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
“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.”
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 $(\mu, \sigma)$, where
  \[ \mu \] is the population mean and
  \[ \sigma \] is the standard deviation of the population
Target Population

- Denote target patient population by \((\mu, \sigma)\), where \(\mu\) and \(\sigma\) 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
- \((\mu_{\text{Actual}}, \sigma_{\text{Actual}}) = (\mu + \varepsilon, C\sigma)\)
Target Patient Population

\[
\frac{\mu_{\text{Actual}}}{\sigma_{\text{Actual}}} = \frac{\mu + \varepsilon}{C\sigma} = \frac{\Delta \mu}{\sigma} = |\Delta| \left| \frac{\mu}{\sigma} \right|
\]

where \( \Delta = \frac{1 + \varepsilon / \mu}{C} \)
Target Patient Population

- $\Delta$ 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 $\Delta = 1$ (i.e., the sensitivity index is 1).
Target Patient Population

- Based on data collected from the actual patient population, statistical inference is for $(\mu, \sigma)$ not for $(\mu_{\text{Actual}}, \sigma_{\text{Actual}})$

- What is the impact of the modifications made to the target patient population?
Power & Sample Size

- Test for equality
  \[ H_0: \mu = \mu_0 \text{ vs } H_a: \mu \neq \mu_0 \]

- Classic sample size:
  \[ n_{\text{classic}} = \frac{\left( z_{1-\alpha/2} + z_{1-\beta} \right)^2 \tilde{\sigma}^2}{\delta^2} \]

- Adaptive sample size:
  \[ n_{\text{adaptive}} = Rn \]
  \[ R = \left( 1 - \frac{\left( z_{1-\alpha/2} + z_{1-\beta} \right)^2 \tilde{\sigma}^2}{\delta^2} \right) \frac{\tilde{\sigma}^2_\mu}{m+1} \]
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
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
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)