Shein-Chung Chow
Duke University
USA

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# Dr. Shein-Chung Chow Biography

- Shein-Chung Chow, PhD. is a Professor of Biostatistics and Bioinformatics, Duke University School of Medicine, Durham, North Carolina. Prior to joining Duke University, he was Executive Director of National Clinical Trial Network Coordination Center of Taiwan. Prior to that, Dr. Chow held various management positions in the pharmaceutical industry. Dr. Chow is the Editor-in-Chief of the Journal of Biopharmaceutical Statistics and the Editor-in-Chief of the Biostatistics Book Series at Chapman and Hall/CRC Press of Taylor & Francis Group. He was elected Fellow of the American Statistical Association in 1995. He was the recipient of the DIA Outstanding Service Award (1996), and ICSA Extraordinary Achievement Award (1996). Dr. Chow is the author or co-author of over 200 methodology papers and 20 books, which include Design and Analysis of Bioavailability and Bioequivalence Studies, Design and Analysis of Clinical Trials, Sample Size Calculations in Clinical Research, and Adaptive Design Methods in Clinical Trials

## Dr. Shein-Chung Chow Research Interest

- Biostatistics
- Bioinformatics
- Adaptive Design Methods in Clinical Trials

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# Recent Publication of Dr. Shein-Chung Chow （2012~2014）

## Books:

- Liu, J.P., Chow, S.C., and Hsiao, C.F. (Ed) (2012). Design and Analysis of Bridging Studies. Taylor & Francis, New York, New York.
- Chow, S.C. and Liu, J.P. (2013). Design and Analysis of Clinical Trials – Revised and Expanded, Third Edition, John Wiley & Sons, New York, New York. In press.
- Chow, S.C. (2013). Biosimilars: Design and Analysis of Follow-on Biologics. Chapman and Hall/CRC Press, Taylor & Francis, New York.
- Chow, S.C. (2015). Statistical Methods for Traditional Chinese Medicine. Publishing agreement awarded. Scheduled to be published in August, 2015.

## Research Papers:

- Chow, S.C., Chiang C., Liu, J.P., and Hsiao, C.F. (2012). Statistical methods for bridging studies. *Journal of Biopharmaceutical Statistics,* 22, 903-915.
- Jung, S.H. and Chow, S.C. (2012). On sample size calculation for comparing survival curves under general hypotheses testing. *Journal of Biopharmaceutical Statistics*, 22, 485-495.
- Chow, S.C. and Pong, A. (2012). Issues in global pharmaceutical development. To appear.
- Tsou, H.H., Chow, S.C., Chang, W.J., Ko, F.S., Chen, Y.M., and Hsiao, C.F. (2012). Considering regional differences in the design and evaluation of multi-regional clinical trials. To appear.
- Chow, S.C. (2012). Scientific issues for assessing biosimilars in the United States. Journal of Biometrics and Biostatistics, 3:e107, doi10.4172/2155-6180.1000e107.
- Chow, S.C., Corey, R., and Lin, M. (2012). On independence of data monitoring committee in adaptive clinical trial. *Journal of Biopharmaceutical Statistics*, 22, 853-867.
- Lu, Q.S., Tse, S.K., Chow, S.C., and Lin, M (2012). Analysis of time-to-event data with non-uniform patient entry and loss to follow-up under a two-stage seamless adaptive design with Weibull distribution. *Journal of Biopharmaceutical Statistics*, 22, 773-784.
- Wang, J. and Chow, S.C. (2012). On regulatory approval pathway of biosimilar products. *Pharmaceuticals*, 5, 353-368; doi:10.3390/ph5040353.
- Chow, S.C. (2012). Flexible, adaptive or attractive clinical trial design. *Drug Designing*, 1:e104, doi:10.4172/ddo.1000e104.

# Recent Publication of Dr. Shein-Chung Chow （2012~2014）

## Research Papers:

- Lin, A. and Chow, S.C. (2013). Data monitoring committees in adaptive clinical trials. *Clinical Investigation*, Vo. 3, No. 7, 605-607.
- Chow, S.C. and Ju, C. (2013). Assessing biosimilarity and interchangeability of biosimilar products under the Biologics Price Competition and Innovation Act. *Generics and Biosimilars Initiative Journal*, 2, 20-25.
- Chow, S.C., Wang, J., Endrenyi, L., and Lachenbruch, P. (2013). Scientific considerations for assessing biosimilar products. *Statistics in Medicine*, 32, 370-381
- Chow, S.C., Endrenyi, L., and Lachenbruch, P.A. (2013). Comments on FDA draft guidances on biosimilar products. *Statistics in Medicine*, 32, 364-369.
- Endrenyi, L., Chang C., Chow, S.C., and Tothfalusi, L. (2013). On the interchangeability of biologic drug products. *Statistics in Medicine*, 32, 434-441.
- Hsieh, T.C., Chow, S.C., Yang, L.Y., and Chi, E. (2013). The evaluation of biosimilarity index based on reproducibility probability for assessing follow-on biologics. *Statistics in Medicine*, 32, 406-414.
- Chow, S.C., Yang, L.Y., Starr, A., and Chiu, S.T. (2013). Statistical methods for assessing interchangeability of biosimilars. *Statistics in Medicine*, 32, 442-448.
- Yang, J., Zhang, N., Chow, S.C., and Chi, E. (2013). An adaptive F-test for heterogeneity of variability in follow-on biologic products. *Statistics in Medicine*, 415-423.
- Zhang, H., Chow, S.C., and Chi, E. (2013). Comparison of different biosimilarity criteria under various designs. *Journal of Biopharmaceutical Statistics*, To appear.
- Chow, S.C. (2013). Assessing biosimilarity and interchangeability of biosimilar products. *Statistics in Medicine*, 32, 361-363.
- Kang, S.H. and Chow, S.C. (2013). Statistical assessment of biosimilarity based on relative distance between follow-on biologics. *Statistics in Medicine*, 32, 382-392.
- Lin M., Yang R., and Chow S. C. (2013). A joint model for identifying haplotypes that control drug response and time-to-event. *Statistics in Medicine*, currently under revision.
- Zhang, N., Yang, J., Chow, S.C. and Chi, E. (2013). Impact of variability on the choice of biosimilarity limits in assessing follow-on biologics. *Statistics in Medicine*, 32, 424-433.

# Recent Publication of Dr. Shein-Chung Chow （2012~2014）

## Research Papers:

- Lin, J.R., Chow, S.C., Chang, C.H., Lin, Y.C., and Liu, J.P. (2013). Application of the parallel line assay to assessment of biosimilar products based on binary endpoints, *Statistics in Medicine*, 32, 449-461.
- Chow, S.C. and Chiu, S.T. (2013). Sample Size and Data Monitoring for Clinical Trials with Extremely Low Incidence Rate. *Therapeutic Innovation & Regulatory Science,* 47, 438-446.
- Chow, S.C. and Chiu, S.T. (2013). On design and analysis of clinical trials. Journal of Drug Designing, 2:1http://dx.doi.org/10.4172/2169-0138.1000102
- Lu, Y., Chow, S.C. and Zhang, Z.Z. (2013). Statistical designs for assessing interchangeability of biosimilar products. Drug Designing, 2, No.3, 109-114.
- Zhang, A., Tzeng, J.Y., and Chow, S.C. (2013). Establishment of reference standards in biosimilars. Generic and Biosimilar Initiatives, 2, 173-177.
- Zhang, A., Tzeng, J.Y., and Chow, S.C. (2013).Statistical considerations in biosimilar assessment using biosimilarity index. *Journal of Bioavailability & Bioequivalence*, 5, 209-214.
- Chow, S.C. (2014). Adaptive clinical trial design. *Annual Review of Medicine*. 65, 405-415.
- Chow, S.C. (2014). Bioavailability and bioequivalence in drug development. *WIRES Computational Statistics*. 6 (4), 304-312.
- Tothfalusi L., Endrenyi L., and Chow, S.C. (2014). Statistical and regulatory considerations in assessments of interchangeability. *European Journal of Health Economics,* 15 (Suppl 1):S5–S11
- DOI 10.1007/s10198-014-0589-1.
- Wu, Y.J., Tan, T.S., Chow, S.C., and Hsiao, C.F. (2014). Sample size estimation of multiregional clinical trials with heterogeneous variability across regions. *Journal of Biopharmaceutical Statistics*, 24, 254-271.
- Zhang, A., Tzeng, J.Y., and Chow, S.C. (2014). The assessment of biosimilarity with SABE and IBE criteria under a switching/alternating design. *Journal of Generics and Biosimilar Initiatives*, 2, In press.
- Lu, Y., Chow, S.C., and Zhu, S.C. (2014). *In vitro* and *in vivo* bioequivalence testing. *Journal of Bioavailability and Bioequivalence*, 6, 67-74.
- Chiu, S.T., Chen C., Chow, S.C., and Chi, M. (2014). Assessing biosimilarity of biosimilar products using GPQ. *Journal of Generics and Biosimilars Initiatives*, 2, No. 3, 130-135.

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# Adaptive Design Methods in Clinical Research

Shein-Chung Chow, PhD
Department of Biostatistics and Bioinformatics
Duke University School of Medicine
Durham, North Carolina
sheinchung.chow@duke.edu

2424 Erwin Road, Suite 1102, Room 11068
Durham, NC 27710, USA
Tel: 1-919-668-7523 Fax: 1-919-668-5888

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# Outline

- Background and motivation
- What is adaptive design?
- Type of adaptive designs
- Regulatory perspectives
- Statistical perspectives
- Possible benefits
- Remarks

# Background

- Increasing spending of biomedical research does *not* reflect an increase of the success rate of pharmaceutical development.
- Many drug products were *withdrawn* or *recalled* due to safety issues after regulatory approval.

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# The causes – Woodcock (2004)

- A *diminished margin* for improvement that escalates the level of difficulty in proving drug benefits.
- *Genomics* and other new science have not yet reached their full potential.
- *Mergers* and other business arrangements have decreased candidates.
- Easy targets are the focus as chronic diseases are harder to study.
- *Failure rates* have not improved.
- Rapidly escalating *costs* and complexity decrease willingness/ability to bring many candidates forward into the clinic.

# Critical Path Initiative

- In its 2004 Critical Path Report, the FDA presented its diagnosis of the scientific challenges underlying the medical product pipeline problems.
- On March 16, 2006, the FDA released a *Critical Path Opportunities List* that outlines
  - *76* initial projects (*six* broad topic areas)

  to bridge the gap between the quick pace of new biomedical discoveries and the slower pace at which those discoveries are currently developed into therapies.

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# Critical path opportunities list

1. Better evaluation tools
2. Streamlining clinical Trials
   - *Advancing innovative trial designs*
3. Harnessing *bioinformatics*
4. Moving *manufacturing* into the 21st century
5. Developing products to address *urgent public health needs*
6. Specific at-risk populations - *pediatrics*

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# Advancing innovative trial designs

- Design of active controlled trials
- Enrichment designs
- *Use of prior experience or accumulated information in trial design*
- Development of best practices for handling missing data
- Development of trial protocols for specific therapeutic areas
- Analysis of multiple endpoints

# Use of prior experience or accumulated information in trial design

- The use of Bayesian approach in clinical trial design
  - CDRH has published a guidance on Bayesian approach in devices
- The use of *adaptive design* methods in clinical trials
- The use of Bayesian adaptive design in clinical trials

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# Motivation

- The use of adaptive design is to give the investigator(s) the *flexibility* for identifying any signal, possible trend/pattern, and ideally optimal benefit regarding safety/efficacy of the test treatment under investigation
- The use of adaptive design is to *speed up* the development process in a more *efficient* way without undermining the *scientific validity* of the development

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# An example – the development of Velcade

- Indication
  - Multiple myeloma (accelerated track for orphan drug)
  - Approved by the FDA on June 23, 2008
- Flexibility
  - Modified clinical trial design during the conduct of the trials such as *change primary study endpoint , change hypotheses,* and *two-stage adaptive design*
- Efficiency (speed up development process)
  - It only took 2 years and 4 months (from first patient in to the last patient out) to receive approvable letter from FDA based on a phase II study.

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# What do we learn from this example?

- If the drug is promising and/or no alternative treatments are available, FDA is willing to help the sponsor to identify clinical benefits of the drug under investigation.
- New methodology is acceptable to the FDA as long as the sponsor can demonstrate the following
  - Statistical/scientific *validity* and integrity of the proposed method
  - *Integrity* of the data collected from the trial

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# What is adaptive design?

- There is *no* universal definition.
  - Adaptive randomization, group sequential, and sample size re-estimation, etc.
  - Chow, Chang, and Pong (2005)
  - US PhRMA (2006)
  - US FDA (2010)
- Adaptive design is also known as
  - Flexible design (EMEA, 2002, 2006)
  - Attractive design (Uchida, 2006)

# Chow, Chang, and Pong's definition

*Chow SC, Chang M, Pong A (2005).*
*J. Biopharm. Stat., 15 (4), 575-591.*

An adaptive design is a design that allows modification (*adaptation*) to some aspects (e.g., *trial* and/or *statistical procedures*) of *on-going trials* after initiation without undermining the *validity* and *integrity* of the trials.

# Trial procedures

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

etc.

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# Statistical procedures

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

  etc.

# Chow-Chang-Pong's definition

- Characteristics
  - Adaptation is *not limited to* a design feature
  - Changes can be made prospectively, concurrently, and/or retrospectively.
- Comments
  - It reflects real clinical practice (e.g., concurrent protocol amendments and/or SAP).
  - It is flexible and attractive.

# PhRMA's definition

*PhRMA (2006), J. Biopharm. Stat., 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
    - *Ad hoc* protocol amendments
  - It may *not* be flexible as it means to be
    - Adaption is *by design* only

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# FDA's definition

*FDA Guidance for Industry – Adaptive Design Clinical Trials for Drugs and Biologics  Feb, 2010*

An adaptive design clinical study is defined as a study that includes a *prospectively* planned opportunity for *modification* of one or more specified aspects of the study design and hypotheses based on *analysis of data (usually interim data)* from subjects in the study

# FDA's definition

- Characteristics
  - Adaptation is a *prospectively* planned opportunity.
  - Changes are made based on *analysis of data* (usually interim data).
- Comments
  - It is not flexible because only prospective adaptations are allowed
  - It does *not* reflect real practice (e.g., protocol amendments)
  - It does not mention *validity* and *integrity*?

# FDA's definition

- Comments
  - The interpretations vary from statistical reviewer (and/or medical reviewer) to statistical reviewer (and/or medical reviewer)
  - FDA encourages the sponsors consulting with statistical/medical reviewers when utilizing adaptive design in the intended clinical trials
  - It classifies adaptive designs into
    - *well-understood designs* and
    - *less well-understood designs*
  - It is general guidance not a *design-specific* guidance.

# FDA's definition

- *Well-understood design*
  - Has been in practice for years
  - Statistical methods are well established
  - FDA is familiar with the study design
- *Less well-understood design*
  - Relative merits and limitations have not yet been fully evaluated
  - Valid statistical methods have not yet been developed/established
  - FDA does not have sufficient experience for submissions utilizing such study design

# Adaptation

- An *adaptation* is defined as a change or modification made to a clinical trial before and during the conduct of the study.
- Examples include
  - Relax inclusion/exclusion criteria
  - Change study endpoints
  - Modify dose and treatment duration

  etc.

# Types of adaptations

- Prospective adaptations
  - Adaptive randomization
  - Interim analysis
  - Stopping trial early due to safety, futility, or efficacy
  - Sample size re-estimation, etc.
- Concurrent adaptations
  - Trial procedures
- Retrospective adaptations
  - Statistical procedures

# Implementation of adaptations

- Prospective adaptations
  - Design features
  - Implemented by *study protocol*
- Concurrent adaptations
  - Changes made during the conduct of the study
  - Implemented by *protocol amendments*
- Retrospective adaptations
  - Changes made after the conduct of the study
  - Implemented by *statistical analysis plan* prior to database lock and/or data unblinding

# Ten adaptive designs

- Adaptive randomization design
- Group sequential design
- Flexible sample size re-estimation design
- Drop-the-losers (pick-the-winner) design
- Adaptive dose-finding design
- Biomarker-adaptive design
- Adaptive treatment-switching design
- Adaptive-hypotheses design
- Adaptive seamless design
  - Two-stage phase I/II (or II/III) adaptive design
- Multiple adaptive design (any combinations of the above designs)

# Most popular adaptive designs

- Adaptive randomization design
- *Group sequential design*
- Flexible sample size re-estimation design
- Drop-the-losers (pick-the-winner) design
- *Adaptive dose finding design*
- *Biomarker-adaptive design*
- Adaptive treatment-switching design
- Adaptive-hypotheses design
- *Two-stage phase I/II (or II/III) adaptive design*
- Multiple adaptive design

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# Adaptive randomization design

- A design that allows modification of randomization schedules (during the conduct of the trial)
  - Increase the probability of success
- Type of adaptive randomization
  - Treatment-adaptive
  - Covariate-adaptive
  - Response-adaptive

# Comments

- Randomization schedule may *not* be available prior to the conduct of the study.
- It may not be feasible for a *large* trial or a trial with a relatively *long* treatment duration.
- Statistical inference on treatment effect is often difficult to obtain if it is not impossible.

# Group sequential design

- An adaptive design that allows for (i) prematurely stopping a trial due to
  - safety,
  - futility/efficacy, or
  - both

  based on interim analysis results, and (ii) sample size re-estimation either in a blinded fashion or a unblinded fashion, which often conducted by an independent data monitoring committee (IDMC)

# Comments

- FDA considers group sequential design is a well-understood design
- What is *adaptive* group sequential design?
  - *Other adaptations*
- Overall type I error rate may not be preserved when
  - there are *changes in hypotheses and/or study endpoints*
  - there is a *shift* in target patient population due to *protocol amendments*

# Flexible sample size re-estimation design

- An adaptive design that allows for sample size adjustment or re-estimation based on the observed data at interim
- Sample size adjustment or re-estimation is usually performed based on the following criteria
  - Controlling variability
  - Maintaining treatment effect
  - Achieving *conditional power*
  - Reaching desired reproducibility probability
  - Other criteria such as probability statement

# Comments

- Question to regulatory agency
  - Can we always start with a small number and perform sample size re-estimation at interim?
- It should be noted sample size re-estimation is performed based on *estimates* from the interim analysis.
  - Should account for the *variability* associated with the estimates
- This design is also known as an N-adjustable design.

# Drop-the-losers design

- Drop-the-losers design is a multiple stage adaptive design that allows dropping the inferior treatment groups
  - drop the inferior arms
  - retain the control arm
  - may modify current treatment arms
  - may add additional arms
- It is useful where there are *uncertainties* regarding the dose levels.

# Comments

- The selection criteria and decision rules play important role for drop-the-losers designs.
- Dose groups that are dropped may contain valuable information regarding dose response of the treatment under study.
- How to utilize all of the data for a final analysis?
- Some people prefer *pick-the-winner*.

# Adaptive dose finding design

- Often used in early phase clinical development to identify the maximum tolerable dose (MTD), which is usually considered the optimal dose for later phase clinical trials
- Adaptive dose finding designs often used in cancer clinical trials
  - Dose escalation designs
  - Bayesian sequential designs

# Adaptive dose finding design

- Algorithm-based design
  - Traditional dose escalation rule (TER) design
  - Strict TER design
  - Extended TER design
- Model-based design
  - Continued re-assessment method (CRM)
  - Based on dose-toxicity model
  - CRM may be used in conjunction with Bayesian approach

# An example – the “3+3” TER design

- The traditional escalation rule is to enter three patients at a new dose level and then enter another three patients when a DLT is observed
- The assessment of the six patients is then performed to determine whether the trial should be stopped at the level or to escalate to the next dose level

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# Comments

- Traditional escalation rule (TER) design is considered standard dose escalation design
- Drawbacks of the standard dose escalation design
  - No room for dose de-escalation
  - No sample size justification
  - No further analysis of data
  - No objective estimation of MTD with statistical model
  - No sampling error and no confidence interval

# Comments

- Continued re-assessment method (CRM) design is considered Bayesian sequential design
- Concerns of Bayesian sequential design
  - Validation of dose-toxicity model
  - Sensitivity for selection of prior distribution
  - Safety concern for possible of dose jump
  - The probability of overdosing
  - The probability of correctly achieving the MTD (maximum tolerable dose)

# Comments

- How to select the *initial dose*?
- How to select the *dose range* under study?
- How to achieve statistical significance with a desired power with a *limited number of subjects*?
- What are the selection criteria and decision rules?
- What is the *probability of achieving the optimal dose*?

# Biomarker- adaptive design

- A design that allows for adaptation based on the responses of biomarkers such as pharmacokinetic (PK) and pharmacodynamics (PD) markers and genomic markers
- Types of biomarker
  - Classifier marker
  - Prognostic marker
  - Predictive marker

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# Type of biomarkers

- A *classifier marker* usually does not change over the course of study and can be used to identify patient  population who would benefit from the treatment from those do not.
  - DNA marker and other baseline marker for population selection
- A *prognostic marker* informs the clinical outcomes, independent of treatment.
- A *predictive marker* informs the treatment effect on the clinical endpoint.
  - Predictive marker can be population-specific. That is, a marker can be predictive for population A but not population B.

# Enrichment strategies with classifier biomarkers

| | Population Size | Response (Treatment A) | Response (Treatment B) | Sample size (90% power ) |
|---|---|---|---|---|
| Biomarker (+) | 10M | 50% | 25% | 160* |
| Biomarker (-) | 40M | 30% | 25% | |
| Total | 50M | 34% | 25% | 1800 |

* 800 subjects for screening.

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# Comments

- Classifier marker is commonly used in enrichment process of *target clinical trials*
- Prognostic vs. predictive markers
  - Correlation between biomarker and true endpoint make a prognostic marker
  - Correlation between biomarker and true endpoint *does not* make a predictive biomarker
- There is a *gap* between identifying genes that associated with clinical outcomes and establishing a predictive model between relevant genes and clinical outcomes

# Adaptive treatment-switching design

- A design that allows the investigator to switch a patient's treatment from an initial assignment to an alternative treatment if there is evidence of lack of efficacy or safety of the initial treatment
  - commonly employed in cancer trials

# Comments

- Estimation of survival is a challenge to biostatistician.
- A high percentage of subjects who switched could lead to a change in hypotheses to be tested.
- Sample size adjustment for achieving a desired power is critical to the success of the study.

# Adaptive-hypotheses design

- A design that allows change in hypotheses based on interim analysis results
  - often considered before database lock and/or prior to data unblinding
- Examples
  - switch from a superiority hypothesis to a non-inferiority hypothesis
  - change in study endpoints (e.g., switch primary and secondary endpoints)

# Comments

- Switch between non-inferiority and superiority
  - The selection of *non-inferiority margin*
  - Sample size calculation
- Switch between the primary endpoint and the secondary endpoints
  - Perhaps, should consider the switch from the primary endpoint to a *co-primary* endpoint or a *composite* endpoint

# Adaptive seamless design

- An adaptive seamless design is a trial design that combines two separate independent trials into one single study
- The single study would be able to address study objectives of individual studies
- This design usually consists of two phases (stages)
  - Learning (exploratory) phase
  - Confirmatory phase
- This design is known as a *two-stage adaptive seamless design*

# Examples

- A two-stage phase I/II design
  - First stage is for a phase I study for dose finding
  - Second stage is phase II study for early efficacy confirmation
- A two-stage phase II/III design
  - First stage is a phase IIb study for treatment selection
  - Second stage is a phase III study for efficacy confirmation

# Comments

- Characteristics
  - Will be able to address study objectives of individual phase IIb and phase III studies
  - Will utilize data collected from phase IIb and phase III for final analysis
- Commonly asked questions/concerns
  - Is it valid?
  - Is it efficient?
  - How to perform a combined analysis if the study objectives/endpoints are different at different phases?
  - How to perform sample size calculation?

# Multiple adaptive design

- A multiple adaptive design is any combinations of the above adaptive designs
  - very flexible
  - very attractive
  - very complicated
  - statistical inference is often difficult, if not impossible to obtain

# Regulatory 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.

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# Operational bias

- Operational bias results when information from an ongoing trial causes *changes to the participant pool*, *investigator behavior*, or other *clinical aspects* that affect the conduct of the trial in such a way that conclusions about important *efficacy* or *safety* parameters are biased.

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# An example – questions from FDA

- Provide strategy for preventing *operational biases*
- Provide detailed description of power analysis for *sample size* calculation
- Provide detailed information as to how the overall *type I error* is controlled
- Provide justification for the *validity* of the statistical methods for data analysis
- Provide justification for *stopping boundaries* based on the proposed alpha spending function

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# Statistical perspectives

- Major (or significant) adaptations (e.g., modifications or changes) to trial and/or statistical procedures could
  - introduce *bias/variation* to data collection
  - change in *target patient population*
  - lead to *inconsistency* between hypotheses to be tested and the corresponding statistical tests

# 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

# Possible benefits

- Correct *wrong* assumptions
  - e.g., sample size re-estimation
- Select the *most promising* option *early*
  - e.g., stop trial early; drop inferior treatments, etc.
- Make use of emerging external information to the trial
  - e.g., modification of dose or treatment duration
- React earlier to *surprises* (positive and/or negative)
  - e.g., stop trial early

# Possible benefits

- May have a second chance to *re-design (modify)* the trial after seeing data from the trial itself at interim (or externally)
- Sample size
  - may start out with a smaller sample size with up-front commitment of sample size
- *Speed up* development process
- More *flexible* but more problematic operationally due to potential bias

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# Obstacles
# protocol amendments

- 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
- Some protocols may have up to 12 protocol amendments
- There are no regulations on the number of protocol amendments that one can have

# Obstacles
# Data Safety Monitoring Committee

- DSMB is responsible for the quality and integrity of the conduct of the trial
- DSMB may *not* have experience in monitoring clinical trials utilizing adaptive designs
- The *independence* of DSMB is a concern
- Role and responsibility of usual DSMB need to be well-defined

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# Future perspectives

- Design-specific guidances are necessarily developed
  - *Misuse*
  - *Abuse*
- Statistical methods need to be derived
  - *Validity*
  - *Reliability/reproducibility*
- Monitoring of adaptive trial design
  - *Quality*
  - *Integrity*

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# 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.
  - Specific guidelines regarding different types of less-well-understood adaptive designs are necessary developed.

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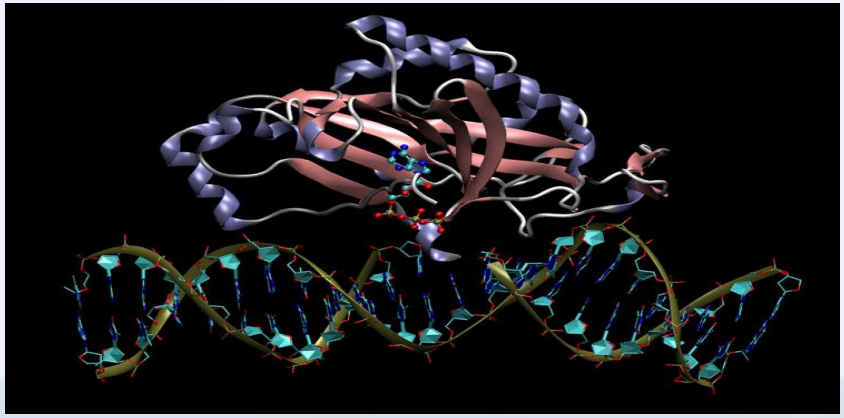

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