HW#3

100 simulation trials

(not 1000)

* CRM
* TITE - CRM
* Toxicity interval
* Two agents

$(p_d^0)^{\exp(a)}$: book

$(p_d^0)^{a}$: HW#3

$a \sim Exp(1)$

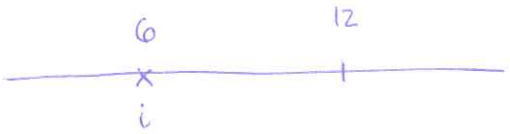
- The exponent should be positive for monotonicity of tox prob. in dose

† Advantages

- Model-based method with clearly defined objective.
- Treat more patients at close to the target MTD level, hence, reduce the number of patients treated at low or ineffective dose levels.
- Use all data to model the dose-toxicity curve.

† Disadvantages

- The dose assignment may be too aggressive.
- The success depends on a proper choice of the dose-toxicity curve $p(d)$ and prior $p(a)$.
- Need special software to implement the design.

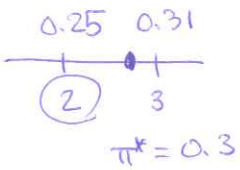


† Modified CRM

Faries (1994, J of Biopharm. Stat); Korn et al (1994, Stat Med); Goodman et al (1995, Stat Med)

- Start at a lowest dose level.
- Do not skip doses. (untried)
- No dose escalation to new patients until all treatment in patients from the previous doses are completed.
- Use asymmetric metrics to determine the current MTD. e.g. the level closest but no higher than the TTL.

$$d^\star(\mathbf{y}) = \max\{d : \mathrm{E}(p(d) \mid \mathbf{y}) \leq \pi^\star\}.$$



- Use cohort size of 2 or 3. $E(p(d) \mid y) \approx \pi^*$
- Add stopping rules. e.g. no more than 2 of 6 developed MTD at given any dose level.

$E(p(d) \mid y)$ is too high for all d

$\Rightarrow$ Stop the trial

† Comparison of the performance of the 3+3 designs and two CRM designs using simulations.

- Methods: 3+3, CRM 1 (with cohort size 1), CRM 3 (with cohort 3)
- Three scenarios with the target MTD 0.30.

  * The true $P(DLT)$ (Assumed, remember no one knows what the truth is like in an actual trial)

Sc	1	2	3	4	5
Sc 1	0.05	0.15	**0.30**	0.45	0.60
Sc 2	0.05	0.10	0.20	**0.30**	0.50
Sc 3	0.15	**0.30**	0.45	0.60	0.85

  * To assess their performance, simulate 1000 trials from the assumed $P(DLT)$

- Evaluation criteria: the percentages of patients treated at the five dose levels, the percentages of trials recommending the true MDT as the MTD.

⋆ Simulation studies for comparing the operating characteristics of the 3+3 designs versus the CRM designs.

		Dose 1	2	3	4	5	Ave N	% DLT
Scenario 1	P(DLT):	0.05	0.15	0.30	0.45	0.60		
3+3	% patients	26.0	32.5	**27.2**	12.1	2.3	15.2	21.1
	% MTD	20.5	42.7	**27.5**	5.7	0		
CRM 1	% patients	15.6	24.1	**34.7**	19.0	6.7	18.5	27.0
	% MTD	1.0	21.4	**52.4**	23.0	2.2		
CRM 3	% patients	21.3	31.4	**29.1**	15.8	2.5	19.0	23.3
	% MTD	1.5	22.6	**49.8**	23.7	2.4		
Scenario 2	P(DLT):	0.05	0.10	0.20	0.30	0.50		
3+3	% patients	21.6	25.7	26.4	**18.9**	7.3	16.9	18.3
	% MTD	9.5	28.5	33	**21.1**	0		
CRM 1	% patients	13.0	13.2	23.3	**30.4**	20.2	18.6	25.7
	% MTD	0.1	6.4	25.6	**49.4**	18.5		
CRM 3	% patients	19.3	19.8	25.2	**25.2**	10.5	19.1	20.8
	% MTD	0.2	5.5	25.4	**48.3**	20.5		
Scenario 3	P(DLT):	0.15	0.30	0.45	0.60	0.85		
3+3	% patients	43.9	**36.4**	16.3	3.2	0.2	11.6	27.0
	% MTD	***65.4***	**27.9**	6.3	0.4	0.0		
CRM 1	% patients	40.5	**35.4**	17.7	6.1	0.3	18.5	28.7
	% MTD	24.5	**52.8**	19.9	2.8	0.1		
CRM 3	% patients	41.5	**39.0**	15.3	4.1	0.1	18.5	27.3
	% MTD	23.6	**53.7**	19.6	3.0	0.1		

† **Summary:** Comparison of the performance of the 3+3 designs and two CRM designs using simulations.

- CRM designs are much more likely to find the true MTD.
- CRM 3 offers protection for just a bit higher Ave N (the number of patients treated in the trial).
- CRM also beats 3+3 when the assigned doses are less and more toxic than anticipated, respectively.

⋆⋆ Exposing patients to overly toxic doses ⇒ remedy: escalation with overdose control (Section 3.2.2)

- What is remaining and what is coming next?
  - ⋆⋆ (3.2.3) Time-to-event (TITE)-CRM: CRM with survival endpoint:
    - Abandon constraint to **binary** endpoint
  - ⋆⋆ (3.2.5) Ordinal toxicity intervals:
    - Abandon constraint to **single** target toxicity
  - ⋆⋆ (3.4.4) Combination therapy: 2 agents
    - ~~Abandon constraint to **monotonicity**~~

Time-to-event.

† TITE-CRM: CRM with survival endpoint

∗ CRM: binary outcome,

- + model robustness— single prob indexes a binary r.v.

  good modeling is more important for design than for data analysis

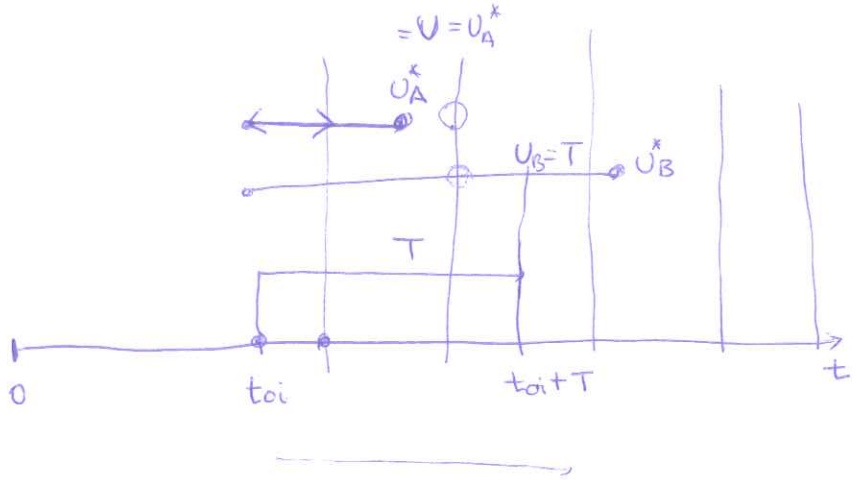
- - limited information and delayed response

  ⋆⋆ delayed response: outcomes that are observed with a substantial time delay after assigning a treatment or enrolling a patient.

  ⋆⋆ Why possibly a problem? It creates challenges when a stopping decision or treatment allocation requires outcomes for earlier enrolled patients.

* Recall CRM: $p(d, a)$ = prob toxicity at dose d given parameter a and y_i = I(toxicity). Then,

$$p(\mathbf{y} \mid a) = \prod_{i=1}^{n} p(d_i, a)^{y_i} \{1 - p(d_i, a)\}^{1-y_i}.$$

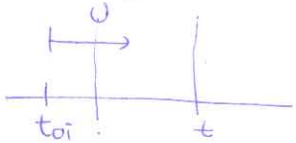


* TITE-CRM: Cheung and Chappell (2000, Biometrics)

** Each patient in a trial remains in the study until the end of follow-up or a toxic response is reported.

- max follow-up time: T
- calendar time: t
- recruitment time: t_{0i}
- time to toxicity outcome truncated by T: U_i, with minimal model assumptions
- $y_i \in \{0, 1\}$: binary outcome with $y_i = 1$ indicating that the survival outcome was observed.

  $\Leftrightarrow \; y_i(t) = \mathrm{I}\{(U_i < T) \text{ and } (t > t_{0i} + U_i)\}$



* TITE-CRM: Cheung and Chappell (2000, Biometrics) — contd

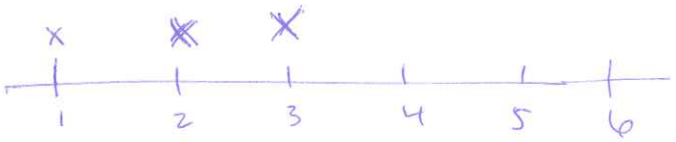
  - For a patient observed (or censored) at time $t_{i0} + u$, let $w_i = \min\{1, u/T\}$ and replace $p(d_i, a)$ by

$$g(d_i, a) \equiv w_i p(d_i, a) = w_i P(y_i = 1 \mid a, d_i).$$

$$\Rightarrow \quad p(\mathbf{y} \mid a) = \prod_{i=1}^{n} g(d_i, a)^{y_i} \{1 - g(d_i, a)\}^{1-y_i}.$$

Justification: for $u < T$,

$$P(U_i \leq u) = \underbrace{P(U_i \leq T)}_{p(d_i, a)} \underbrace{P(U_i \leq u \mid U_i \leq T)}_{\approx w_i = \frac{u}{T}}$$



* **Algorithm 3.4**: TITE-CRM

  - **Step 0. Initialization** $t \equiv 0$, $n \equiv 0$ and cohort size $k = 3$.

  - **Step 1. Initial dose escalation** Start at the lowest dose level and escalate to the next dose only if no toxicity is observed among the previously accrued patients. In this initial design, all patients are completely followed up before admitting a new patient.

    e.g. In a trial, patients are followed for 6 months. Groups of three are admitted at 6–month intervals in the initial design.

    ⋆⋆ Stop if the first toxicity ($U_i \leq T$) is observed or $d = 6$ (max dose).

    ⋆⋆ At the end of the initial escalation change the cohort size to $k = 1$.

* **Algorithm 3.4**: TITE-CRM – contd

- **Step 2. Posterior update** Compute $\bar{a} = \mathrm{E}(a \mid y_1, d_1, \ldots, y_n, d_n)$ based on the pseudo likelihood

$$p(\mathbf{y} \mid a) = \prod_{i=1}^{n} g(d_i, a)^{y_i} \{1 - g(d_i, a)\}^{1-y_i}.$$

- **Step 3. Allocation** Estimate toxicity probabilities $\hat{p}(d, \bar{a}) = d^{\bar{a}}$, and select dose $d^\star = \arg\min |\hat{p}(d, \bar{a}) - p^\star|$.

  e.g. In a trial, patients are followed for 6 months. A trial conducted by the TITE–CRM admits a patient every .5 month.

* **Algorithm 3.4**: TITE-CRM – contd

- **Step 4. Next cohort**

  ⋆⋆ Simulate (when evaluating operating characteristics) OR recruit (when carrying out the trial) the next cohort of k patients, $i = n+1, \ldots, n+k$, allocated at d^*.

  ⋆⋆ Record the recruitment times $t_{0i} = t$.

  ⋆⋆ When *simulating*, generate and save the (future) response time D_i.

  Increment $n \equiv n+k$ and advance the calendar time $t = t+0.5$.

- **Step 5. Stopping** If $n > n_{\max}$, stop and report posterior estimated toxicity probabilities (computed as in Step 2). Otherwise repeat with Step 2.

* Evaluating $\bar{a}$
* Evaluating the posterior expectation as average over a grid:
  - **Posterior expectation:**

$$\bar{a} = \mathrm{E}(a \mid y_1, d_1, \ldots, y_n, d_n) = \int a \times p(a \mid y_1, d_1, \ldots, y_n, d_n) da$$
$$\approx \text{ sum over grid.}$$

  - **Grid:** $(a_1, \ldots, a_M)$ with $M = 50$, $a_1 = 0.01$ and $a_M = 7.0$
  - **Posterior:** Evaluate the pointwise posterior

$$p(a_m \mid \mathbf{y}) \propto \exp\{\ell(a_m) + \log p(a_m)\},$$

with $\log p(a_m) = -a_m$.

* Evaluating $\bar{a}$

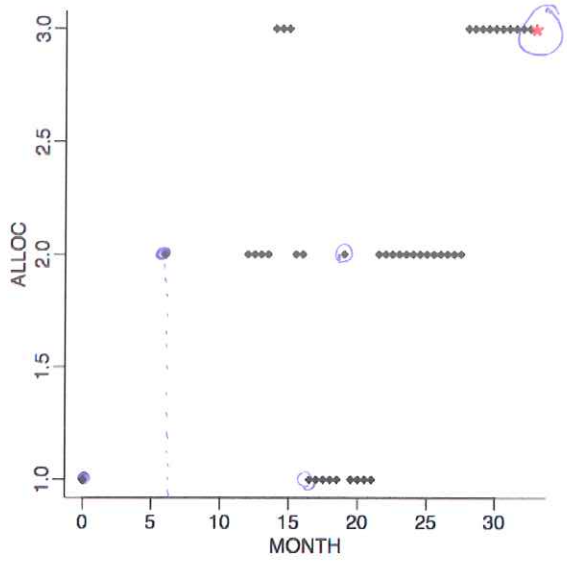
  - **Log Likelihood:** Let $w_{ti} = \min\{1, (t - t_{0i})/T\}$ and $y_{ti} = \mathsf{I}\{(U_i = T) \cap (t > t_{0i} + U_i)\}$.

$$\begin{aligned} \ell(a_m) &= \log p(\mathbf{y} \mid a = a_m) \\ &= \sum_{i|y_i=1} \log\{w_{ti} p(d_i \mid a = a_m)\} \\ &\quad + \sum_{i|y_i=0} \log\{1 - w_{ti} p(d_i \mid a = a_m)\}, \end{aligned}$$

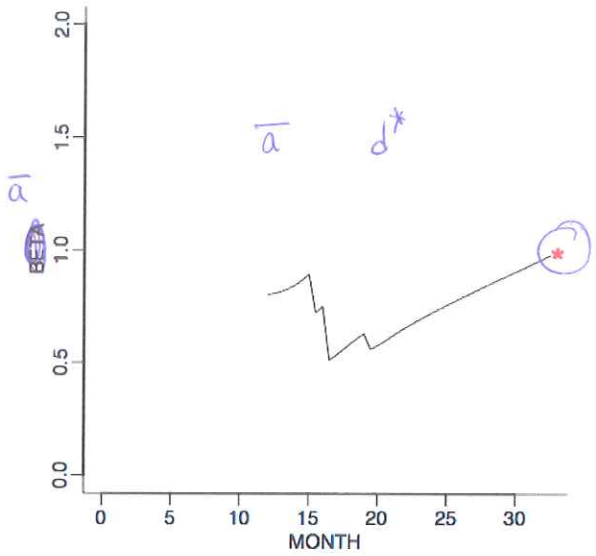
* **Evaluate:** $\bar{a} \approx \sum_m a_m p(a_m \mid \mathbf{y}) / \sum_m p(a_m \mid \mathbf{y})$.

* Example: TITE-CRM Cheung and Chappell (2000, Section 5)
  - **Simulation truth:**
    $p^o = 0.05, 0.1, \mathbf{0.2}, 0.3, 0.5, 0.7$ for $d = 0.05, 0.1, 0.2, 0.3, 0.5, 0.7$,
    i.e., CRM model with $a = 1$.
  - **Target:** $p^\star = 20\%$
  - **Initial dose escalation:** first two cohorts $t = 0$ and 6.
  - **Posterior updating:** starting with $t = 12$

* Example: TITE-CRM Cheung and Chappell (2000, Section 5)



(a) Allocation d^* by t



(b) Estimate θ by t

* Ordinal Toxicity Intervals (BCLM 3.2.5)
* Neuenschwander et al (2008 StatMed)
  - The assumption that a single target toxicity exits and can be reliably identified by the investigator is *unrealistic*.
  - **Toxicity probability intervals:** Replace unrealistic *single* target toxicity by intervals for $p_i = Pr(\text{Tox at dose } i)$, $i = 1, \ldots, m$.
  - Let $\bar{p}_i$ denote the posterior probability of a DLT at dose i. Classify the probability of a DLT into four categories;
    ** Under-dosing: $\bar{p}_i \in [0, 0.20]$ (I_U)
    ** Targeted toxicity: $\bar{p}_i \in (0.20, 0.35]$ (I_T)
    ** Excessive toxicity: $\bar{p}_i \in (0.35, 0.60]$ (I_E)
    ** Unacceptable toxicity: $\bar{p}_i \in (0.60, 1.00]$ (I_A)