Bayesian Approach in Adaptive Clinical Trial Designs and Analyses

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• Introduction to Bayesian Approach
  › Advantages
  › The Central Concept
  › An Illustration Example
  › Software and Packages

• Bayesian Adaptive Designs and Analyses
  › Types of Bayesian Adaptive Designs
  › Applications of Bayesian Adaptive Designs and Analyses

• Questions and Comments
Why Bayesian Approach?

• Bayesian approach are becoming more and more practical and popular in clinical trial design, monitoring and data analysis due to:
  › Its flexibility and efficiency
  › Use accumulated evidence through out both design and analysis stages (all phases)
  › Easy to make predictions
  › Straightforward interpretation (Pr (treatment difference > target difference))
  › Software and packages (SAS\R\WinBUGS etc) are available
  › Optimize the drug development process (increased chances of success & reduced cost)

• Bayesian approach is accepted by FDA/NIH/Journals/Industries
  › Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials, 2010
  › Guidance for Industry, Adaptive Design Clinical Trials for Drugs and Biologics, 2010
  › DIA Bayesian Scientific Working Group (DIA BSWG)
Bayes’ Rule/ Bayes’ Theorem: The central concept of Bayesian approach:

• Given a prior state of knowledge or belief, Bayes’ Rule tells how to update knowledge or belief based on current observations.

• For random variables (or events) A and B:

\[ P(A|B) = \frac{P(A,B)}{P(B)} = \frac{P(B|A)P(A)}{P(B)} \]

• For any parameter \( \theta \) with prior distribution \( P(\theta) \), the posterior probability of \( \theta \) given data:

\[ P(\theta | \text{Data}) = \frac{P(\text{Data} | \theta )P(\theta)}{P(\text{Data})} \]

Posterior distribution \( \propto \) Likelihood * Prior distribution

• For a hypothesis H given observed data, the posterior probability of the hypothesis:

\[ P(H|\text{Data}) = \frac{P(\text{Data}|H)P(H)}{P(\text{Data})} \]
Example: Suppose that an experimental treatment is being used in a disease for which the historical success rate for standard treatment was 35%, observation is SSFSSFSSSF for 10 patients.

Frequentist  Design 1: Treating exactly 10 patients in the trial.

Design 2: Continue the trial until the third F (failure).

p = 0.35 is called the null hypothesis. The table below shows the binomial distribution probabilities

<table>
<thead>
<tr>
<th>Successes</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>p = 0.35</td>
<td>0.013</td>
<td>0.072</td>
<td>0.176</td>
<td>0.252</td>
<td>0.238</td>
<td>0.154</td>
<td>0.069</td>
<td><strong>0.021</strong></td>
<td>0.004</td>
<td>0.001</td>
<td>0.000</td>
</tr>
<tr>
<td>p = 0.70</td>
<td>0.000</td>
<td>0.000</td>
<td>0.001</td>
<td>0.009</td>
<td>0.037</td>
<td>0.103</td>
<td>0.200</td>
<td><strong>0.267</strong></td>
<td>0.233</td>
<td>0.121</td>
<td>0.028</td>
</tr>
</tbody>
</table>

- For design 1, the probability of observing data SSFSSFSSSF is in bold, the Frequentist p-value is pr=0.026 (1-sided) or pr=0.039 (2-sided). The probability of observing a result as or more extreme than that observed assuming that the treatment is ineffective.

- For design 2, the probability of observing data SSFSSFSSSF is pr=0.011(stronger) from negative binomial distribution (R function sum(dnbinom(7:1000,3,0.65))).
**Bayesian:** In the example, because $p$ is unknown, it has a probability distribution. This distribution can be used for calculating such quantities as the probability that $p$ is equal to 0.35 or greater than 0.50 and so on. In the example, probabilities regarding $p$ are calculated conditionally on having observed 7 successes and 3 failures. Sequence of probability distributions for success rate $p$ corresponding to data SSFSSFSSSF can be calculated based on Bayes’ rule.

- Assume prior $\text{pr}(p=0.35)=\text{pr}(p=0.7)=0.5$, then posterior probability is $\text{pr}(p=0.35)=0.021\times0.5/(0.021\times0.5+0.267\times0.5)=0.073$ from Bayes’ rule compared with the prior probability of 0.5 - Easy to interpret.

- If we use flat (non-informative) prior, the distribution of $p$ can be updated with each observation S or F.
Updated distribution graph after each patient
Updated distribution graph after each patient
Predicted probabilities

• After observing the 10th patient, the updated posterior probability that $p \leq 0.35$ is 0.014, or the probability that the therapy was not an improvement over the historical success rate was only 0.014. One can conclude the therapy is working better.

• The predictive probability that the eleventh observation will be a success given the results of the first ten patients is $(7 + 1)/(10 + 2) = 0.67$ and the remaining 0.33 probability is for failure.

• In addition to predictions, Bayesian approached can be used in trial design including sample size estimations and monitoring.
In the past, computation was a major hurdle
  › Limited to close forms, available conjugate priors
MCMC algorithm was a major breakthrough
Currently multiple software and languages are available for Bayesian analyses which make the learning of Bayesian computation much easier and more practical
  › WinBUGS /OpenBUGS
  › SAS
  › JAGS (Just Another Gibbs Sampler)
  › Stan
  › R interfaces: R2WinBUGS, BRugs, RJAGS, RStan
Types of Bayesian Adaptive Designs (AD):

› Group Sequential AD
› Sample-size re-estimation AD
› Drop-losers AD
› Dose-escalation AD/Dose-finding AD
› Adaptive randomization design
› Biomarker AD
› Clinical trial simulations
› Others (could be combinations)
Advanced Statistical Methods and Analytics Group at iVC

- Projects done for clients
  - 2011-2013: ~ 15 projects every year

- Projects in different therapeutic areas
  - Preclinical, Autoimmune, Cardiovascular, Diabetes
    Musculoskeletal, Neuroscience, Oncology

- Different types of projects
  - Critical Success Factor (CSF)/ Probability of Study Success (PrSS) projects based on phase 2 study data to help in making decision for drug development
  - Meta-analyses projects
  - Enrollment Prediction: (rare events and randomization predictions)
  - Diabetes Data Monitoring Committee (DMC)
  - Web tools development
Bayesian adaptive designs and analysis:

- Bayesian Adaptive Dose-Escalation/Bayesian Adaptive Dose Finding
- Bayesian Enrollment Predictions
- Bayesian Futility Monitoring and Sample Size Re-estimation
- Bayesian Critical Success Factors/Probability of Study Success
Bayesian Adaptive Dose-Escalation:

Continual Reassessment Method (CRM):

• The first Bayesian model-based adaptive design in phase I study
  › Hyperbolic tangent mode, Logistic model, Power model

• Key steps:
  › After each patient (or cohort), posterior distribution of model parameter is updated
  › Calculate the predicted toxicity rate for each pre-specified dose
  › Locate the dose with predicted toxicity closest to the target rate
  › Assign next patient (or cohort) to this dose
  › Repeat above until reaching a certain stopping rule

• Recommend maximum toxicity dose, dose with predicted probability closest to the target rate
Bayesian Adaptive Dose Finding with Adaptive Randomization:

Goal: Find and study the $ED_{90}$ or similar variable

- **Model:** Dose response model is a normal dynamic linear model (NDLM)
  
  Let $P_d$ be the probability of a response (binary variable) for dose $d$,
  
  Let $\mu_d$ be the log-odds response for dose $d$ for $d=0,1,2,3$. $\mu_d = \log\left(\frac{P_d}{1-P_d}\right)$, $d=0$ is placebo dose.

  Prior: $\mu_0 \sim N(\log(0.15/0.85), 1)$  
  $\mu_d \sim N(\log(0.3/0.7), 1)$  
  $\mu_d \sim N(\mu_{d-1}, s^2)$  
  $s^2 \sim \text{Inverse Gamma}(a, b)$

- **Adaptation:** At each interim look a new randomization algorithm is to find the smallest dose that achieves at least 90% of the efficacy of the most effective dose ($ED_{90}$).

  $ED_{90}$: Define as the smallest dose achieving a response probability at least 0.9 ($\max(P_1,..P_3) - P_0$)

  The probability assigned to the placebo dose is held constant at a rate say 0.30.

  $Pr(d=ED_{90})$: The posterior probability that dose $d$ is the $ED_{90}$

  Randomization probability for each dose $d$: $0.7 \times Pr(d=ED_{90})/ \sum(Pr(i=ED_{90}))$, $1<=i<=3$

- **Stopping Rules:** If the most likely $ED_{90}$ dose has a posterior probability of 0.30 or less of achieving the clinically significant difference (CSD) of 0.20.
Bayesian Enrollment Predictions

- **Objectives:**
  - Predict number of events to find out how many patients to enroll
  - Predict the time (given the sample size) when will hit the targeted events
  --Under-estimation will result in more patients need to be enrolled with shorter follow up period than anticipated and over-estimation will result in longer follow up, added cost and delay in regulatory submissions and approval.

- **Methods and models:**
  - Bayesian piece-wise exponential models based on literature data or current available data;
  - Bayesian Poisson models
  - Predictive probabilities
  - Perform sensitivity analyses if the assumed rates varies

- **Key steps for number of events and time predictions:**
  - Use priors from literature data and current available data
  - Generate posteriors
  - Use posteriors to predict events and time

- **Implemented with R and SAS;**
Bayesian Futility Monitoring

- Bayesian Predictive Power (vs. Frequentist conditional power)
- Trial Monitoring/Interim Analysis
  - Sample size re-estimations
  - Implementation using R
Frequentist Powers

- Power = Pr(reject H0|H0 is false)
- Conditional power (CP) is the conditional probability of a statistically significant benefit at the final analysis given the data observed at the time of the interim analysis

Bayesian Power

- Bayesian Predictive Power (PP) is the average conditional power w.r.t. the posterior distribution of the treatment effect given the observed data

Comparison of CP and PP

- Frequentist CP in the planned interim analysis time points in trial monitoring
- Bayesian PP in a trial at any time point, given the currently available data information in clinical trial monitoring

- Improve the ability to quantify the uncertainty about future data
A Phase II study with one interim analysis planned:

- **Descriptions**
  - \( Y \) = Number of responses of an efficacy endpoint (binary case)
  - Parallel arms with 144 patients in each arm. With assumed incidence (success) rates of \( p_1 = 0.25, p_2 = 0.15 \), 1-sided significance level of 0.1, 80% power would require 144 pts per arm
  - Assume that 72 patients at the interim analysis in each group

- **Implemented CP and PP in R:**
  - Data at the interim, 15/72 and 10/72 events in the two groups
  - CP=65%, PP=71%

- **Question:** Since all CPs and PPs <80%, how many additional patients should be added after interim analysis to get CP or PP power of 80% or above?

- **Sample Size Re-estimation:** At the interim, if there are 15/72 and 10/72 events in the two groups, the sample size (SS) needed for CP=80% , SS = 213; for PP=80%, SS=181
Critical Success Factors (CSF)/Probability of Study Success (PrSS)

- **Objectives:**
  - To assess key CSFs based on phase 2 study
  - To access the PrSS for future phase 3 study based on CSFs to help in making decision for drug development

- **CSFs:**
  - Assume there are 3 treatment doses (TRT) and placebo (PL) with multiple post-baseline visits
  - \( \Pr[(\text{TRT} - \text{PL at 12W}) \geq 30\%] \) for binary efficacy variable
  - \( \Pr[\text{TRT at 12W} \leq 0.5*\text{PL at 12W}] \) for continuous efficacy variable

- **PrSS:** \( \PrSS > 0.80, 0.85, 0.90, 0.95 \)
  - Based on clinical significance (cs): \( \Pr(\text{TRT- PL} \geq \text{cs of 30\%}) \) ;
  - Based on statistical significance (ss): \( \Pr(\text{TRT}-\text{PL is ss}); \)
Applications of Bayesian Adaptive Designs and Analyses

• **Models/Methods:**
  - Response rates differences between different visits or active treatment and placebo groups were analyzed using a logistic regression model which includes dose group as fixed factor;
  - Continuous efficacy variable for each dose versus placebo using ANCOVA model which includes dose group as a fixed factor and the baseline value of the measure as a continuous covariate;
  - Generate posterior distribution based on phase II data
  - Calculate PrSS based on simulated data for future study design

• **Implementations:**
  - SAS and WinBUGS (sas2bgs)
  - R, R2bugs, r2jags
  - Web tools
Thanks!

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Adaptive Design in Oncology

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Definition of Adaptive Design

- 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 Draft Guidance, Feb. 2010)
Definition of Adaptive Design

- Analyses performed at time points that are prospectively defined
- Potential protocol changes are described prospectively
- Analyses can be performed in blinded or unblinded manner
- May involve formal hypothesis testing
Goals of Adaptive Designs in Oncology Trials

- Fewer patients on placebo
- Fewer patients on ineffective or unsafe doses
- More patients on treatments/doses with higher probability of success
- Speed up drug development process
- Identify failures early
- Save money
Types of Adaptations

- Adaptive randomization
- Sample size adjustments
- Drop the loser
- Adaptive dose finding
- Biomarker adaptive designs
- Seamless Phase II/III designs
- Others
Situations Where Adaptive Design Useful in Oncology

- Little knowledge of endpoint characteristics when planning study
- Patient recruitment is slow
- Efficacy/safety assessments measured quickly and easily
- Study not considered confirmatory
- Stable endpoint
Situations Where Adaptive Designs Not Useful

- Fast recruitment
- Slow to observe endpoint (e.g. survival, disease progression)
- High placebo response
Early Phase Oncology Trials

- Cytotoxic vs. targeted agents
- Typical goals: Safety, Maximum Tolerated Dose, Signal that drug works
- 3+3 Design
- Accelerated Dose Titration (ADT)
- Continuous Reassessment Method (CRM)
- Other Bayesian approaches
3+3 Design

- Treat 3 subjects at initial dose level
- If no DLTs, proceed to next dose level
- If one DLT, treat 3 more subjects.
  - If no DLTs, proceed to higher dose
  - If 2nd DLT, MTD exceeded.
- MTD is dose below the toxic level that has 2 DLTs
  - Often confirm MTD in an expansion cohort
  - Can use a Bayesian rule for expansion
Accelerated Dose Titration

- More rapid dose escalation
- Single subject cohorts
- Fewer subjects treated at sub-therapeutic doses
- Can double doses if supported by preclinical data
- Convert to 3+3 when pre-specified safety or PK criteria met
Continual Reassessment Method

- Determine the MTD with ongoing risk assessment
- Requires model of toxicity response as a function of dose
- After each cohort, dose-toxicity model is updated and dose for next cohort is selected mathematically based on prior subjects
- Requires simulation to design
Summary

- Adaptive designs can increase trial efficiency and expose fewer oncology patients to ineffective doses or placebo.
- Seek regulatory guidance before implementing adaptive designs in late-stage trials.
- Many useful adaptive designs have been proposed for Phase I and Phase II studies.
Adaptive designs in confirmatory trials

Introduction to adaptive design concepts

Jeff Maca
Sr. Director, Center for Statistics in Drug Development, Quintiles Inc.
Overview of Adaptive designs

Outline:

1) Introduction
   a) Motivation
   b) What can change?
2) Adaptive Designs
   a) Sample size re-estimation
   b) Adaptive Dose Finding
   c) Seamless designs
   d) Enrichment designs
3) Conclusions
Introduction and Motivation

Pressure continues to grow to conduct clinical trials

• **Faster** - Can a trial be completed within faster timelines
• **Earlier** - Can we start a trial with a piece of needed design information missing?
• **Smaller** – Can sample size be reduced and still achieve the trial objectives?

**Overall challenge** – Not all the information we need at the design stage is available.

→ Can we correct assumptions during the conduct of the study
Introduction and Motivation

With proper planning, changes can be made at interim to change the conduct of the study

Adaptive design examples:

• Group sequential designs
• Futility analysis
• Sample size re-estimation
• Adaptive dose finding
• Seamless designs
• Enrichment designs
• . . . .
Overview of Adaptive Designs

Motivation

Adaptive Designs: Using accumulating data to decide on how to modify aspects of the trial design, during the conduct of the trial and without violating the integrity of the trial

• An adaptive trial can plan at the design stage to correct for incorrect assumptions
• Adaptive trials can merge what might be considered two separate trials into one trial
• Careful planning is necessity
What can Change?

Adaptive designs is a broad class of studies, and can be quite different from each other.

Some Examples:

- Sample Size (sample size re-estimation)
  - Can be on *Blinded* or *Unblinded* review of data
  - Can be related to the hypothesis of interest
- Treatment arms (delete, add, change)
  - Adaptive dose finding
  - Adaptive Seamless Phase II/III trials
- Population of interest
Sample Size Re-estimation

- Number of patients in a clinical trial are such that desired power is achieved.
  > Required sample size depends on **variability of primary endpoint** (and hypothesized treatment effect)
  > Variability estimate may be uncertain for new indications/some disease areas:
    - **increased risk of failure** (too low sample size)
    - **unnecessary cost** (too high sample size).

- **Sample size re-estimation** aims to correct for the initial uncertainty of variability, and to **maintain the desired power**.
Blinded sample size re-estimation

Sample size re-estimation can be performed:

> **Blinded**
> **Unblinded**

- **Blinded:** sample size re-estimation possible without unblinding the study
  > Generally more acceptable
  > - No DMC required
  > - No independent interim analysis team necessary
  > Decisions on sample size re-estimation can be
  > - made by the trial team
  > - openly communicated
**Consequence of mis-specification: power loss**

The loss of power if the standard deviation is larger than the pre-trial initial estimate.

Risk increases from 10% to 36%
Unblinded sample size re-estimation

**Unblinded:** sample size re-estimation unblinds the study

- More precise information on the variability of the primary endpoint (and the treatment effect)
- Requires DMC and independent interim analysis team
- Some concerns on trial integrity:
  - Potential biasing the trial if the investigators/patients think the drug works better/worse than “expected”
  - “Backward calculation“ based on adjusted sample size may give hint on treatment effect

Can be integrated as part of flexible/group sequential design
Decision rules

Sample size re-estimation

Once the data is seen at interim, how to decide on new sample size?

- Should be very careful: the treatment effect estimate is a random variable
- The variability of the treatment estimate at interim could be quite high
Sample Size Re-estimation

Sample size re-estimation cannot be used in all clinical trials:

- There must be a quick readout of the primary endpoint compared to enrollment time in order to estimate the variability during enrollment.
- Logistics and drug supply may in some cases prevent use of sample size re-estimation.
Overview of Adaptive Designs

Prior to study the true position of dose response curve is unknown

In the adaptive dose finding approach, a small number of patients on many initial doses are used to outline the unknown dose-response.

As the dose response emerges more patients are allocated to doses (including new doses) within the dose-range of interest. In addition the number of patients allocated to ‘non-informative’ doses (‘wasted doses’) is decreased.

\[ X = \text{Mean dose response after a pre-defined number of patients} \]
Adaptive Seamless designs

Primary objective – combine “dose selection” and “confirmation” into one trial

• Although dose is most common phase IIb objective, other choices could be made, e.g. population
• After dose selection, only change is to new enrollments (patients are generally not re-randomized)
• Patients on terminated treatment groups could be followed
• All data from the chosen group and comparator is used in the final analysis. Appropriate statistical methods must be used
Overview of Adaptive Designs

Adaptive Seamless Designs

- Dose A
- Dose B
- Dose C
- Placebo

Phase II: Stage A (learning)  Phase B (confirming)

Phase III: < white space >

Time
Adaptive Seamless designs

Statistical methodology for Adaptive Seamless Designs must account for potential biases and statistical issues

• Selection bias (multiplicity)
• Multiple looks at the data (interim analysis)
• Combination of data from independent stages
  > Closed testing procedure and Bonferroni adjustment are two possible methods

Note: Statistical methodology must account for these issues to ensure the validity of the trial
Adaptive Seamless designs

With the added flexibility of seamless designs, comes added complexity.

- Careful consideration should be given to the feasibility for a seamless design for the project.
- Not all projects can use seamless development.
- Even if two programs can use seamless development, one might be better suited than the other.
- Many characteristics add or subtract to the feasibility.
Adaptive Seamless designs

Enrollment vs. Endpoint

• The length of time needed to make a decision relative to the time of enrollment must be small
  > Otherwise enrollment must be paused
• Endpoint must be well known and accepted
  > If the goal of Phase II is to determine the endpoint for registration, seamless development would be difficult
• If surrogate marker will be used for dose selection, it must be accepted, validated and well understood
Adaptive Seamless designs

Clinical Development Time

• There will usually be two pivotal trials for registration
• Entire program must be completed in shorter timelines, not just the adaptive trial

Possible dose responses

• Various dose responses should be examined to determine the effect on the study
  > Power
  > Selection probabilities
Enrichment designs

- **Enrichment designs** target a predetermined subpopulation for registration
- The decision to focus on this population can be made at an interim stage of the study
- Usually uses a predetermined biomarker to define the subgroup
- Sample size could also be adjusted at interim to ensure the right size in the right population is used
Conclusions

- Adaptive designs have an ability to improve the development process by reducing timelines for approval
- Available statistical methods are available to account for adaptive trial designs
- Extra planning is necessary to implement an adaptive design protocol
- Benefits should be carefully weighed against the challenges of such designs before implementation

Think what could be possible(and think early and often)