Adaptive Design Methods in Clinical Trials

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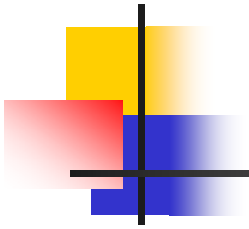
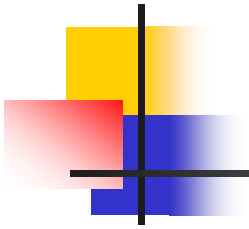


Outline

- What and why?
- Type of adaptive designs
- Regulatory/statistical perspectives
- Moving target population
- Statistical inference
- Concluding remarks



What Is Adaptive Design?

- There is no universal definition
  - Adaptive randomization, group sequential, and sample size re-estimation, etc.
  - Chow, Chang, and Pong (2005)
  - PhRMA (2006)
- Adaptive design is also known as
  - Flexible design (EMEA, 2002, 2006)
  - Attractive design (Uchida, 2006)

PhRMA's Definition

PhRMA (2006), J. Biopharm. Stati., 16 (3), 275-283.

An adaptive design is referred to as a clinical trial design that uses *accumulating data* to decide on how to *modify* aspects of the study as it *continues*, without undermining the *validity* and integrity of the trial.

PhRMA's Definition

- Characteristics
  - Adaptation is a design feature.
  - Changes are made "by design" not on an "ad hoc" basis.
- Comments
  - It does not reflect real practice.
  - It may not be flexible as it means to be.

Type of Adaptation

- Prospective adaptation
  - Adaptive randomization
  - Interim analysis
  - Stop trial early due to safety, futility/efficacy
  - Sample size re-estimation

    etc.
- Concurrent adaptation
  - Trial procedures
- Retrospective adaptation
  - Statistical procedures

Nature of Adaptation

- Prospective adaptation
  - By design
- Concurrent adaptation
  - Ad hoc
- Retrospective adaptation
  - Prior to database lock and/or unblinding

Adaptive Designs

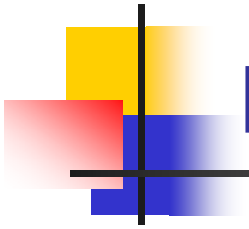
- Adaptive randomization design
- Adaptive group sequential design
- N-adjustable design
- Drop-the-loser design
- Adaptive dose-escalation design
- Biomarker-adaptive design
- Adaptive treatment-switching design
- Adaptive-hypotheses design
- Adaptive seamless phase II/III trial design
- Any combinations of the above (multiple adaptive design)

Regulatory/Statistical Perspectives

- May introduce operational bias.
- May not be able to preserve type I error rate.
- P-values may not be correct.
- Confidence intervals may not be reliable.
- May result in a totally different trial that is unable to address the medical questions the original study intended to answer.

Implementation of Adaptation

- Prospective adaptation
  - By design
  - Study protocol
- Concurrent adaptation
  - Ad hoc
  - Protocol amendments
- Retrospective adaptation
  - Prior to database lock and/or unblinding
  - Statistical analysis plan



Practical Issues in Clinical Trials

- On average, for a given clinical trial, we may have 2-3 protocol amendments during the conduct of the trial.
- It is not uncommon to have 5-10 protocol amendments regardless the size of the trial.

Protocol Amendments

- Rationale for changes
  - Clinical
  - Statistical
- Review process
  - Internal protocol review
  - IRB
  - Regulatory agencies

Target Patient Population

- Has the disease under study
- Inclusion criteria to describe the target patient population
- Exclusion criteria to remove heterogeneity
- Subpopulations may be defined based on some baseline demographics and/or patient characteristics

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Target Patient Population

- Denote target patient population by (μ, σ), where μ and σ are population mean and standard deviation, respectively.
- After a modification made to the trial procedures, the target patient population lead to the actual patient population of

$$(\mu_{Actual}, \sigma_{Actual}) = (\mu + \varepsilon, C\sigma)$$

Target Patient Population

$$\left|\frac{\mu_{Actual}}{\sigma_{Actual}}\right| = \left|\frac{\mu+\varepsilon}{C\sigma}\right| = \left|\frac{\Delta\mu}{\sigma}\right| = |\Delta|\left|\frac{\mu}{\sigma}\right|,$$

$$where \quad \Delta = \frac{1+\varepsilon/\mu}{C}$$

Target Patient Population

- $\left|\frac{\mu}{\sigma}\right|$ is usually referred to as the effect size
- The effect size after the modification made is inflated or reduced by the factor of Δ.
- “Clinically meaningful difference” may have been changed after the modification (adaptation) is made.

Target Patient Population

- Δ is referred to as a sensitivity index.
- When $\varepsilon = 0 \, and \, C = 1$ (i.e., there are no impact on the target patient population after the modifications made). In this case, we have Δ =1 (i.e., the sensitivity index is 1).

Sensitivity Index

- A shift in mean of the target patient population may be offset by the inflation (or reduction) of the variability, e.g.,
  - A shift of 10% (-10%) in mean could be offset by a 10% inflation (reduction) of variability
- Δ may not be sensitive due to the masking effect between ε and C.

Moving Target Patient Population

- Under the moving target patient population, the effect size is the original effect size times the sensitivity index, that is

$$\left|\frac{\mu_{Actual}}{\sigma_{Actual}}\right| = |\Delta|\left|\frac{\mu}{\sigma}\right|$$

- How will this impact statistical inference?

Inference with Protocol Amendments

Chow SC and Shao J. (2005). J. Biopharm. Stat., 15, 659-666.

Model the population deviations due to protocol amendments using some covariates and develop a valid statistical inference procedure.

Inference with Protocol Amendments

- The idea is to relate the means before and after protocol amendments by means of some covariates. In other words,

$$\mu_k = f(x_k), k = 1,..., m,$$

where μ_k and x_k are the mean and the corresponding covariate after the kth protocol amendment, f is a given function (linear or non-linear), and m is the number of protocol amendments.

Statistical Inference

- Notations

  P_o : Target patient population

  P_k : Patient population after the kth protocol amendment, $k = 1, ..., m$

  μ_o : Target patient population mean

  μ_k : Patient population mean after the kth protocol amendment

Statistical Inference

- Assumption

  $$\mu_k = \beta_0 + \beta^{'} \mathrm{x}_k \qquad k = 1, \ldots, m$$

  where β_0 is an unknown parameter, β is an unknown parameter vector whose dimension is the same as x, $\beta^{'}$ denotes the transpose of β, and x_k is the value of x under the kth amendment

- Note that although $\mu_1, \ldots \mu_m$ are different from μ_0, the above assumption relates them with the covariate.

Conditional Inference

- First $\begin{pmatrix} \hat{\beta}_0 \\ \hat{\beta} \end{pmatrix} = \left(X'WX \right)^{-1} X'W\bar{y}$

  where $\bar{y} = (\bar{y}_0, \bar{y}_1, \ldots, \bar{y}_m)'$, X is a matrix whose kth row is $(1, \mathrm{x}'_K)$, $\mathrm{K}=0,\ldots,\mathrm{m}$, and W is a diagonal matrix whose diagonal elements are $n_0, n_1, \ldots, n_m$.

- An unbiased estimate of μ_0 can then be obtained as

$$\hat{\mu}_0 = \hat{\beta}_0 + \hat{\beta}'\mathrm{x}_0$$

Conditional Inference

- Assumptions
  - Conditional on the given protocol amendments, data from P_k are normally distributed with a common standard deviation σ .
  - Data from different P_k's are independent
- $\hat{\mu}_0$ is distributed as, $N(\mu_0, \sigma^2 C_0)$ where

$$C_0 = (1, \mathrm{x}_0)(X'WX)^{-1}(1, \mathrm{x}_0)'$$

Conditional Inference

Thus, confidence interval for μ_0 can be obtained based on the t-statistic

$$t = \frac{\hat{\mu}_0 - \mu_0}{\sqrt{C_0 s^2}} \quad ,$$

where

$$s^2 = \sum_{k=0}^{m} \frac{\left(n_{k-1}\right) s_k^2}{N - m}$$

$$N = \sum_{k=0}^{m} n_k$$

Conditional Inference

When P_k's have different standard deviations and/or data from P_k are not normally distributed, we may consider the following approximation for large sample

$$\hat{\mu}_0 \underset{\text{approx}}{\sim} N\left(\mu_0, r^2\right) \quad ,$$

where

$$r^2 = (1, x_0)\left(X'WX\right)^{-1} X'W \sum X \left(X'WX\right)^{-1} (1, x_0)'$$

when $\sum$ is the diagonal matrix whose kth diagonal element is the population variance of P_k , $k = 1..., m$

Unconditional Inference

- Notations

  C_K = a particular set of K protocol amendments

  C = the collection of all possible protocol amendments indexed by 1, 2,…, M

- Thus $C_K = \{i_1, ..., i_K\} \in C = \{1, ..., M\}$
- C_K is chosen based on a (random) decision rule ξ (adaptation rule)

Unconditional Inference

- For a particular C_K , let Z_{C_K} be the z-statistic. Also, let $L\left(Z_{C_K} \middle| \xi = C_K\right)$ be the conditional distribution of Z_ξ given $\xi = C_K$.

- Suppose that $L\left(Z_{C_K} \middle| \xi = C_K\right)$ is approximately standard normal. We have

$$L\left(Z_\xi\right) = E\left[\sum_{C_K \in C} L\left(Z_{C_K} \middle| \xi = C_K\right) I_{\xi = C_K}\right]$$

where $I_\xi = C_K$ is the indicator function of the set $\left\{\xi = C_K\right\}$

Unconditional Inference

$$P\left(Z_{C_K} \le t \middle| \xi = C_K\right) \to \Phi(t) \quad \text{a.s.}$$

$$\Rightarrow P\left(Z_{C_K} \le t \middle| \xi = C_K\right) I_{\xi = C_K} \to \Phi(t) I_{\xi = C_K} \quad \text{a.s.}$$

$$\Rightarrow E\left[P\left(Z_{C_K} \le t \middle| \xi = C_K\right) I_{\xi = C_K}\right] \to E\left(\Phi(t) I_{\xi = C_K}\right)$$

$$= \Phi(t) E\left(I_{\xi = C_K}\right)$$

$$= \Phi(t) P\left(C_K\right)$$

$$\Rightarrow P\left(Z_{C_K} \le t\right) = \sum_{C_K \in C} E\left[P\left(Z_{C_K} \le t \middle| \xi = C_K\right) I_{\xi = C_K}\right]$$

$$\to \sum_{C_K \in C} \Phi(t) P\left(C_K\right) = \Phi(t)$$

Practical Issues

- In practice, covariates that will link the population means before and after protocol amendments may not exist or not observed.
- The impact of protocol amendments may be examined through the assessment of sensitivity index.

Concluding Remarks

- Clinical
  - Adaptive design reflects real clinical practice in clinical development.
  - Adaptive design is very attractive due to its flexibility and efficiency.
  - Potential use in early clinical development.
- Statistical
  - The use of adaptive methods in clinical development will make current good statistics practice even more complicated.
  - The validity of adaptive methods is not well established.

Concluding Remarks

- Regulatory
  - Regulatory agencies may not realize but the adaptive methods for review/approval of regulatory submissions have been employed for years - no scientific basis.
  - Guidelines regarding the use of adaptive methods are necessary developed.
- IDMC (Independent Data Monitoring Committee)
  - Independent data monitoring, administrative looks, and/or interim analyses.
  - Integrity and validity of the trial