# Up-and-down designs for Phase I trials: An evaluation of different designs and estimator

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# Outline

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   - Comparison of Designs

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- A clinical trial is just one step in a long and careful research process that usually starts with an original scientific idea and may end with a new treatment or drug.
- Clinical trial is a type of research study that tests an Investigational New Drug (IND) or method to see how well it works on people.

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- Medical Dictionary Definition: studies, involving patients, aimed at finding better ways to prevent, detect, diagnose, or treat cancer.
- Biology Dictionary Definition: The experimental administration of new drugs or medical therapies to human patients in tightly controlled settings, to find out if there are any unexpected harmful side effects, before making the new drug or therapy available to the general population.

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- If possible, phase I studies are used to determine how effective the drug is.
- Phase I studies are usually conducted on 20 to 80 subjects.

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- If unacceptable side effects are not seen in the first patient, the next patient gets a higher dose.
- This continues until a dose is reached which is too toxic, then the next patient gets a lower dose.

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- Up-and-down designs have been proposed to govern the assignment of patient to a suitable dose level in order to balance the ethical consideration and efficient of estimation of MTD.
- There are several up-and-down designs available in the literature and each of them has its own merit.

# Notations

| | |
|---|---|
| $K$ | number of dose levels |
| $N$ | total number of subjects |
| $\mu$ | the maximum tolerated dose (MTD) |
| $\Gamma$ | $\Pr(Y=1\|\mu)$ (in phase I trials in oncology $\Gamma$ is usually 0.2 or 0.3) |
| $d_j, j=1,\ldots,K$ | the set of ordered dose levels |
| $Y(n), n=1,\ldots,N$ | outcome for the $n$-th subject (1 or 0) |
| $D(n), n=1,\ldots,N$ | dose assignment for the $n$-th subject |
| $Q(d_j), j=1,\ldots,K$ | $\Pr(Y=1\|d_j)$, a nondecreasing function of dose |
| $X_j(n)$ | number of toxic response at dose $d_j$ including the $n$-th patient |
| $N_j(n)$ | number of assignments to dose $d_j$ including the $n$-th patient |

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- four per dose ($k = 4$) if $\Gamma = 0.15$ etc.

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- where $k$ is the solution of $\Gamma = 1 - 0.5^{1/k}$.

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- Go to the next higher dose level if no toxicity in the group is observed.
- Stop after the first toxicity, go to the next lower level and revert to the primary design.

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- A Bayesian designs for phase I clinical trial, the continual reassessment method, was proposed by O'Quigley, Pepe and Fisher (1990, Biometrics).
- The restricted CRM suggested by Faries (1994, J Biopharm Stat) and Korn *et al.* (1994, Stat Med) to avoid a rapid escalation of the dose by prohibited the skipping of a dose level.
- We choose a simple one-parameter dose-response model as the working model for the CRM

$$\Pr(Y = 1 | d_j, a) = \left( \frac{\tanh d_j + 1}{2} \right)^a .$$

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- Assume that $n$ patients have been assigned so far and the $n$-th subject was allocated to level $d_j$, $j = 1, \ldots, K$.
- After observing the toxic response from the $n$-th patient, we have the data

$$\Omega_n = \{(D(1), Y(1)), \ldots, (D(n), Y(n))\}$$

and the likelihood function is

$$L_{\Omega_n}(a) = \prod_{j=1}^{n} [\Pr(Y = 1|d_j, a)]^{Y(j)} [1 - \Pr(Y = 1|d_j, a)]^{1-Y(j)} .$$

# Continual Reassessment Method (CRM)

- The posterior density of $a$ given $L_{\Omega_n}(a)$ can be computed as

$$f(a|L_{\Omega_n}) = \frac{L_{\Omega_n}(a)g(a)}{\int_0^\infty L_{\Omega_n}(u)g(u)du},$$

and the posterior mean is

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- The dose-response probabilities can be updated as $\Pr(Y = 1|d_j, \hat{a}_n)$. According to the restricted CRM, the $(n+1)$-th patient is assigned to one of the dose level $d_i$ such that $|\Pr(Y = 1|d_i, \hat{a}_n) - \Gamma|$, $i = j-1, j, j+1$ is minimized.

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- Empirical mean estimator which the (N+1)-th dose assignment is taken into account:

$$\hat{\mu}_1 = \frac{1}{N - r + 2} \sum_{i=r}^{N+1} D(i),$$

here $r$ is the first subject in the design stage.

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- Estimators based on isotonic regression:
  - $\hat{Q}(d_1), \hat{Q}(d_2), \ldots, \hat{Q}(d_h)$ may not be isotonic
  - The pool adjacent violators algorithm (PAVA) is used to adjust $\hat{Q}$'s to obtain $\hat{Q}^*(d_1) \leq \hat{Q}^*(d_2) \leq \ldots \leq \hat{Q}^*(d_h)$.

# Isotonic Regression Estimators

We can use linear interpolation and denoting the estimator

$$\hat{\mu}_{2(linear)} = d_m + \frac{\Gamma - \hat{Q}^*(d_m)}{\hat{Q}^*(d_{m+1}) - \hat{Q}^*(d_m)}(d_{m+1} - d_m),$$

or logistic type interpolation and denoting the estimator

$$\hat{\mu}_{2(logit)} = d_m + \frac{logit(\Gamma) - logit[\hat{Q}^*(d_m)]}{logit[\hat{Q}^*(d_{m+1})] - logit[\hat{Q}^*(d_m)]}(d_{m+1} - d_m)$$

where $\hat{Q}^*(d_m) < \Gamma \leq \hat{Q}^*(d_{m+1})$ and $logit(Z) = \log \frac{Z}{1-Z}$.

# Isotonic Regression Estimators

- Based on linear interpolation, we proposed the estimator (ISLIN) :

$$\hat{\mu}_{2a} = \begin{cases} d_1, & \text{if } \Gamma < \hat{Q}^*(d_1), \\ d_h, & \text{if } \Gamma > \hat{Q}^*(d_h), \\ \hat{\mu}_{2(linear)}, & \text{otherwise.} \end{cases}$$

- Based on linear interpolation, we proposed the estimator (ISLOG):

$$\hat{\mu}_{2b} = \begin{cases} d_1, & \text{if } \Gamma < \hat{Q}^*(d_1), \\ d_h, & \text{if } \Gamma > \hat{Q}^*(d_h), \\ \hat{\mu}_{2(linear)}, & \text{if } \hat{Q}^*(d_m) < \Gamma \leq \hat{Q}^*(d_{m+1}), \\ & \hat{Q}^*(d_m) = 0 \text{ or } \hat{Q}^*(d_{m+1}) = 1, \\ \hat{\mu}_{2(logit)}, & \text{otherwise.} \end{cases}$$

# Maximum Likelihood Estimator (MLE)

- Consider the two-parameter logistic model for dose-toxicity function

$$Q(d_j, a, b) = \frac{\exp(a + bd_j)}{1 + \exp(a + bd_j)}, \quad j = 1, 2, \ldots, K.$$

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- To ensure the existence of the MLE of $a$ and $b$, the data are augmented by adding two observations so that the fitted probability shrinks towards $\Gamma$ by Clogg's correction (Clogg *et al.*, 1991).
- Denote the resulting $\hat{Q}$'s after Clogg's correction by $\hat{Q}_c(d_1), \hat{Q}_c(d_2), \ldots, \hat{Q}_c(d_h)$.

# Maximum Likelihood Estimator (MLE)

Then the MLE of $\mu$ is given by

$$\hat{\mu}_3 = \begin{cases} d_1 & \text{if } \hat{\mu}'_3 < d_1, \\ d_K & \text{if } \hat{\mu}'_3 > d_K, \\ \hat{\mu}'_3 & \text{otherwise.} \end{cases}$$

where $\hat{\mu}'_3 = \dfrac{\log\left(\frac{\Gamma}{1-\Gamma}\right) - \hat{a}}{\hat{b}}$.

## Modified Maximum Likelihood Estimator (MMLE)

- Since $\hat{Q}_c(d_1), \hat{Q}_c(d_2), \ldots, \hat{Q}_c(d_h)$ may not be isotonic, so we suggest to apply the PAVA before computing the MLE of $a$ and $b$,

## Modified Maximum Likelihood Estimator (MMLE)

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- Compute the MLE based on $\hat{Q}_c^*(d_1) \leq \hat{Q}_c^*(d_2) \leq \ldots \leq \hat{Q}_c^*(d_h)$, the resulting MLE's are, say $\hat{a}^*$ and $\hat{b}^*$:

$$\hat{\mu}_4 = \begin{cases} d_1, & \text{if } \hat{\mu}_4' < d_1, \\ d_K, & \text{if } \hat{\mu}_4' > d_K, \\ \hat{\mu}_4', & \text{otherwise.} \end{cases}$$

where $\hat{\mu}_4' = \frac{\log\left(\frac{\Gamma}{1-\Gamma}\right) - \hat{a}^*}{\hat{b}^*}$.

# Illustrative Example

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- The simulated observations are based on the logistic model $Q(d_j) = \frac{\exp(a+bd_j)}{1+\exp(a+bd_j)}$ with $a = -6$ and $b = 1$.

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- $\Gamma = 0.3$ ($k = 2$), $K = 11$ and $N = 15$, Narayana design is used
- The simulated observations are based on the logistic model $Q(d_j) = \frac{\exp(a+bd_j)}{1+\exp(a+bd_j)}$ with $a = -6$ and $b = 1$.
- The true value of $\mu$ is 5.1527.

# Illustrative Example

| $n$ | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| $D(n)$ | 1 | 1 | 2 | 2 | 3 | 3 |
| $Y(n)$ | 0 | 0 | 0 | 0 | 1 | 0 |

| $n$ | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 (if we have) |
|---|---|---|---|---|---|---|---|---|---|---|
| $D(n)$ | **2** | **3** | **3** | **4** | **5** | **6** | **5** | **4** | **5** | **4** |
| $Y(n)$ | **0** | **0** | **0** | **0** | **0** | **1** | **1** | **0** | **0** | |

Empirical Mean Estimators: $r = 7$,

$$\hat{\mu}_1 = \frac{1}{10}(2+3+3+4+5+6+5+4+5+4) = 4.10$$

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| $j$ | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| $\hat{Q}(d_j)$ | 0.0000 | 0.0000 | 0.2500 | 0.0000 | 0.3333 | 1.0000 |
| $\hat{Q}^*(d_j)$ | 0.0000 | 0.0000 | 0.1250 | 0.1250 | 0.3333 | 1.0000 |
| $\hat{Q}_c(d_j)$ | 0.0353 | 0.0353 | 0.2559 | 0.0353 | 0.3294 | 0.9176 |
| $\hat{Q}_c^*(d_j)$ | 0.0353 | 0.0353 | 0.1456 | 0.1456 | 0.3294 | 0.9176 |

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| $\hat{Q}_c^*(d_j)$ | 0.0353 | 0.0353 | 0.1456 | 0.1456 | 0.3294 | 0.9176 |

- Isotonic Regression Estimators: $m = 4$ since $\hat{Q}^*(d_4) < 0.3 < \hat{Q}^*(d_5)$,

$$\hat{\mu}_{2a} = 4 + \frac{0.3 - 0.125}{0.333 - 0.125} = 4.84,$$

$$\hat{\mu}_{2b} = 4 + \frac{logit(0.3) - logit(0.125)}{logit(0.333) - logit(0.125)} = 4.877.$$

# Illustrative Example

- Maximum Likelihood Estimator Based on $\hat{Q}_c(d_j)$, $j = 1, \ldots, 6$, we computed the MLE of $a$ and $b$ as -5.391 and 1.065, respectively,

$$\hat{\mu}_3 = \frac{\log(\frac{0.3}{0.7}) + 5.391}{1.065} = 4.266.$$

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- Modified MLE Based on $\hat{Q}^*_c(d_j)$, $j = 1, \ldots, 6$, we computed the MLE of $a$ and $b$ as -5.876 and 1.171, respectively

$$\hat{\mu}_4 = \frac{\log(\frac{0.3}{0.7}) + 5.876}{1.171} = 4.296.$$

# Monte Carlo Simulation Study

Dose-response curves

$$Q(d_j, a, b) = H(a + bd_j), \quad j = 1, 2, \ldots, K,$$

where $H(\cdot)$ is a monotone function which is twice differentiable.

# Monte Carlo Simulation Study

- The following models are used in the simulation study:
  - Logistic:

$$H(x) = \frac{\exp(x)}{1+\exp(x)}.$$

  - Extreme-value:

$$H(x) = 1 - \exp\left[\exp(x)\right].$$

  - Probit:

$$H(x) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{x} \exp\left(-\frac{u^2}{2}\right)\, du.$$

  - Generalized Logistic:

$$H(x) = \left[\frac{\exp(x)}{1+\exp(x)}\right]^{\alpha}, \alpha > 0.$$

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- $a = -6.0, b = 1.0$; $a = -4.5, b = 0.5$, $a = -3.0, b = 0.5$, $a = -6.0, b = 0.5$, $a = -1.5, b = 0.25$
- For the CRM, we considered the dose levels $d'_j$, where $d'_j = (a - 3) + bd_j$.
- Dose levels: $K = 11$, $d_j = j, j = 1, 2, \ldots, 11$.
- Sample sizes: $N = 15, 25, 35$ and $50$.
- Target toxicity: $\Gamma = 0.15, 0.2, 0.3$ and 0.5.
- Number of simulations: In each scenarios, we simulated $M = 10,000$ times.

# Results and Discussions

## Comparison of Estimators

- Bias (BIAS) and Mean Squared Error (MSE)

$$\text{Bias} = \frac{1}{M}\sum_{i=1}^{M}\hat{\mu}^{(i)} - \mu,$$

$$\text{MSE} = \frac{1}{M}\sum_{i=1}^{M}(\hat{\mu}^{(i)} - \mu)^2,$$

where $\hat{\mu}_i, i = 1, \ldots, M$ are the resulting estimates of $\mu$ in each simulation.

# Comparison of Estimators

- Bias (T-BIAS) and Mean Squared Error (T-MSE) of probability of toxicity at target dose

$$\text{T-Bias} = \frac{1}{M}\sum_{i=1}^{M}\left[Q(\hat{\mu}^{(i)},a,b)-\Gamma\right],$$

$$\text{T-MSE} = \frac{1}{M}\sum_{i=1}^{M}\left[Q(\hat{\mu}^{(i)},a,b)-\Gamma\right]^2,$$

where $\hat{\mu}_i, i=1,\ldots,M$ are the resulting estimates of $\mu$ and $Q(\hat{\mu}^{(i)},a,b)$ is the true probability of toxicity at $\hat{\mu}^{(i)}$ (assume that we know the underlying dose-response curve) in each simulation.

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- Even the underlying does-response curves are not logistic, the parametric estimators (MLE and MMLE) which assumed the does-response curves to be logistic perform well.

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- ISLOG perform better than the MMLE in a few scenarios
- For large sample sizes, the performance of MLE and MMLE are very close.
- Overall speaking, MMLE is a better estimator.

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- If we do not go into the design stage (all subjects are in start-up), this quantity will equal to 0, therefore, we will not take these cases into account.

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We divided the dose-response curves considered in the simulation study into three groups by the location of the true MTD:

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- In terms of TOX, it is clear that BCD give the lowest average proportion of toxic responses and the average proportion of toxic responses of NAR and RNAR are higher than BCD and lower than KROW and CRM.
- Avoiding overdose: BCD is the best choice although one may suffer from a lost of efficient in estimation of MTD.

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- From estimation point of view:
  - CRM outperform the other designs in general for $\Gamma = 0.15$ and 0.2.
  - $\Gamma$ = 0.3 and 0.5, NAR and RNAR are better designs to use.
- Balance between estimation and TOX: NAR (or RNAR if one prefer a randomized design to a deterministic one) since it performs well and has relatively lower TOX.

# Future Research Directions

- Construction of confidence interval for the probability of toxicity at the target dose.

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- Comparison of designs with delayed responses.
- For CRM, we can consider different work models.

# References


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