Bayesian clinical trials

19.05.28

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What is adaptive design?

- In this article, we will refer to the adaptations(or modification) made to the trial and/or statistical procedures as the adaptive design methods.
- An adaptive design is defined as a design that allows adaptations to trial and/or statistical procedures of the trial after its initiation without undermining the validity and integrity of the trial.
- The purpose is not only to efficiently identify clinical benefits of the test treatment under investigation, but also to increase the probability of success of clinical development.

Why we need adaptive design

- Clinical development of a new drug product is a lengthy and costly process(Including phase I to IV)
- For life-threatening diseases or rare diseases, this lengthy clinical development process is not acceptable.
- In this case, the purpose is to shorten the development process(speed) without compromising the safety and efficacy of the drug product.

Adaptive design : 3 categories

- Prospective adaptation : adaptive randomization, stopping a trial early, drop the losers, sample size re-estimation...
- Concurrent adaptation : modifications in inclusion, evaluability criteria, change in hypotheses.
- Retrospective adaptation : modification and changes made to statistical analysis.

Type of adaptive designs

- Adaptive randomization design - Allowing modification of randomization schedules in order to increase the probability of success.
- Group sequential design - design that allows for prematurely stopping a trial due to futility/efficacy.
- Sample size re-estimation - Allowing sample size adjustment or re-estimation based on the observed data at interim.
- Drop the losers design - design that dropping the inferior treatment groups

Type of adaptive designs

- Adaptive dose finidng design - to identify the minimum effective dose(MED) and/or the maximum tolerable dose(MTD).
- Biomarker-adaptive design - design that allows for adaptations based on the response of biomakers such as genomic markers.
- Adaptive-hypothesis design - design that allows modifications or changes in hypotheses based on interim analysis results.
- Multiple adaptive design - any combinations of the above adaptive designs.

Drawback of adpative design

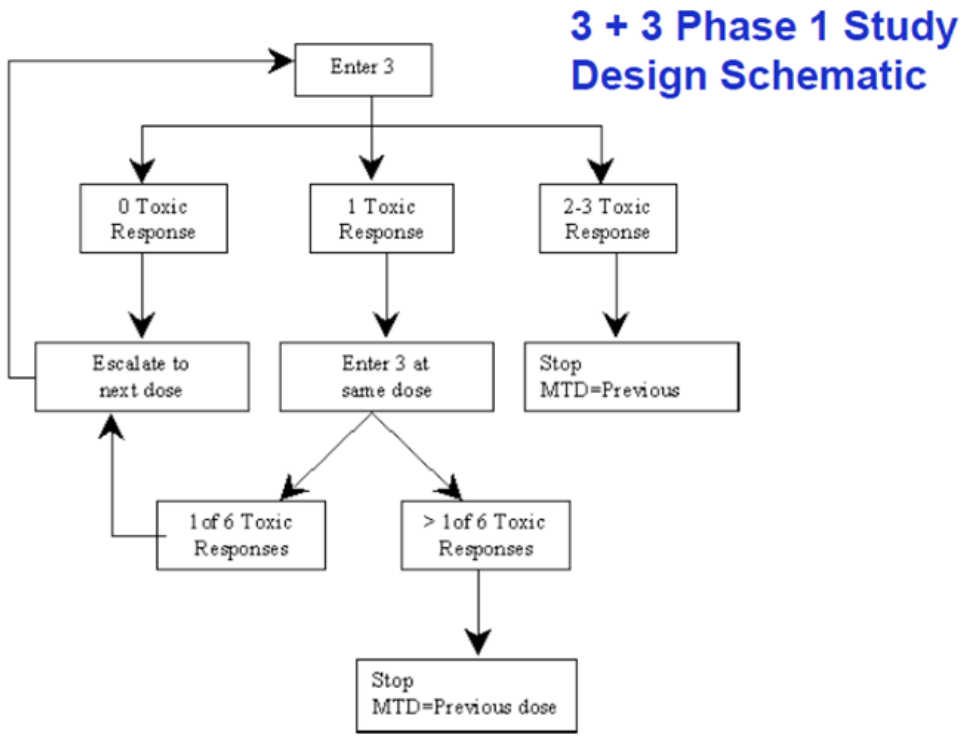
- Interpretation of trial results is difficult.
- It may not be able to preserve the overall type I error rate at the pre-specified level of significance.
- Could introduce bias/variation to data collection.
- result in a shift in location and scale of the target patient population.

Example : Dose-finding design

- Suppose that the primary objective is to identify the maximum tolerated dose(MTD) for a new test drug.
- The dose limiting toxicity (DLT) rate at MTD is defined as 0.25 and the MTD is estimated to be 150 mg/m^2
- A typical approach(3+3 design) vs adaptive type approach(Bayesian CRM)

3+3 design

- Rule based design.
- Start by allocating lowest dose level to firt cohort.
- Adaptively escalate/de-escalate based on observed DLTs
- Repeat until MTD obtained or trial is stopped



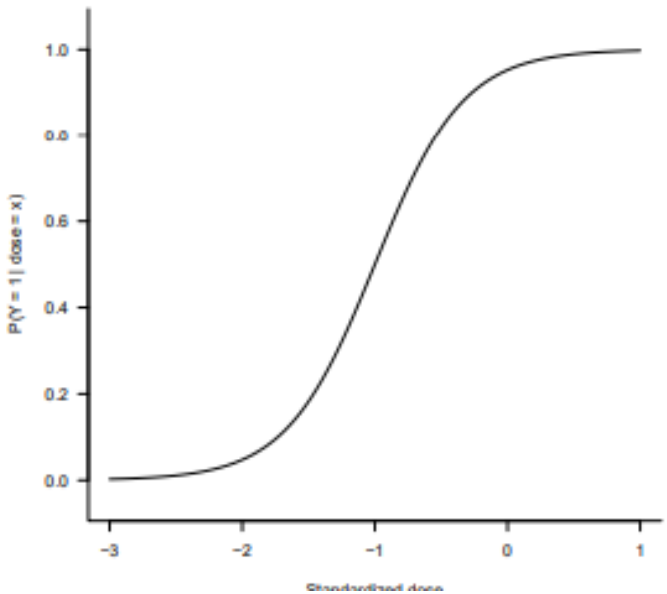
Bayesian CRM

- (Idea) After each patient outcome is observed, dose-response relationship is re-estimated
- Next patient is given the dose that is the current estimate of the MTD.
- Observation Y_j on each patient is whether they have a toxic response.
- Let θ be the targeted toxicity level (TTL) (probability of toxicity)
- Objective is to find corresponding dose x^*(MTD)

Bayesian CRM

- Choose any one-parameter function $\psi(x, a)$, monotonic in x and a.
- We assume that there exists an $a_0 : \psi(x^*, a_0) = \theta$.
- logistic model :

$$\psi(x, a) = \frac{e^{3+ax}}{1 + e^{3+ax}}$$



Bayesian CRM

- Let the current posterior for a_0 be $q(a|data)$
- Estimate the probability of toxicity it by its mean, integrating over all possible values of a_0 at each dose.

$$\widehat{P(Y = 1|x = x_j)} = \int_0^\infty \psi(x_i, a) q(a|data) da$$

- For one patient, $P(Y_j = y_j) = (\phi(x_j, a))^{y_j}(1 - \phi(x_j, a))^{1-y_j}$
- Common priors for a_0 : gamma, uniform, lognormal.

Dose-finding design result

Table 1: Summary of simulation results for the designs

Method	Assumed True MTD	Mean Predicted MTD	Mean Number of Patient	Mean Number of DLTs
3+3 TER	100	86.7	14.9	2.8
CRM	100	99.2	13.4	2.8
3+3 TER	150	125	19.4	2.9
CRM	150	141	15.5	2.5
3+3 TER	200	169	22.4	2.8
CRM	200	186	16.8	2.2

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Introduction

- The scope of the paper is not a complete review of all the work that has been done on Bayesian methods in clinical trials.

Bayesian statistics

- By Bayes theorem, $q(\theta|D) \propto L(\theta|D)\pi(\theta)$ where $L(\theta|D)$ is the likelihood function and $\pi(\theta)$ is the prior distribution.
- The big advantage with the Bayesian approach is that one could produce posterior distributions that addresses the quantitative integration of the current data with the prior information.

FDA : Bayesian initiative for medical devices

- Around 1997, The Food and Drug Administration(FDA) embarked on an effort to consider the use of Bayesian statistics for submissions to the agency by medical device companies.
- There is often a great deal of prior information for a medical device.
- Why medical devices ? - The nature of device development is that devices evolve whereas pharmaceutical drugs once discovered remain virtually unchanged.

FDA : Bayesian initiative for medical devices

- Using good prior information can often get to the same decision faster without any lowering of the scientific standards.
- But for a Bayesian design, a company needs to consult early ensuring that the prior information identified in advance and mutually agreed upon.

FDA : The challenge and early decisions

- One early decision was to restrict to prior information directly based on quantitative, rather than subjective, information from data from previous clinical studies.
- But, Good subjective prior is the company's assets.
- For a Bayesian submission using prior information, FDA and the company need reach an agreement on the validity of any prior quantitative information.

FDA : Guidance for medical device clinical trials(2010)

- It describes the two main types of Bayesian submissions, Bayesian hierarchical modeling with data from previous studies and Bayesian adaptive trial usually with a non-informative prior.
- Consideration : Exchangeability for hierarchical modeling
  (Often a careful examination of exchangeability results in concluding that the new study is not exchangeable since it is more likely to be better in some sense than its predecessors.)
- issue a statement on statistical significance and p-values.

Adaptive Bayesian methods and modeling

- Adaptive Bayesian design is to use accumulating information from the trial, usually with a non-informative prior distribution, to make pre-planned changes to the trial.
- The big advantage of the Bayesian approach with a non-informative prior is that the accumulating data is being used not only to stop early for success or futility but also to model to the primary outcome variable using intermediate endpoints.