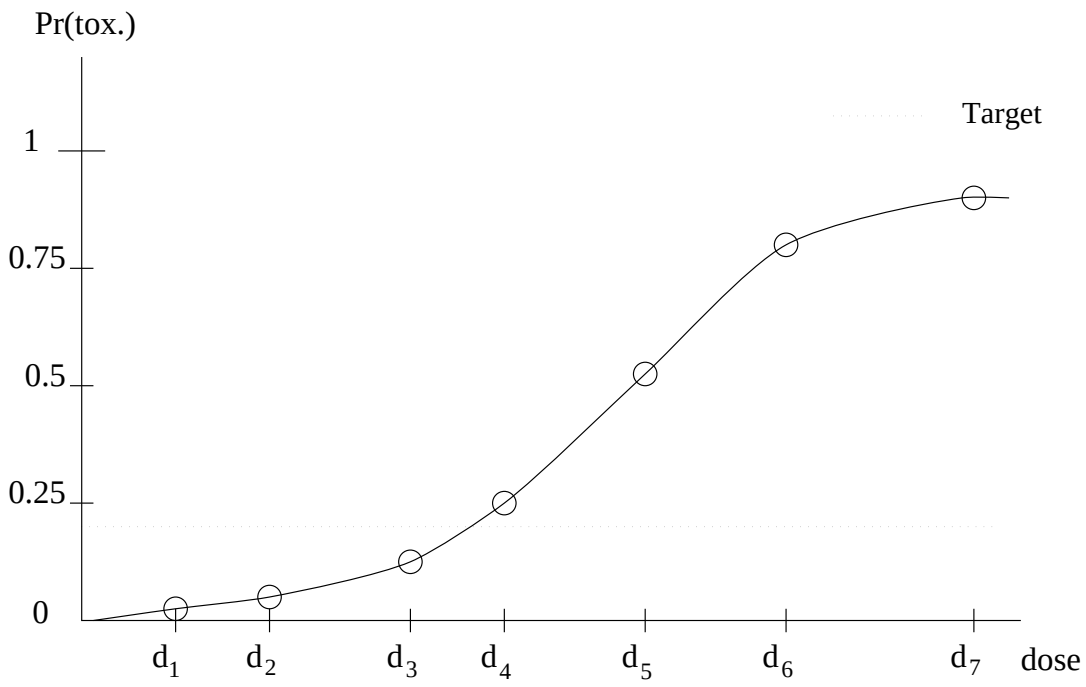


Figure 2: Dose toxicity curve for population

Continual Reassessment Method

1. $\Pr(Y_i = 1 | X_i = d_j) = \psi(d_j, a_j)$
2. Estimate $\hat{a}$ and $\psi(d_j, \hat{a})$
3. Choose d_j such that $\Delta\{\psi(d_j, \hat{a}), \theta\}$ minimized.

Two stage designs

1. Early escalation stage until first DLT.
2. Model driven stage.

Two stage designs using grade

eg. let $S(i)$ to be average toxicity severity at level i.

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 1: Toxicity "grades" (severity) for trial.

The rule is to escalate providing $S(i)$ is less than 2.

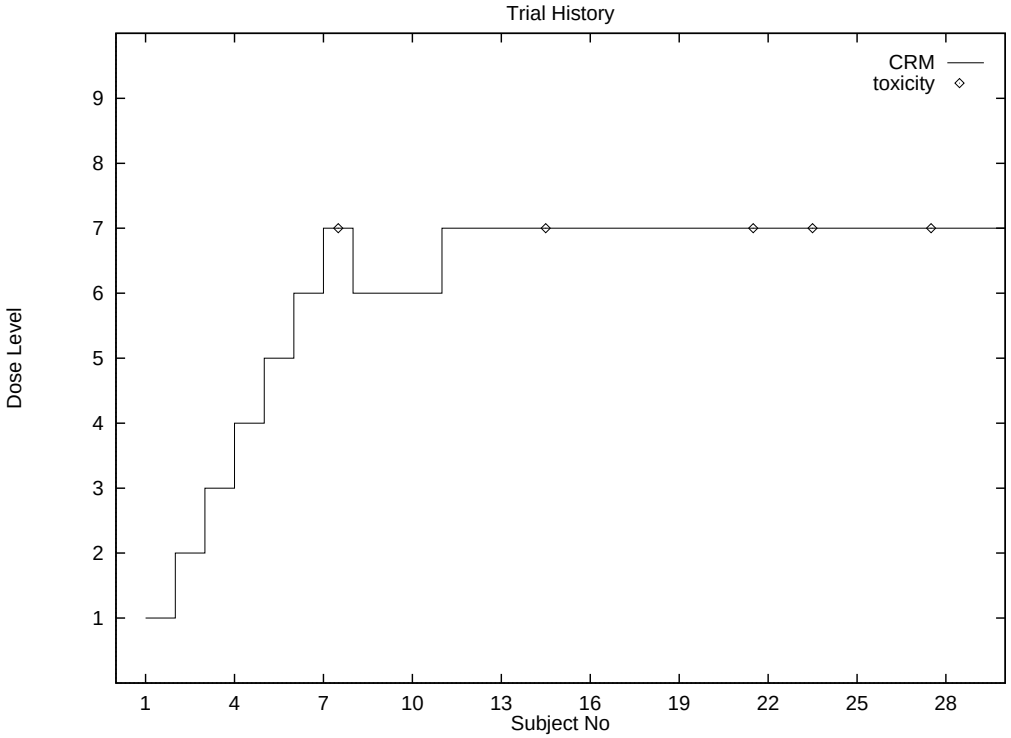
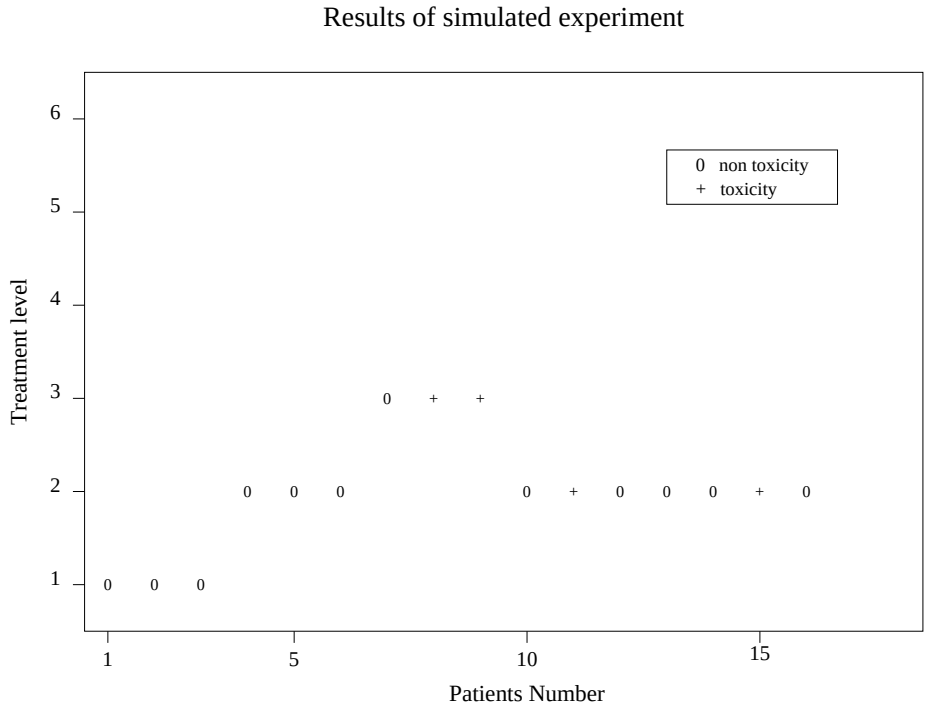


Figure 3: A typical trial history using rapid early escalation; target is level 7.

unknown probabilities at level i						
R_i	.05	.22	.31	.37	.45	.53

recommended level = level 2

$\hat{\psi}(2) = .212$ $\quad$ 90%CI $= (.07, .39)$



Non parametric optimal design

CRM fully efficient for large samples. For finite samples consider;

- Subject h experiences a toxicity at d_5.
- Subject j a non-toxicity at level d_3.

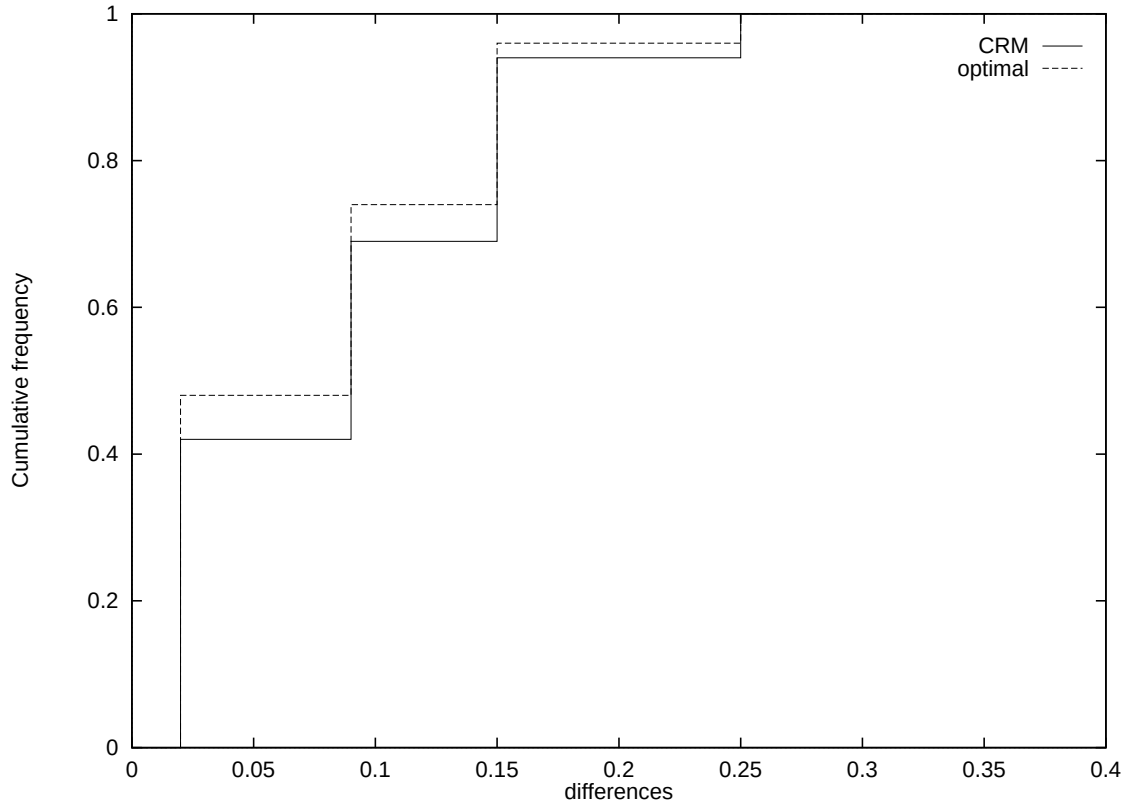
Doses	d_1	d_2	d_3	d_4	d_5	d_6
Observed Y_{hk}	*	*	*	*	1	1
Unobserved Y_{hk}	0	0	1	1	1	1
Observed Y_{jk}	0	0	0	*	*	*
Unobserved Y_{jk}	0	0	0	0	0	1

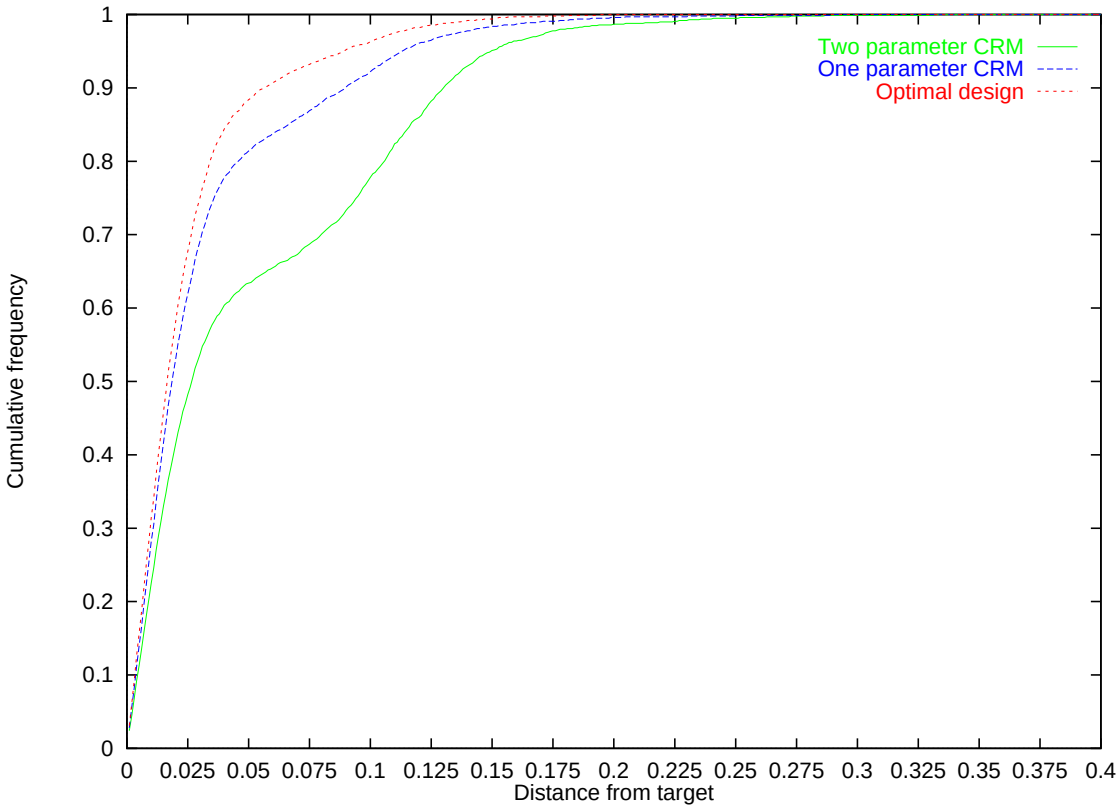
Consider;

Dose	d_1	d_2	d_3	d_4	d_5	d_6
$R_k = \Pr(Y_k = 1)$	0.05	0.11	0.22	0.35	0.45	0.60

Subject j	v_j	s_j	Toxicity at dose level					
			1	2	3	4	5	6
1	.53	6	0	0	0	0	0	1
2	.08	2	0	1	1	1	1	1
3	.29	4	0	0	0	1	1	1
4	.41	5	0	0	0	0	1	1
5	.79	-	0	0	0	0	0	0
6	.04	1	1	1	1	1	1	1
7	.87	-	0	0	0	0	0	0
8	.15	3	0	0	1	1	1	1
9	.63	-	0	0	0	0	0	0
10	.56	6	0	0	0	0	0	1
11	.32	4	0	0	0	1	1	1
12	.72	-	0	0	0	0	0	0
13	.20	3	0	0	1	1	1	1
14	.97	-	0	0	0	0	0	0
15	.52	6	0	0	0	0	0	1
16	.24	4	0	0	0	1	1	1
Frequencies		$\hat{R}_k$	0.06	0.13	0.25	0.44	0.50	0.69
		R_k	0.05	0.11	0.22	0.35	0.45	0.60

d_k	1	2	3	4	5	6
R_k	0.05	0.11	0.22	0.35	0.45	0.60
$p_k(16)$	0.05	0.26	0.42	0.21	0.06	0.0
$q_k(16)$	0.04	0.27	0.48	0.17	0.04	0.0




Two parameter CRM
One parameter CRM
Optimal design
Cumulative frequency
Distance from target
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
0.025
0.05
0.075
0.1
0.125
0.15
0.175
0.2
0.225
0.25
0.275
0.3
0.325
0.35
0.375
0.4

Efficiency measures

Define;

$$\begin{aligned} q_k(n) &= \frac{1}{n} \times \text{ \#choose level } k \text{ for optimal method} \\ p_k(n) &= \frac{1}{n} \times \text{ \#choose level } k \text{ for other method} \end{aligned}$$

then;

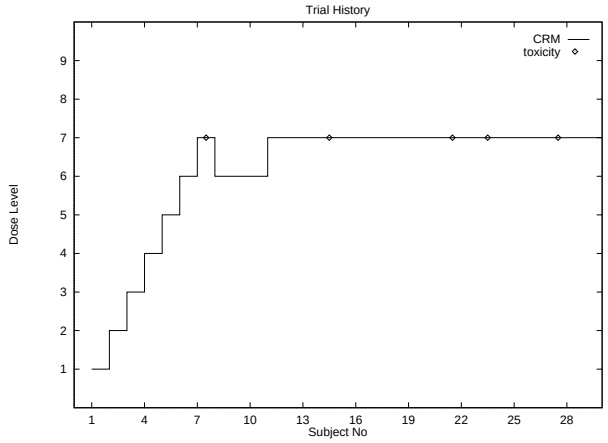
$$e(n) = \frac{\sum_k p_k(n)\, q_k(n)}{\max(\sum_k p_k(n)^2, \sum_k q_k(n)^2)}$$

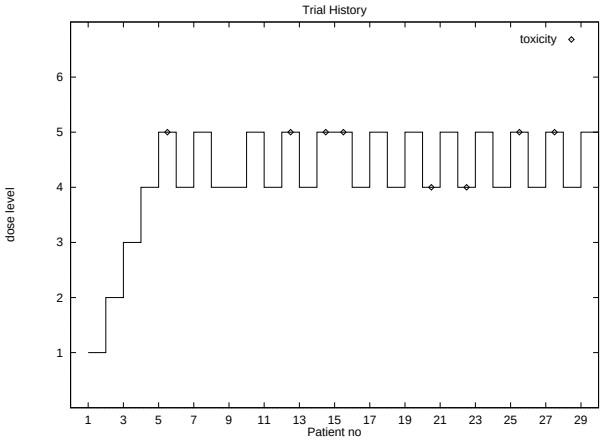
is the efficiency of the reference method.

Average efficiency from $e = \sum_n e(n)\, g(n)$ where $g(n)$ is some chosen distribution on the integers n, most often discrete uniform between values such as 12 and 40

Distance measures

- Overdose control.
- Underdose control.
- Randomization. Choose one of the two levels on the basis of some probability mechanism





More on two stage designs

Additional flexibility of two stage designs enable us to relatively easily;

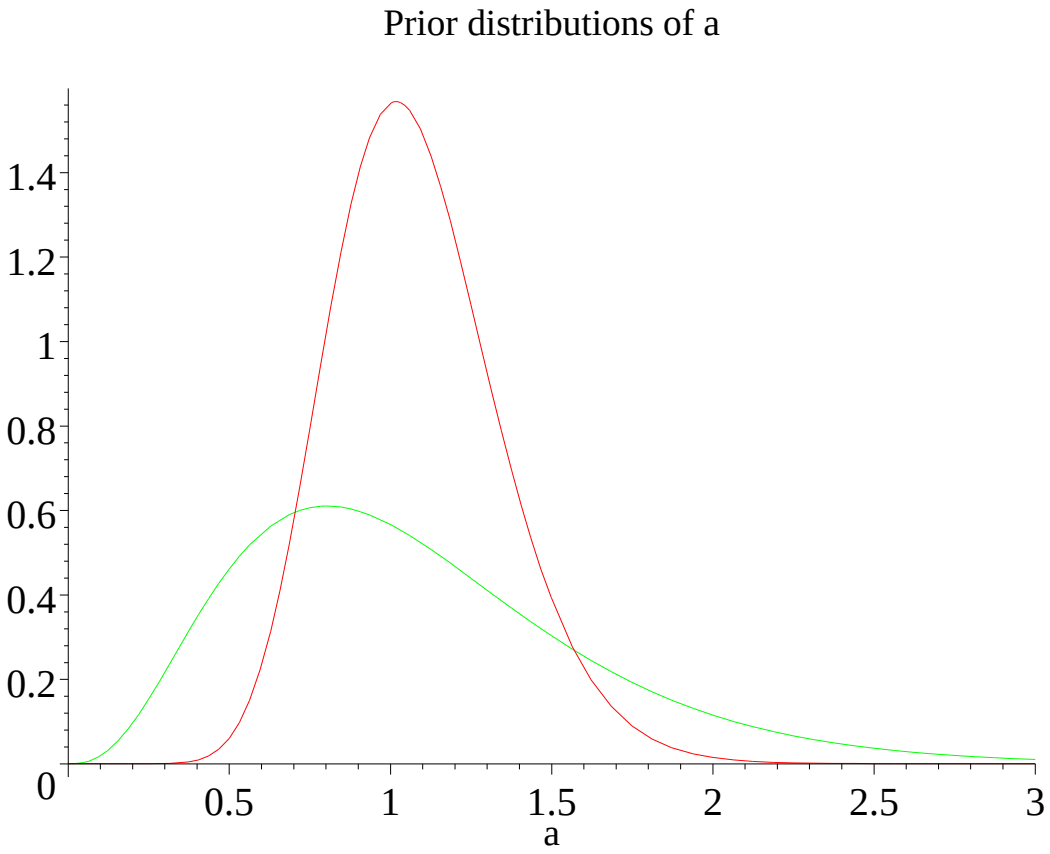
- Mimic standard 3 by 3 design initially.
- Accelerate based on low grade toxicities.
- Establish dose spacing.
- Exploit within patient escalation

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
6				3	

- More efficient escalation in the case of two or many groups.

Bayesian inference

- Can specify toxic probability vector in terms of product of beta priors (Gasparini and Eisele 2000). Equivalent to model based CRM under non informative priors.
- Informative priors difficult generally but can be used to advantage in secondary aspects of problem, eg, ordered groups.
- Drug related toxicities.
- Closely related studies.



Dose finding 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. $P(d_i) = Q(d_i)\{1 - R(d_i)\}$.

Underparameterized models

Let;

1. $R(x_j) = E(Y_j|x_j) = \psi(x_j, a)$
2. $Q(x_j) = E(V_j|x_j, Y_j = 0) = \phi(x_j, b)$
3. $P(x_j) = \phi(x_j, b)\{1 - \psi(x_j, a)\}$
4. $Q(x) = H\{R(x)\}$

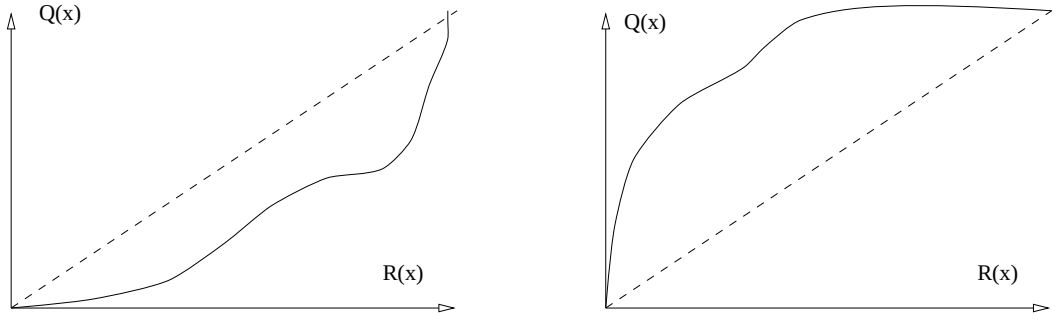


Figure 4: Possible relationships for $Q(x) = H\{R(x)\}$

	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	

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

Table 2: Recommendation and in-trial allocation for the 4 schemes