CT 33: 第一期臨床試驗
Phase I Design

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目錄

Continual Reassessment Method (CRM)

- O'Quigley, Pepe and Fisher, 1990
- It is creative application of regression techniques.
- Model the probability of binary outcome (DLT yes/no) against single covariate (dose) using standard parametric models
- Models will be Generalized Linear Models or others.
- Estimate model parameters using a posterior mean, i.e. a Bayesian analysis.

CRM Methods I

- Prespecified set of dose levels $\{d_1, d_2, d_3, d_4, d_5, d_6\}$
- prior: pre-specify dose-toxicity function
- pre-specify π_{target}
- Start at dose level thought closest to target π_{trarget}
- select parameters

CRM Methods II

- Treat a patient and observe outcome
- Perform Bayesian updating of the dose-response curve
- function is re-fit
- new estimate of parameter is obtained

  after each subject's observed toxicity
- new function is determined

CRM Methods III

- next subject is treated at the dose level whose $\widehat{\pi}_j$ is closest to π_{target}
- Repeat for a fixed n of patients
- MTD is dose level that would be hypothetically assigned for $n{+}1^{th}$ subject

Logistic Model

- two parameters

$$\text{logit}(\pi_j) = \beta_0 + \beta_1 \log(d_j). \tag{1.1}$$

- one parameter

$$\text{logit}(\pi_j) = c + \beta \log(d_j). \tag{1.2}$$

- c is constant, i.e., $c = 3$.

Hyperbolic Tangent Function

- Shen and O'Quigley (1996)
- Two stage design
- Stage one: various methods, get heterogeneous responses
- Stage two: fit one parameter

$$\tanh(x) = \frac{e^x - e^{-x}}{e^x + e^{-x}} = \frac{e^{2x} - 1}{e^{2x} + 1}. \tag{1.3}$$

$$\pi_j = \left(\frac{1 + \tanh(d_j)}{2}\right)^{\beta} = \left(\frac{e^{d_j}}{e^{d_j} + e^{-d_j}}\right)^{\beta}. \tag{1.4}$$

- Estimate parameter and MTD, assign next subject dose level.
- Stop when a pre-set # subjects have been accrued

Scaled Tanh Function

- one parameter:

$$\pi_j = \left(\frac{e^{2d_j} - 1}{2e^{2d_j} + 2} + \frac{1}{2} \right)^{\beta}. \tag{1.5}$$

Probit Model

- CDF of Normal Distribution

$$\pi_j = \Phi(d_j). \tag{1.6}$$

CRM: Advantages

- Few subjects are treated at low, ineffective doses.
- Subjects are treated at doses believed at the time to be the most efficacious, yet safe.

CRM: Disadvantages

- Starting dose maybe too high
- Dose escalation is too aggressive
- Trial length maybe too long
- Model misspecification may lead to
  poor operating characteristics, incorrectly select the MTD,
  and may even result in treating a substantial number of subjects
  at excessively toxic doses.
- In practice, we have no information
  to justify whether a specific skeleton is reasonable.

CRM: Modifications

- The modified versions do not change the operating characteristics.
- Start at lowest dose or dose closest to the target.
- Skip dose levels or not (restrict escalation).
- Wait for all patients' responses or not.
- CRM with fixed sample or with stopping rules.

Modified CRM I

- CRM relies on point estimate, ignores uncertainty.
- CRM: same posterior means, different posterior shapes
- Likelihood based (O'Quigley et al., 1996)
- Other modifications (Goodman et al., 1995)
- Enter single patients until first toxicity
- 0/1 DLT, escalate one dose level
- 1/1 DLT, de-escalate one dose level

Modified CRM II

- Enter n cohorts of m patients each
- After each cohort, fit one-parameter logistic model
- Enter next cohort at the dose level d_j such that
  estimated $\pi(d_j)$ is closest to π_{target},
  but not more than one dose level above
  the highest dose level visited previously
- Define MTD as dose level for hypothetical n+1th cohort
- MTD cannot be higher than highest dose level tested

Dose Expansion Cohorts

- 1) Follow dose escalation design
- 2) Find MTD
- 3) Add additional patients (6, 10, 12, 16) at MTD

Bayesian Model Averaging (BAM) CRM

- Overcome the arbitrariness
  and further enhance the robustness of the design.
- Use multiple parallel CRM models,
  each with a different skeleton (Yin and Yuan, 2009).
- Instead of using a single CRM for the trial conduct,
  carry out multiple parallel CRMs
  and rely upon the BMA approach for decision making.
- BMA is known to provide a better predictive performance
  than any single model
- Raftery, Madigan and Hoeting, 1997
- Hoeting et al., 1999

"Practical" CRM

- Piantadosi
- Based on pre-clinical toxicity data:
  - Choose dose that would produce low (10%) rate of DLT
  - Choose dose that would produce high (90%) rate of DLT

  Estimate dose/toxicity curve that fits these 2 points
- Use the dose/toxicity curve

  to find dose for π_{target}.
- Treat three subjects at this level,

  then re-estimate the dose-toxicity curve, dose for parameter,

  and tx 3 more Repeat until target dose changes by < 10%.

Two-Stage CRM Designs

- Stage 1: traditional design
  - 2+2 is a more common first stage than 3+3
  - Continue until first toxicity is observed
- Stage 2: CRM
  - After first toxicity,

    fit the dose-response curve

    using the toxicity data accrued thus far
  - Choose dose for next cohort of 2 as dose

    with estimated rate of DLT closest to π_{target}.

Design Comparisons

- Fitting a model to the data will improve
  the accuracy of the MTD found by rule-based designs
- Model-guided designs only perform well
  if assumptions are met (π_{target} in range of doses tested)
- Conflicting results when designs compared
- Few comparisons made on “level playing field”
- Both rule-based and model-guided designs are in common use,
  for good reason

R Packages: Phase I Design

- `dfcrm`
- `crmPack`
- `CRM`
- `bcrm` one and two-parameter Bayesian CRM designs
- `TEQR` The target equivalence range (TEQR) design
  a frequentist implementation of MTPI
- `dfped` dose-finding trials in paediatrics
- `trialr`
- `titeIR`
- `titecrm`

Thanks!