Lecture 3

Adaptive (Flexible) Design – What Do We Know About It?

Outline

- What and why?
- Regulatory/statistical perspectives
- Target population
- Statistical inference
- Statistical considerations
- Concluding remarks

What is adaptive design?

- There is no universal definition
  - Adaptive randomization
  - Group sequential design
  - Sample size reassessment
- Characteristics
  - Adaptive methods based on accrued information
  - Flexibility

Chow's Definition

- An adaptive design is a design that allows modifications to some aspects of the trial (e.g., trial procedures and/or statistical procedures) after its initiation without undermining the validity and integrity of the trial.
  - *Trial procedures*
  - *Statistical procedures*
- Adaptive design is also known as flexible design

Trial Procedures

- Eligibility criteria
- Study does/duration
- Study endpoints
- Laboratory testing procedures
- Diagnostic procedures
- Criteria for evaluability and/or assessment of clinical responses
- Deletion/addition of treatment groups
- Safety or Efficacy Endpoints

  etc.

Statistical Procedures

- Randomization procedures in treatment allocation
- Study objectives/hypotheses
- Sample size reassessment
- Study design
- Data monitoring and/or interim analysis
- Statistical analysis plan
- Methods for data analysis

etc.

Why?

- Scientific/statistical justifications
  - e.g., validity
- Medical considerations
  - e.g., safety
- Regulatory concerns
  - e.g., regulatory approval
- Business interest/decisions
  - e.g., commercial interest and budget/resource constraints

Commonly Practice

- Protocol amendments
  - Internal protocol review
  - JIRB
  - Regulatory agencies
- What's the potential impact?
  - Regulatory perspective
  - Scientific/statistical perspective

Regulatory Perspectives

- "Modification of the design of an experiment based on accrued data has been in practice for hundreds, if not thousands, of years in medical research. In the past, we have a tendency to adopt statistical procedures in the literature and apply them directly to the design of clinical trials"
- "However, since these procedures were not motivated by clinical practice, they may not be the best tools to handle certain situations."

Regulatory Perspectives

- Major (significant) modifications to trial procedures and/or statistical procedures could lead to a total different trial which is unable to address the scientific/clinical questions that the trial intends to answer.
- Statistical inference regarding the treatment effect such as confidence intervals and/or p-values may not be reliable and consequently the conclusion drawn may be biased and hence misleading.

Regulatory Perspectives

- Accurate estimates
- Reliable confidence intervals
- Correct p-values

Regulatory Perspectives

- What adaptive methods are acceptable
  - Validity of adaptive methods
- What modifications are considered major (or significant) which may lead to a totally different trial
  - Sensitivity/robustness analysis
- Guidances/guidelines are necessarily developed
  - EMEA (2002) Points to Consider

Statistical Perspectives

- Major (or significant) modifications to trial procedures and/or statistical procedures could introduce bias/variation to data collection
  - These bias/variation will definitely have an impact on the validity, quality, and integrity of the trial.

Sources of Bias/Variation

- Expected and controllable
  - e.g., changes in laboratory testing procedures and/or diagnostic procedures
- Expected but not controllable
  - e.g., change in study dose and/or treatment duration
- Unexpected but controllable
  - e.g., patient non-compliance
- Unexpected and uncontrollable
  - random error

Statistical Perspectives

- Major (or significant) modifications to trial procedures and/or statistical procedures could result in a major difference between the *target* patient population and the *actual* patient population
  - Statistical inference obtained based on data collected from the actual patient population may not be applied directly to the target patient population

Statistical Perspectives

- Major (or significant) modifications to trial procedures and/or statistical trials could lead to inconsistency between hypotheses to be tested and the corresponding statistical tests.
  - Statistical inference regarding the treatment effect is not interpretable.

Statistical Tests

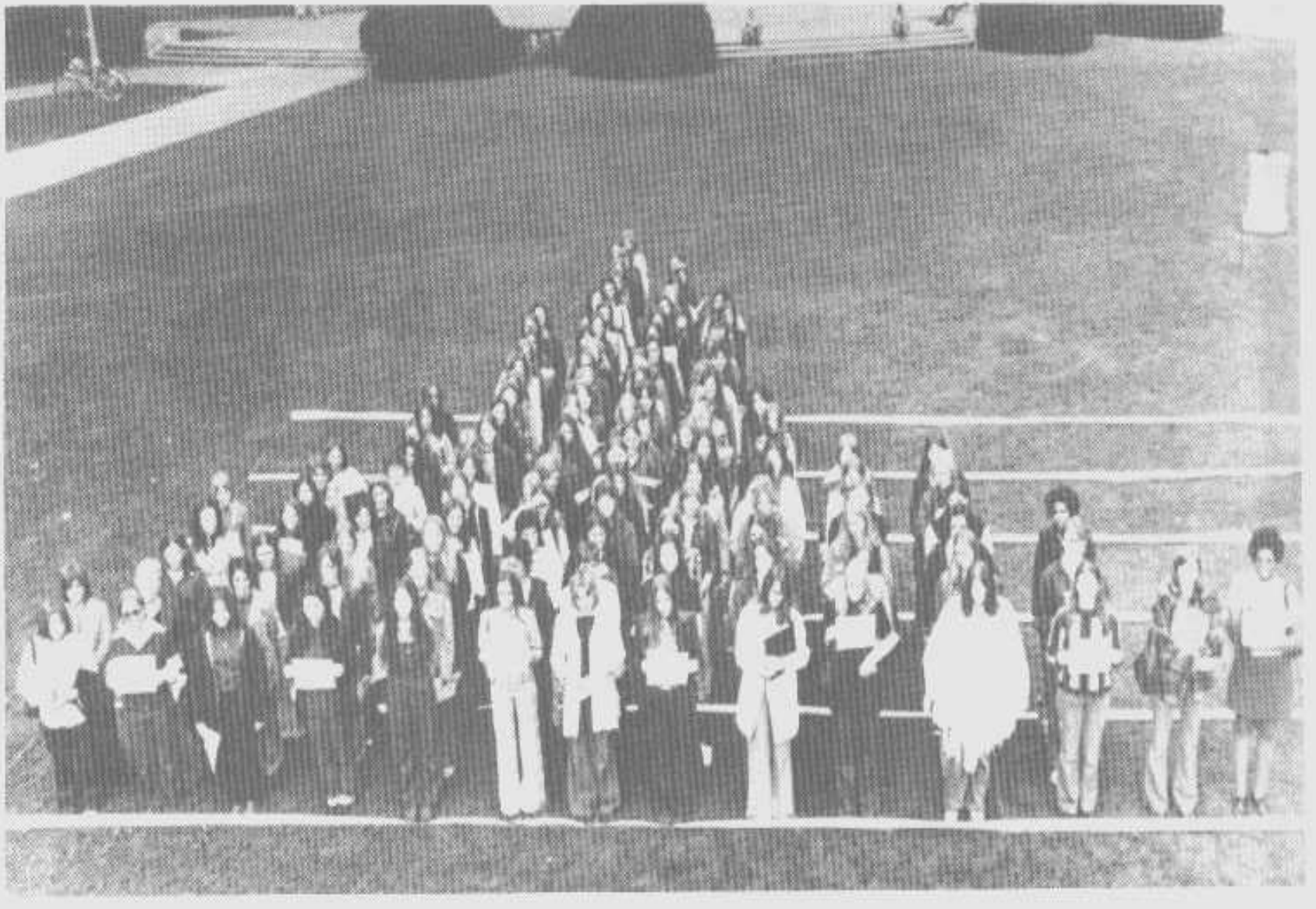
- Wrong tests for the right hypotheses
- Right tests for the wrong hypotheses
- Wrong tests for the wrong hypotheses
- Right tests for the right hypotheses but insufficient power

Patient Population

- Statistically, we can describe a (patient) population by (μ, σ), where

  μ is the population mean and

  σ s the standard deviation of the population



(a)

Target 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

- Δ is usually referred to as a sensitivity index.
- When $\varepsilon = 0 \, and \, C = 1.$, 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).

Target Patient Population

- Based on data collected from the actual patient population, statistical inference is for (μ, σ) not for $(\mu_{Actual}, \sigma_{Actual})$
- What is the impact of the modifications made to the target patient population?

Power & Sample Size

- Test for equality

  H□: $\mu = \mu$□ vs H_a: $\mu \neq \mu$□

- Classic sample size:

$$n_{classic} = \frac{(z_{1-\alpha/2} + z_{1-\beta})^2 \tilde{\sigma}^2}{\delta^2},$$

- Adaptive sample size:

$$n_{adaptive} = Rn$$

$$R = (1 - \frac{(z_{1-\alpha/2} + z_{1-\beta})^2}{\delta^2} \frac{\tilde{\sigma}_{\mu}^2}{m+1}).$$

Statistical Considerations

- Adaptive randomization
- Adaptive double data entry
- Modifications of hypotheses
- Adaptive dose selection
- Group sequential design
- Sample size re-estimation
- Flexible trial design
- Bayesian Approach
- Trial simulation

Adaptive Randomization

- Conventional randomization
  - Simple (complete) randomization
  - Stratified randomization
- Adaptive randomization
  - Treatment-adaptive randomization
  - Covariate-adaptive randomization
  - Response-adaptive randomization

Adaptive Double Data Entry

- 100% Double entry
- Randomly sampled double entry
- Adaptive Double Entry
  - Study specific
  - Form specific
  - Individual dependent

Modifications of Hypotheses

- Single set of hypotheses
  - e.g., efficacy based on the primary study endpoint
- Multiple-endpoints
  - e.g., the primary endpoint plus all secondary endpoints
- Switching of hypotheses
  - e.g., switch from a superiority hypotheses to non-inferiority hypotheses

Adaptive Dose Selection

- Traditional Approach
- Bayesian Adaptive approach (CRM)
- Utility Theory/Decision Theory

Group Sequential Trial

- Why sequential trial
  - Ethical
  - Economical
  - Administrative

Group Sequential Trial (cont.)

- Types of group sequential trial
  - Permit early stopping for futility
  - Permit early stopping for efficacy
  - Permit early stopping for futility and efficacy
  - A smaller expected sample size
  - Slightly increment in maximum sample size

Group Sequential design (Cont.)

- Characteristics
  - Overall alpha level controlled
  - Overall power is preserved
  - Number of analyses
  - Stopping boundaries
  - Alpha levels at interim analyses
  - Conditional powers/futility index
  - Expected sample size
  - Maximum sample size
  - Maximum sample size is pre-fixed

Group Sequential design (Cont.)

- Trial Monitor
  - Why monitor a seq. trial
    - Deviation of analysis schedule
    - Deviation of efficacy variable estimation
    - Safety factors & Others
  - Role of Data Monitoring Committee
  - Statistical tools for monitoring – stopping boundaries
    - O'Brien-Fleming's
    - Pocock's
    - Wang & Tsiatis's
    - Error Spending approach
    - Conditional power approach

Sample Size Re-estimation

- Why
  - Inaccurate initial estimation of treatment effect and its variability
- Type of Re-estimation
  - Treatment code blinded
  - Treatment code unblinded
- How
  - Overall type-I error controlled
  - Power preserved

Flexible Trial Design

- What
  - Sequential design with adjustable boundary
  - Sequential design with adjustable sample size
  - Sequential design with adjustable treatment arms
- Why
  - Practical desirable
- How
  - Overall type-I error controlled
  - Power preserved

Bayesian Approach

- What is Bayesian
  - Balancing prior knowledge and knowledge from current trial
  - Approach with modifiable probability distribution
  - Probability distribution modified to accumulative information
- Bayesian is a popular method for adaptive design
  - Bayesian for adaptive trial design
  - Frequencist for the inferential analysis

Trial simulation

- Why Trial simulation
  - Complication of clinical trials
  - Analytical Statistical approaches fail to model many aspects of trial practice
  - Computer simulations provide sensitivity analyses under various scenarios that likely or unlikely occur in a trial and provide valuable information for decision making
  - Integration of the preclinical, clinical and marketing

Concluding Remarks

- Clinical
  - Adaptive design reflects real clinical practice in clinical development.
  - Adaptive design is very attractive due to its flexibility.
  - Potential use in early clinical development.
- Statistical
  - The use of adaptive methods in clinical development makes current good statistics practice even more complicated.
  - The validity of adaptive methods is not well established.
- Regulatory
  - Regulatory agencies may not realize but the adaptive methods for review/approval of regulatory submissions have been employed for years (with little/no scientific/statistical basis).
  - Guidances/guidelines regarding the use of adaptive methods are needed.

References

- Journal of Biopharmaceutical Statistics (JBS) will publish a special issue on *Adaptive Design Methods in Clinical Research* (Vol. 15, Issue No. 3)
- Chow, S.C. and Chang, M. (2005). *Adaptive Design Methods in Clinical Research*. John Wiley & Sons, New York, New York. In preparation.