Monitor On-Going Clinical Trials with a Dynamic Procedure

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Nearly 70% Phase II trials failed to enter into Phase III
More than 90% FIH drug candidates failed to be qualified for NDA/BLA

**Traditional Trial Design with Single Analysis**

- **Trial A** was slightly short of meeting the success goal (i.e. $p<0.05$). Could we make it success if we knew it?
- **Trial B** was obviously a “hopeless” study. Could we terminate it earlier if we knew it to avoid unethical patient suffering and $$$M financial waste?

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**Diagram Notes:**
- **Efficacy Score** vs. **Time of final analysis**
- **Upper bound for being success**
- **Lower bound for being failure**
- **Trial A**
- **Trial B**
Group Sequential (GS) Design

- Pre-planned interim analysis timepoints, stopping boundary based on limited knowledge on efficacy/safety of the drug at design stage
- Needs an Independent Data Monitoring Committee (IDMC) to review the “snapshot” data at the time of interim lock and to make “go/no-go” decision without knowing the TREND of the trial
- Needs an Independent Statistical Group (ISG) to prepare the interim analysis, which usually takes at least 3-6 months
- No adaptation (no “learning and adjustment”) from data observed at each interim analysis
Adaptive Group Sequential (AGS) Design

- Pre-planned interim analysis timepoints, stopping boundary based on limited knowledge on efficacy/safety of the drug at design stage
- Adaptation (e.g. sample size re-estimation) is performed at the pre-defined timepoint where the observed data could be fluctuating and the adaptation could be not reliable
- Needs an Independent Data Monitoring Committee (IDMC) to review the “snapshot” data at the time of interim lock and to make “go/no-go” decision without knowing the TREND of the trial
- Needs an Independent Statistical Group (ISG) to prepare the interim analysis, which usually takes at least 3-6 months
Accumulated Data over Enrollment

- The data are fluctuated, especially at early stage
- They show notable trend at later stage
- Pre-planned interim analyses may provide non-reliable results
- When should we conduct sample size re-estimation?
- Data-guided adaptation seems like making more senses
- How can we do it?
Limitation in current interim analysis with GSD and ASD

- The planned sample size is based on assumed treatment effect $\theta$
- Pre-define timepoints for interim looks
- If the $\theta_{\text{assume}}$ is off too much from the true $\theta$, the timing for sample size re-estimation may be too early or too late, for example:
  - Only a “snapshot” of data at the time of interim lock is presented to IDMC
  - Binary “go/no-go” decision is made by IDMC without knowing the TREND of the data
  - Needs an Independent Statistical Group (ISG) to prepare the interim analysis, which usually takes at least 3-6 months

90% design power and assume $\sigma = 1$.

<table>
<thead>
<tr>
<th>True $\theta$</th>
<th>SS based on true</th>
<th>Assumed $\theta$</th>
<th>SS based assumed</th>
<th>50% of planned</th>
<th>Comment</th>
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<tr>
<td>0.2</td>
<td>526</td>
<td>0.4</td>
<td>133</td>
<td>67</td>
<td>Too early</td>
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<tr>
<td>0.4</td>
<td>133</td>
<td>0.2</td>
<td>526</td>
<td>263</td>
<td>Too late</td>
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An IDMC could make the same recommendation to these two trials because both were within the boundaries unless Trial B had poor safety profile.
The IDMC could feel that the Trial B may be lack of efficacy. But would want to wait until Interim 2.
Continuous Data Monitoring (interim 2)

- The IDMC could have a convincing evidence to recommend that the Trial B can be stopped.
Continuous Data Monitoring (interim 3)

Without seeing the trace of accumulated data, the IDMC could make the same recommendation to these two trials because both were within the boundaries unless Trial B had poor safety profile.
How can it be possible?

- Nearly all clinical trials nowadays are managed by an EDC system.
- Treatment assignment and drug dispensing are managed through the Interactive Response Technology (IRT) (say IWRS).
- By integration of EDC and IWRS, treatment effect on endpoints of interests (safety or efficacy) can be computed by the system automatically and continuously.
- It allows us to access the accumulative treatment effect without human-involved treatment unblinding.
- This “continuous accessibility” enable us to modify the trial while it is ongoing such as
  - Sample size re-calculation
  - Early termination of a “hopeless” trial
  - Re-strategize the interim analysis for a study with overwhelmingly positive trend
  - And more…..
DDM ECO System

Patient data → IWRS → EDC → DDM Engine

Wearable device

Design parameters

Monitored Results

Simulation Engine (parallel computing)

API available
Dynamic Adaptive Design (DAD) & Dynamic Data Monitoring (DDM)

- Dynamic Adaptive Design: adaptive design with dynamic adaptation
  - Data-guided analysis and simulation for trial modification including timing of interim analysis and SSR
- The process implementing DAD is called dynamic data monitoring (DDM), specifically
  - Continuously monitoring on-going data
  - Data-guided adaptation
  - Using the trend analysis to detect whether the trial is “promising” or “hopeless”
  - Controlling the Type I error rate
GSD/ASD are more like a “Car-GPS”
Trial “Radar” System

- A trial radar system on Z-value space or B-value space is constructed by several disjoint regions where different “trending” statuses of treatment effect (efficacy or safety) are characterized.

- Partition B-value space into 4 regions:
  - The “favorable” region: $B(t) \geq (Z_\beta 1 - t + Z_\alpha) t$, equivalently $CP > 1 - \beta$;
  - The “hopeful” region: $\frac{(Z_\beta 1 - t + Z_\alpha) t}{t + \sqrt{(R_{\text{max}} - t)(1-t)}} \leq B(t) \leq (Z_\beta 1 - t + Z_\alpha) t$, where $R_{\text{max}}$ is the maximum sample size ratio allowed;
  - The “unfavorable” region: $\Phi^{-1}(\gamma_f)\sqrt{1 - t} - \theta_\alpha (1 - t) + Z_\alpha < B(t) < \frac{(Z_\beta 1 - t + Z_\alpha) t}{t + \sqrt{(R_{\text{max}} - t)(1-t)}}$
  - Futility region: $B(t) \leq \Phi^{-1}(\gamma_f)\sqrt{1 - t} - \theta_\alpha (1 - t) + Z_\alpha$. 
Illustration of Trial “Radar” System

LSH=Lan, Simon and Halperin (1982)
Dynamic Data Monitoring (A Promising Trial)

- Favorable Region
- Promising Region
- Unfavorable region

Wald Statistics vs. Total Patients enrolled
Dynamic Data Monitoring (A Hopeless Trial)

Wald Statistics

Favorable Region

Promising Region

Unfavorable region

Total Patients enrolled
Video: make a promising trial to be successful
Guidance for monitoring and decision making

- Let $t_k$ and $C_k$ be the $k^{th}$ interim analysis time and stopping boundary;
- Stop the trial early for benefit if $Z(t_k) \geq C_k$ or $B(t_k) \geq C_k\sqrt{t_k}$;
- If $B(t)$ falls in the “futility” region persistently, we could consider stopping the trial for futility with non-binding decision.
- If $B(t)$ falls in the “favorable” region, continue monitoring without any change;
- If $B(t)$ falls in the “hopeful” region, re-estimate the sample size. Choosing $R_{max}$ depends on sponsor’s affordability.
- If $B(t)$ falls in the “unfavorable” region, if $B(t)$ stays in this region persistently, we may want to terminate the trial based on administrative decision, for the reason of exceeding the affordable budget.
## Simulation Study

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<th>$\delta_{true}$</th>
<th>$\gamma_f$ (CP under $H_a$)</th>
<th>Futility rate</th>
<th>Rejection rate</th>
<th>Average Sample Size</th>
<th>SSR timepoint</th>
<th>Futility timepoint</th>
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- $\delta_{assmue} = 0.4$, $N = 132$ per group; # of simulation=100,000.
- OB-F type boundary for early efficacy stopping with 5 looks, equally spaced;
- SSR and futility are monitored after $t=0.4$ and only one SSR allowed.
Apply to IDMC of a COVID-19 Trial

Ref: Shih, W., Yao, C. and Xie, T (2020), Therapeutic Innovation & Regulatory Science, DOI: 10.1007/s43441-020-00159-7
Comments on future IDMC practice

- With the DDM system, the IDMC plays a role like a “ground controller” in aviation industry to make recommendations not only just the “go/no-go”, but also to guide the trial to “travel” to its destination.
- To minimize potential operational bias, the “radar” screen may be turned on only during IDMC meeting and accessible only by IDMC members.
- For the purpose of closely monitoring the drug safety, IDMC may require turning on the only safety portion display so that it can be monitored by IDMC directly in real time fashion.
Apply to trial diagnosis for completed study (Study I: positive one)

A Multi-Center, Randomized, Double-Blind, Placebo-Control Phase II Study with Oral drug treating elderly patients with Nocturia.
A Randomized, Double-Blind, Placebo-Controlled Phase II Study to Assess the Safety and Efficacy of oral drug in NAFLD Patients. N=96, the study took 2 years to finish.
Potential Applications of DDM

- **Trial optimization**
  - Through DDM and AI technology, we could optimize on-going trial to maximize its success

- **Trial diagnosis**
  - Apply DDM to completed, especially for those failed clinical trials to better understand what was going on during the trials;

- **Early termination of “hopeless” trials**
  - Given the high rate of failure of phase 2/3 trials, DDM could alert the sponsor to conduct a formal futility analysis, or other adaptive procedures (such as population enrichment, or sample size modification)
  - Timely terminating “hopeless” trials is both an ethical and financial issue

- **Drug safety detection**
  - Continue monitor drug safety; signal detection

- **Dose selection**
  - DDM enables a seamless, optimal phase2/3 combination trial by identifying the most potential doses for phase 3.

- **Population selection**
  - DDM could intelligently identify the subpopulation in which the drug could be most effective.
  - DDM could be directly applied to RCT or RWE setting for personalized medicine

- **Sample size re-estimation**
  - DDM could intelligently estimate an optimal sample size for a trial and thus maximizes the probability of success of the trial
Summary

▪ DAD/DDM is based on the well-established methodology of AGSD and utilizes the advanced technologies (EDC/IWRS, high speed computation, simulation, automation) to monitor trial data continuously and dynamically.

▪ As with any useful tools, DDM should be implemented under proper guidance. We emphasize that the study protocol and statistical analysis plan (SAP) should clearly lay out the purpose of interim monitoring and associated analyses.

▪ We are entering the A.I., digital and personalized medicine era. One of the purposes of this presentation is to voice the need for changing the thinking and way of conducting clinical trials to meet the new challenges and opportunities.

▪ The future clinical trials need innovative methods and ways to conduct!
Thank you!

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