(MODIFIED) TOXICITY PROBABILITY INTERVALS
JI ET AL., *Clinical Trials* (2007, 2010)

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The 3+3 Design Still Persists

- Between April and May of 2006, 20/22 phase I clinical trials submitted to IRB (at MD Andersons) called for 3+3 design!
- Why?
  - SIMPLE: Investigators can design trials without help of statistician
  - Large volume of phase I trials $\Rightarrow$ impossible to provide every phase I clinical trial with statistician
  - Computer required throughout for sophisticated designs like CRM
  - In CRM design, simulations required before for calibration

Objective

- Develop a method with better performance than 3+3 design
- BUT easily understood and implemented
- Known as (modified) Toxicity Probability Interval (mTPI)

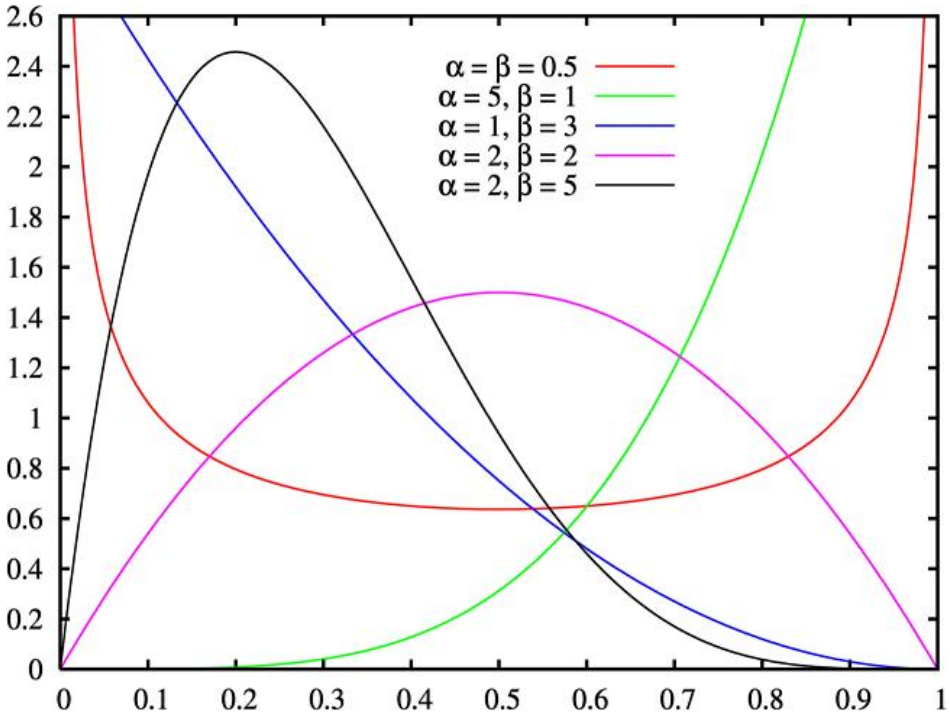
The Model

- Let p_T = the target toxicity probability for a drug
- Goal = find highest dose with toxicity closest to p_T (assume monotonic relationship between dose and toxicity as well as between dose and efficacy)
- Let $p_i = p(\textit{toxicity})$ at dose $i = 1, ..., d$
- $l(p) \propto \prod_{i=1}^{d} p_i^{x_i}(1 - p_i)^{n_i - x_i}$
- Where x_i = total number of subjects treated at dose i that experience toxicity and n_i = total number of subjects treated at dose i
- Assume that priors of p_i are i.i.d $\textit{beta}(\alpha, \beta)$

Beta Priors

- Beta density: $f(p) = \frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\Gamma(\beta)} p^{\alpha-1}(1-p)^{\beta-1}$
- $p \in (0,1)$, $mean = \frac{\alpha}{\alpha+\beta}$, $var = \frac{\alpha\beta}{(\alpha+\beta+1)(\alpha+\beta)^2}$
- In the Bayesian framework, the Beta prior is the conjugate prior for the binomial likelihood (posterior will also be a beta distribution)
- Posterior = $beta(\alpha + x_i, \beta + n_i - x_i)$

More on the Beta Distribution



$\alpha = \beta = 1 \Rightarrow U(0, 1)$
Authors recommend $\alpha = \beta = 0.005$ ("non-informative").

Dose Assignment

If patients are treated at dose i, only have 3 possible actions...

1. De-escalate (D) to dose $i - 1$
2. Stay (S) at dose i
3. Escalate (E) to dose $i + 1$

Partition the interval (0,1) into three parts, such that a posterior probability falling in each interval is too low, close to p_T, or too high, respectively:

- TPI: $\{(0, p_T - k_1\sigma_i), (p_T - k_1\sigma_i, p_T + k_2\sigma_i), (p_T + k_2\sigma_i, 1)\}$
- mTPI: $\{(0, p_T - \epsilon_1), (p_T - \epsilon_1, p_T + \epsilon_2), (p_T + \epsilon_2, 1)\}$
- Choose E,D, or S depending on which interval has highest posterior mass
- It may be difficult to determine k_1 and k_2 and results may be sensitive to k_1 and k_2
- Focus on mTPI (2010) that is based on the equivalence interval $[p_T - \epsilon_1, p_T + \epsilon_2]$

Safety Rules

- Choose $\xi \in (0, 1)$ that is relatively large such that...
- If $p(p_1 > p_T|data) > \xi \Rightarrow$ terminate trial
- If decision is E and $p(p_{i+1} > p_T|data) > \xi \Rightarrow$ Do no escalate.

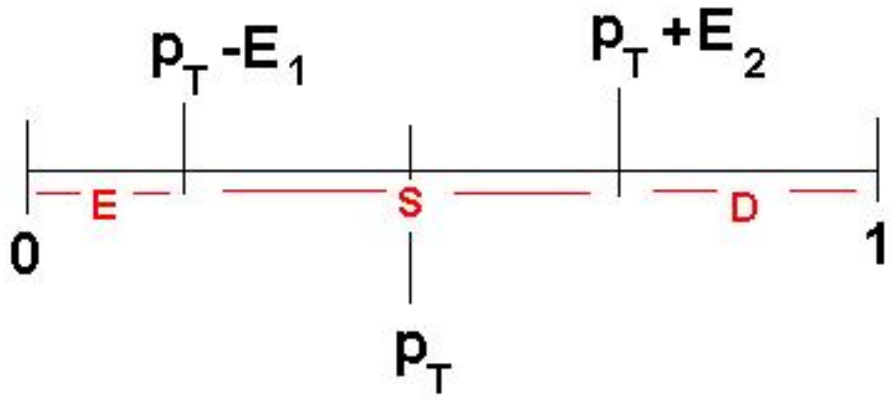
Estimating the MTD

- At end of trial, select dose with smallest difference $|\hat{p}_i - p_T|$ among all tried doses $i = 1, ..., d$
- Must satisfy safety criterion: $p(p_i > p_T|data) \leq \xi$
- Here, $\hat{p}_i$ is a "sensible" estimate of p_i...isotonically transformed posterior mean
- Ji et al (2007) discuss isotonic regression that borrows strength across doses: compute posterior mean $\hat{p}_i$ under beta posterior distribution and then perform pooled adjacent violators algorithm (PAVA) on $\hat{p}_i$ (Goodman et al, *Stat Med*, 1995)
- Dealing with ties: (1)Choose the highest dose that is less results in $\hat{p}_i$ less than p_T or (2)the lowest dose tat results in $\hat{p}_i$ greater than p_T

More on mTPI

- Define Unit Probability Mass (UPM) = the ratio of probability of interval and length of interval
- i.e. if $X \sim F$, UPM of $(a, b] = \dfrac{F(b) - F(a)}{b - a}$
- Calculate the UPM for each interval $\{(0, p_T - \epsilon_1), (p_T - \epsilon_1, p_T + \epsilon_2), (p_T + \epsilon_2, 1)\}$
- Choose E,D, or S corresponding to the interval with largest UPM
- It can be shown that this dose assignment rule minimizes the posterior expected penalty in the Bayesian framework...

Probability Model: mTPI



Define penalties for each decision as follows...

$$L(D,p_i) = \begin{cases} K_D, & \text{if } -\epsilon_1 \le p_i - p_T \le \epsilon_2; \\ 0, & \text{if } p_i - p_T > \epsilon_2; \\ N_D, & \text{if } p_i - p_T < -\epsilon_1; \end{cases} \qquad L(S,p_i) = \begin{cases} 0, & \text{if } -\epsilon_1 \le p_i - p_T \le \epsilon_2; \\ M_S, & \text{if } p_i - p_T > \epsilon_2; \\ N_S, & \text{if } p_i - p_T < -\epsilon_1; \end{cases}$$

$$L(E,p_i) = \begin{cases} K_E, & \text{if } -\epsilon_1 \le p_i - p_T \le \epsilon_2; \\ M_E, & \text{if } p_i - p_T > \epsilon_2; \\ 0, & \text{if } p_i - p_T < -\epsilon_1. \end{cases}$$

Probability Model: mTPI

- $K_D, K_E, M_S, M_E, N_S, N_B$ are all positive real numbers
- Let $X = \{(x_1, n_1), ..., (x_d, n_d)\}$ be accumulated data and let the information set corresponding to X be F
- Define $R(D, p_i) = E\{L(D, p_i)|F\}$, $R(S, p_i) = E\{L(S, p_i)|F\}$, $R(E, p_i) = E\{L(E, p_i)|F\}$ as the corresponding posterior expected penalies
- Let $q_{D_i} = p(p_i - p_T > \epsilon_2|F)$, $q_{S_i} = p(-\epsilon_1 \leq p_i - p_T \leq \epsilon_2|F)$, $q_{E_i} = p(p_i - p_T < -\epsilon_1|F)$
- Then $R(D, p_i) = K_D q_{S_i} + N_D q_{E_i}$, $R(S, p_i) = M_S q_{D_i} + N_S q_{E_i}$, $R(E, p_i) = K_E q_{S_i} + M_E q_{D_i}$
- We want to minimize the expected penalty, and thus we choose the action that corresponds to minimizing $R(m, p_i)$, where $m \in D, S, E$

Probability Model: mTPI

- Set $K_D = K_E = \frac{1}{\epsilon_1 + \epsilon_2}$, $M_S = M_E = \frac{1}{1 - p_T - E_2}$, $N_D = N_S = \frac{1}{p_T - \epsilon_1}$
- Under these conditions, prior expected penalties for D, E, and S are the same (one action is not favored over another a priori)
- Also, under these conditions, the posterior expected penalties $R(D, p_i)$, $R(S, p_i)$, and $R(E, p_i)$ = 1-UPMs for intervals $(0, p_T - \epsilon_1)$, $[p_T - \epsilon_1, p_T + \epsilon_2]$, $(p_T + \epsilon_2, 1)$
- Thus, the interval with the largest UPM will determine the decision to E, D, or S
- Large sample properties: mTPI will choose correct dose in large samples and when enough patients have been treated, this design will always choose a dose in the equivalence interval to treat all future patients (given that this dose is one of target candidates in the trial)

Comparing TPI, mTPI, and CRM

- Simulations in Ji et al. suggest comparable performance between CRM and TPI, but 3+3 design="worst"
- Criteria: Percent of trials choosing correct MTD, toxicity percentage
- Several scenarios examined
- In Ji et al. (2010), mTPI showed lowest toxicity percentage in all but 1 scenario (for model based scenarios)
- 3+3 design = conservative (low toxicity percentage)

Sensitivity Analysis

- Robust to different values of ϵ_1 and ϵ_2 (Table 2)
- Robust to different beta priors (Table 3)
- Additional research (not shown) also suggests these results
- Independence of priors for p_i???
- Most likely dependent (since toxicity probabilities are most likely ordered), but for small sample sizes, authors believe dependence will have large influence on operating characteristics

Software

Software is available online at http://odin.mdacc.tmc.edu/ ylji/

Excel Macro and R programs, BUT authors cannot guarantee bug free! Be careful and check for bugs.

Concluding Remarks

- CRM = excellent method for dose finding and has capacity to outperform (m)TPI
- BUT simplicity = key!
- mTPI over TPI...less confusing, easier parameters to define a priori
- mTPI (or TPI) may be a nice compromise between 3+3 and CRM
- Limitations: Assuming dichotomous outcome, monotonic relationship between toxicity and dose, efficacy not taken into account here
- Priors and independence of p_is