Monitor On-Going Clinical Trials with a Dynamic Procedure

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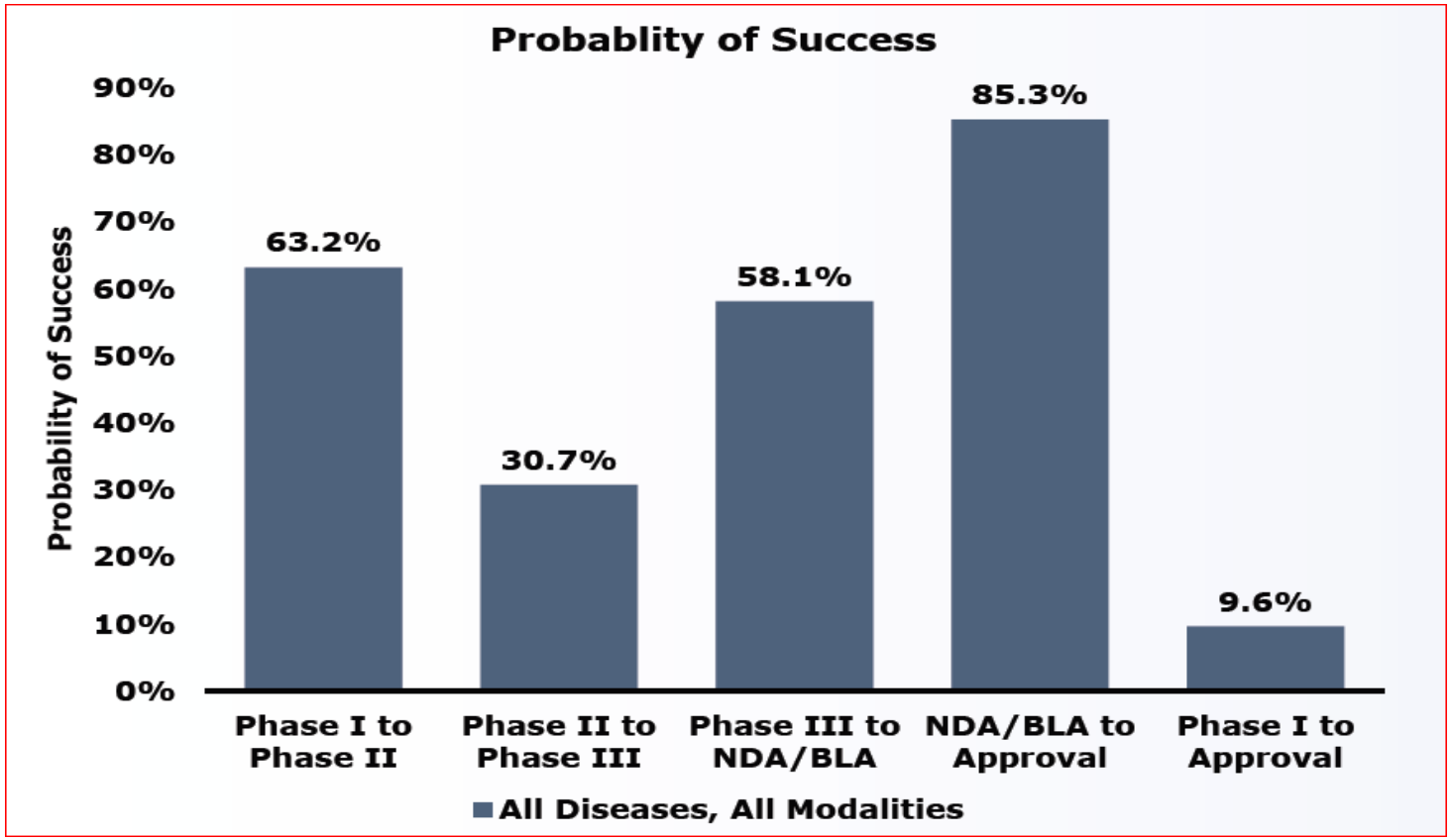
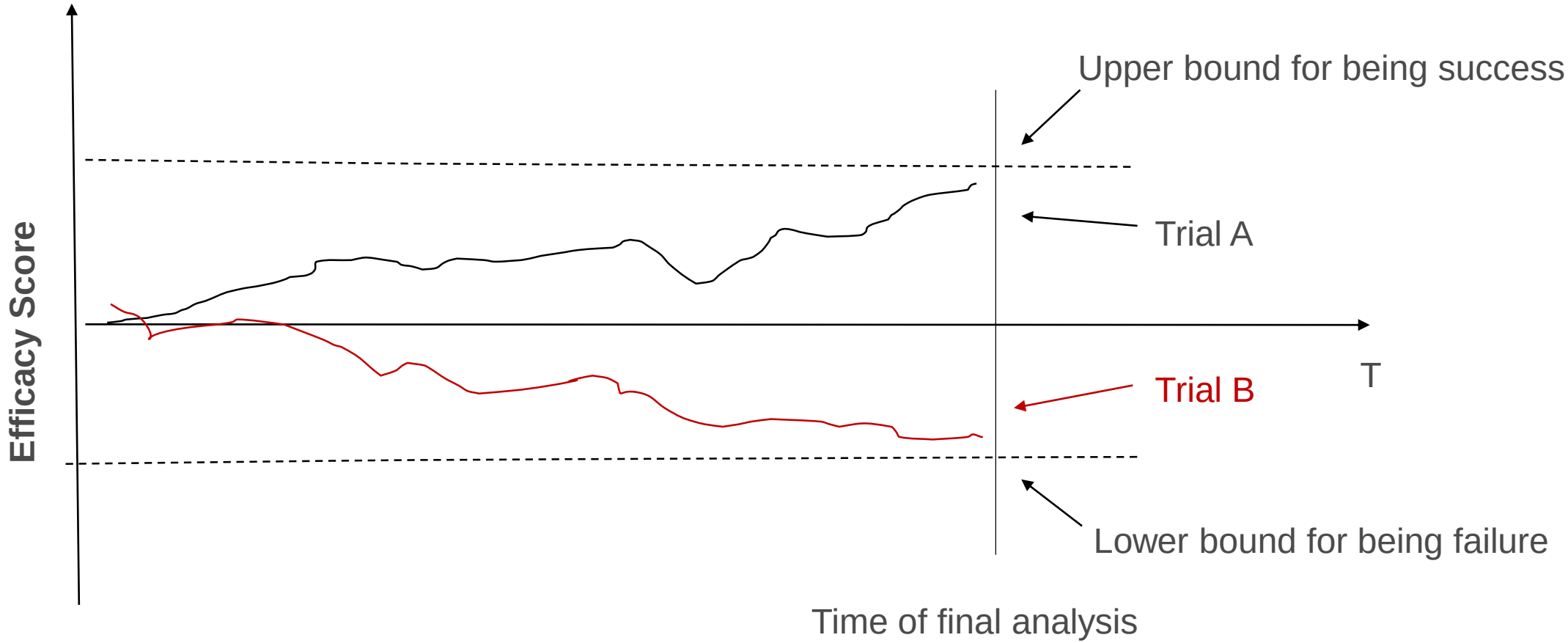
Success Rates for Clinical Trials



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

Michael Hay, David W Thomas, John L Craighead, Celia Economides & Jesse Rosenthal :
Clinical development success rates 2005-2015, 2016 report

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 $$MM financial waste?

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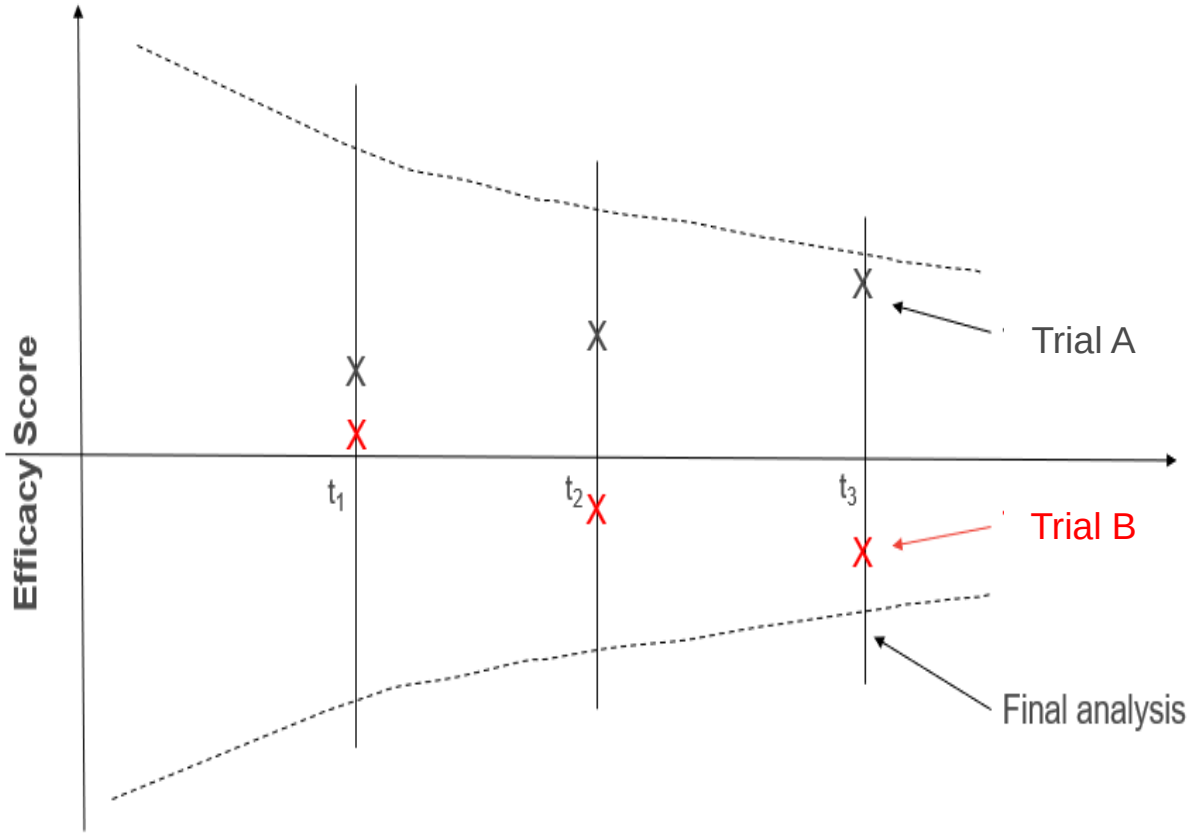
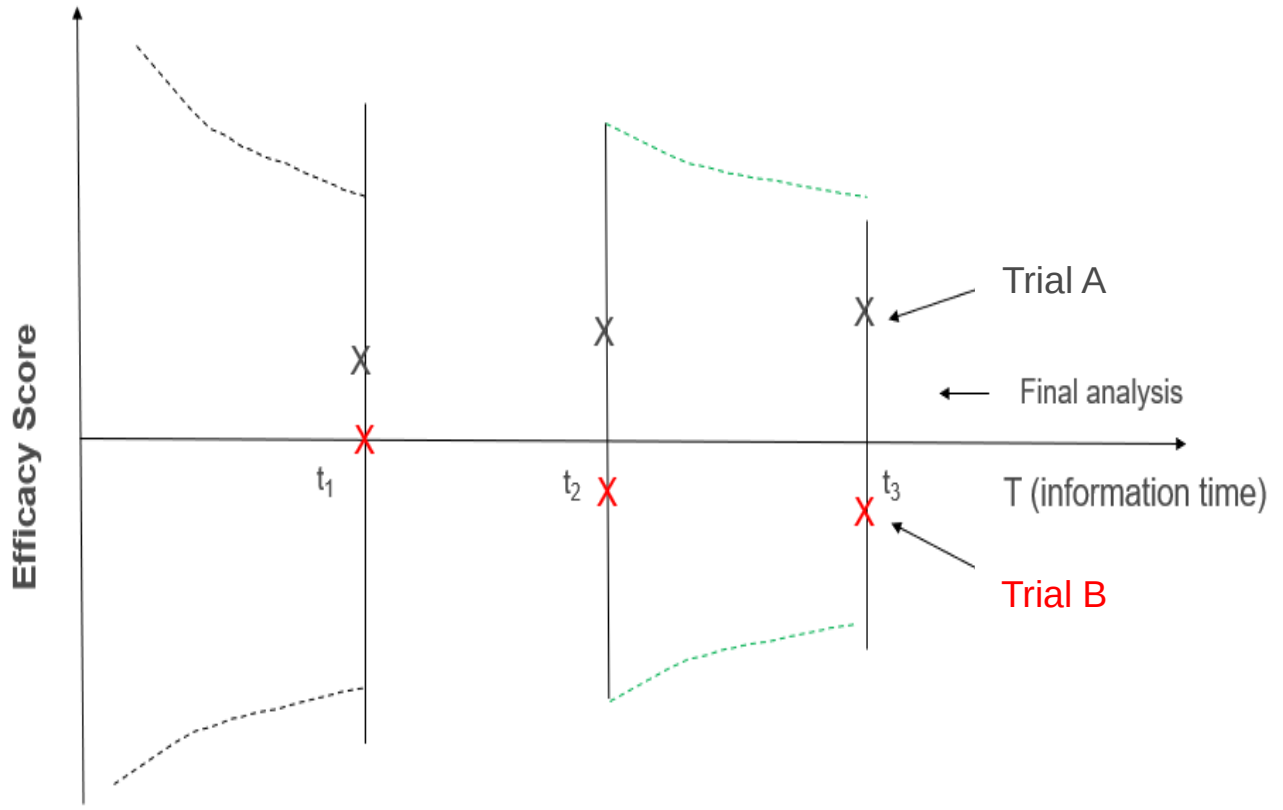
Group Sequential (GS) Design

- 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



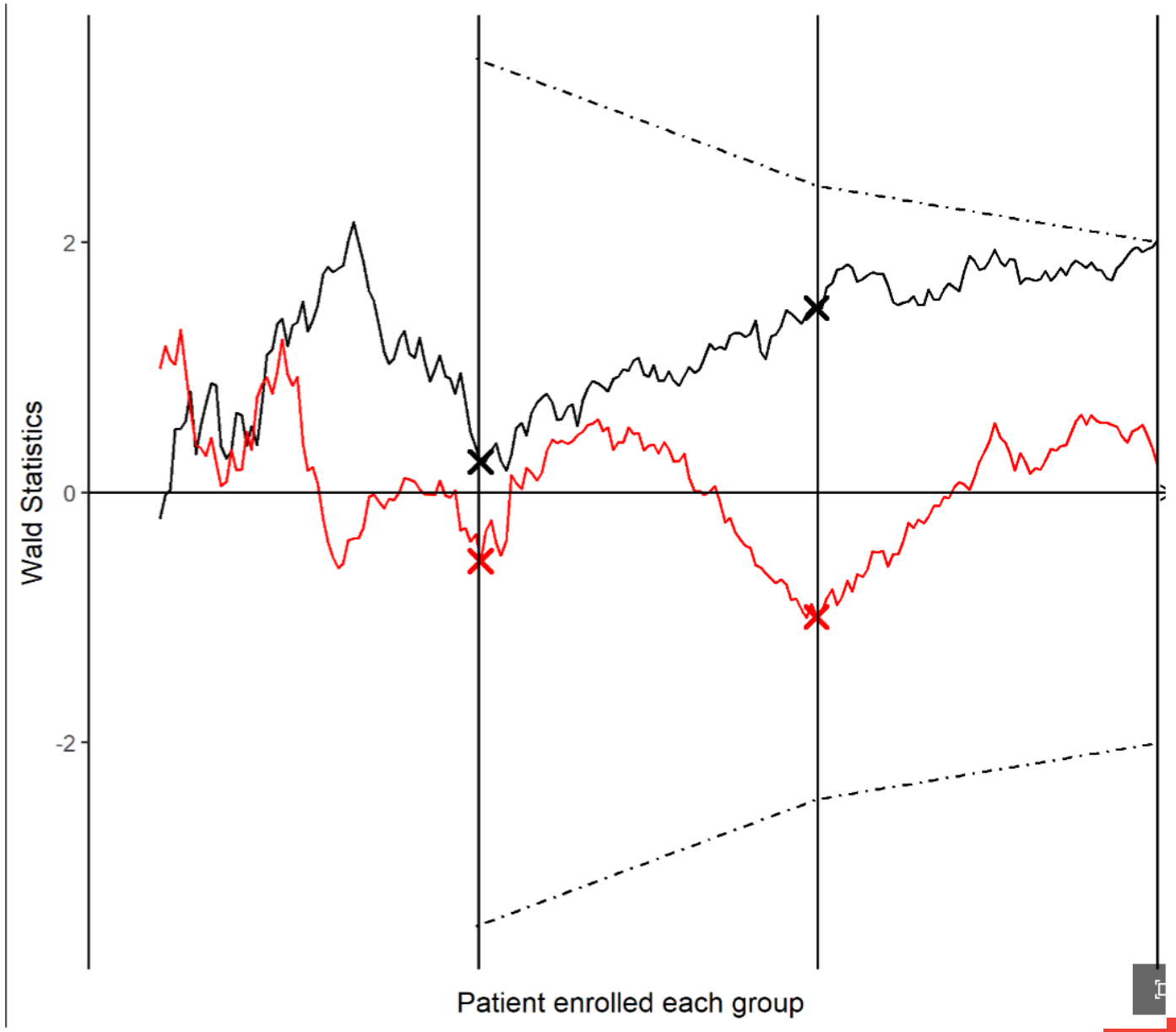
Adaptive Group Sequential (AGS) Design

- 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

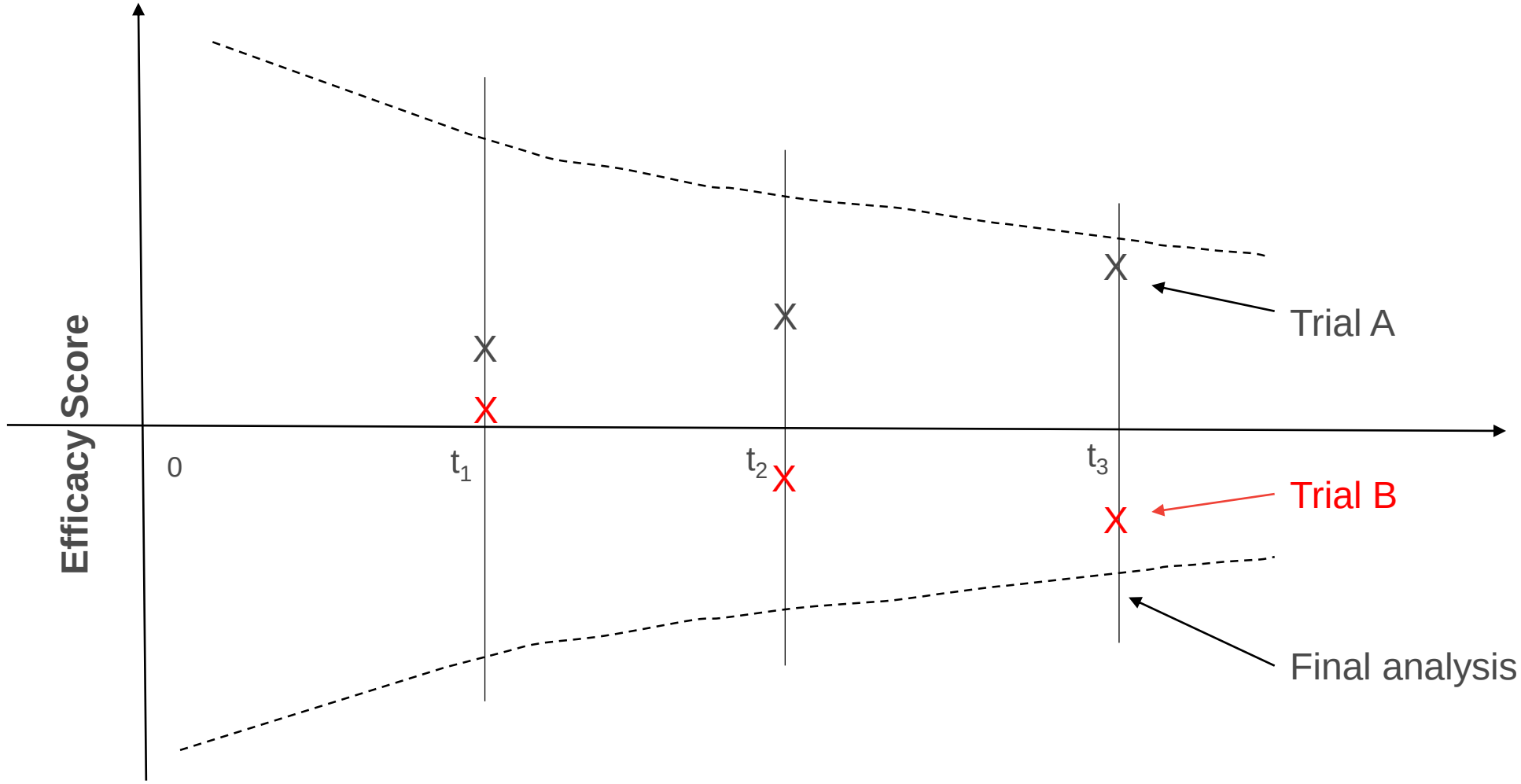
- The planned sample size is based on assumed treatment effect θ
- Pre-define timepoints for interim looks
- If the θ_{assume} is off too much from the true θ, the timing for sample size re-estimation may be too early or too late, for example:

90% design power and assume σ =1.

True θ	SS based on true	Assumed θ	SS based assumed	50% of planned	Comment
0.2	526	0.4	133	67	Too early
0.4	133	0.2	526	263	Too late

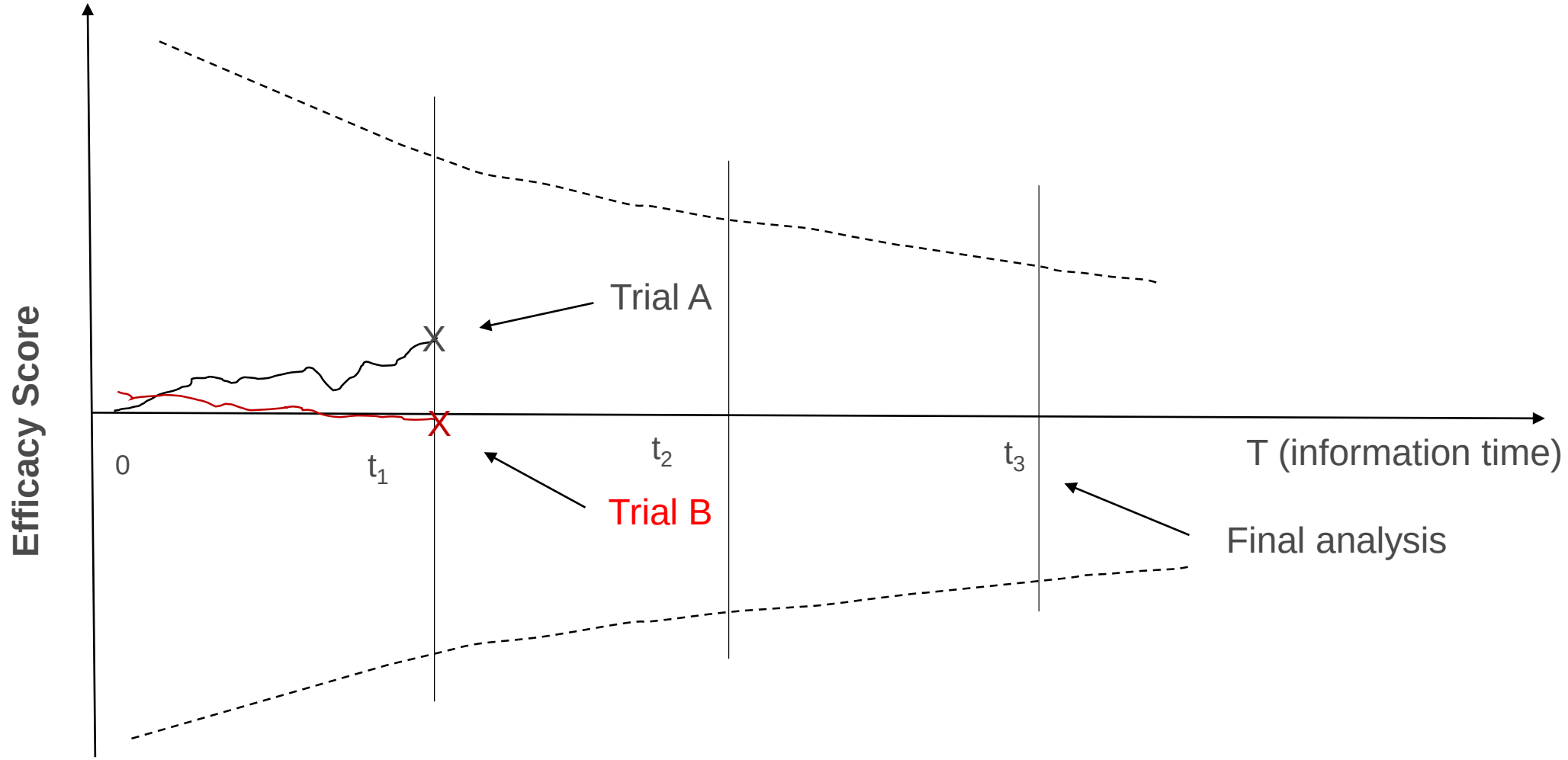
- Only a “snapshot” of data at the time of interim lock is presented to IDMC
- Binary “go/no-go” decision is made by IDMC without knowing the TREND of the data
- Needs an Independent Statistical Group (ISG) to prepare the interim analysis, which usually takes at least 3-6 months

Traditional Group Sequential (GS) Design



An IDMC could make the same recommendation to these two trials because both were within the boundaries unless Trial B had poor safety profile.

Continuous Data Monitoring (CDM) (interim 1)



The IDMC could feel that the Trial B may be lack of efficacy. But would want to wait until Interim 2.

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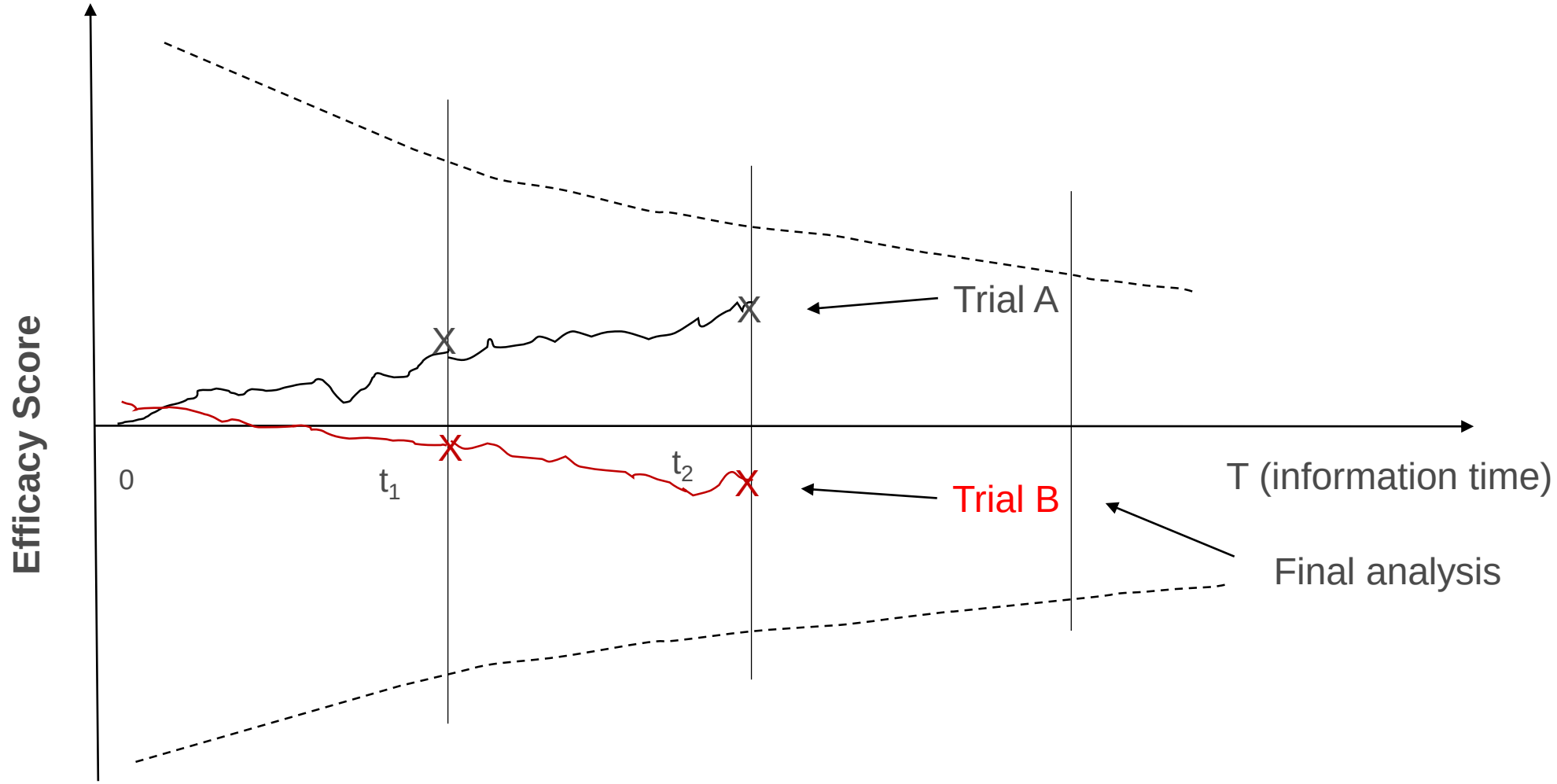
Continuous Data Monitoring (interim 2)



- **The IDMC could have a convincing evidence to recommend that the Trial B can be stopped.**

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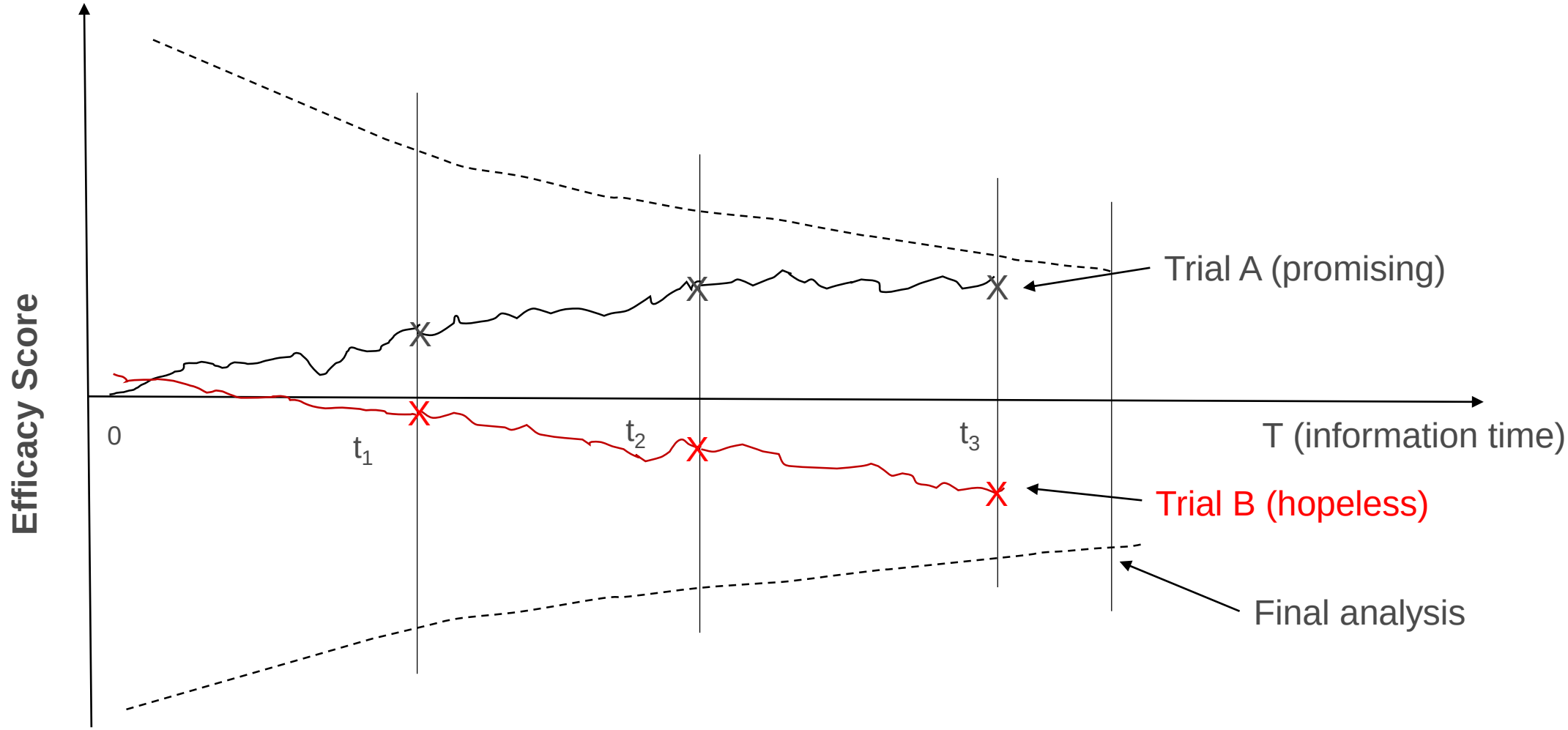
Continuous Data Monitoring (interim 3)



- **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.**

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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 on-going 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…..

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DDM ECO System

Patient data

Wearable device

IWRS

EDC

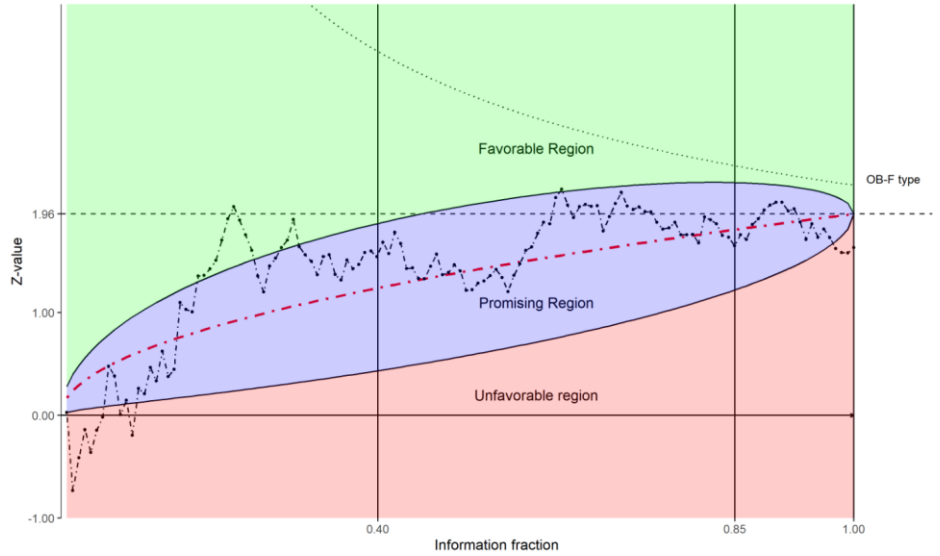
Design parameters

Monitored Results

DDM Engine

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

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Car-GPS

GSD/ASD are more like a "Car-GPS"

Phone-GPS

DDM is more like a "Phone-GPS"

15

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: $B(t) \geq (Z_\beta\sqrt{1-t} + Z_\alpha)t$, equivalently CP$> 1-\beta$;
  - The “hopeful” region: $\frac{(Z_\beta\sqrt{1-t}+Z_\alpha)t}{t+\sqrt{(R_{max}-t)(1-t)}} \leq B(t) \leq \left(Z_\beta\sqrt{1-t} + Z_\alpha\right)t$, where R_{max} is the maximum sample size ratio allowed;
  - The “unfavorable” region: $\Phi^{-1}(\gamma_f)\sqrt{1-t} - \theta_a(1-t) + Z_\alpha < B(t) < \frac{(Z_\beta\sqrt{1-t}+Z_\alpha)t}{t+\sqrt{(R_{max}-t)(1-t)}}$
  - Futility region: $B(t) \leq \Phi^{-1}(\gamma_f)\sqrt{1-t} - \theta_a(1-t) + Z_\alpha$.

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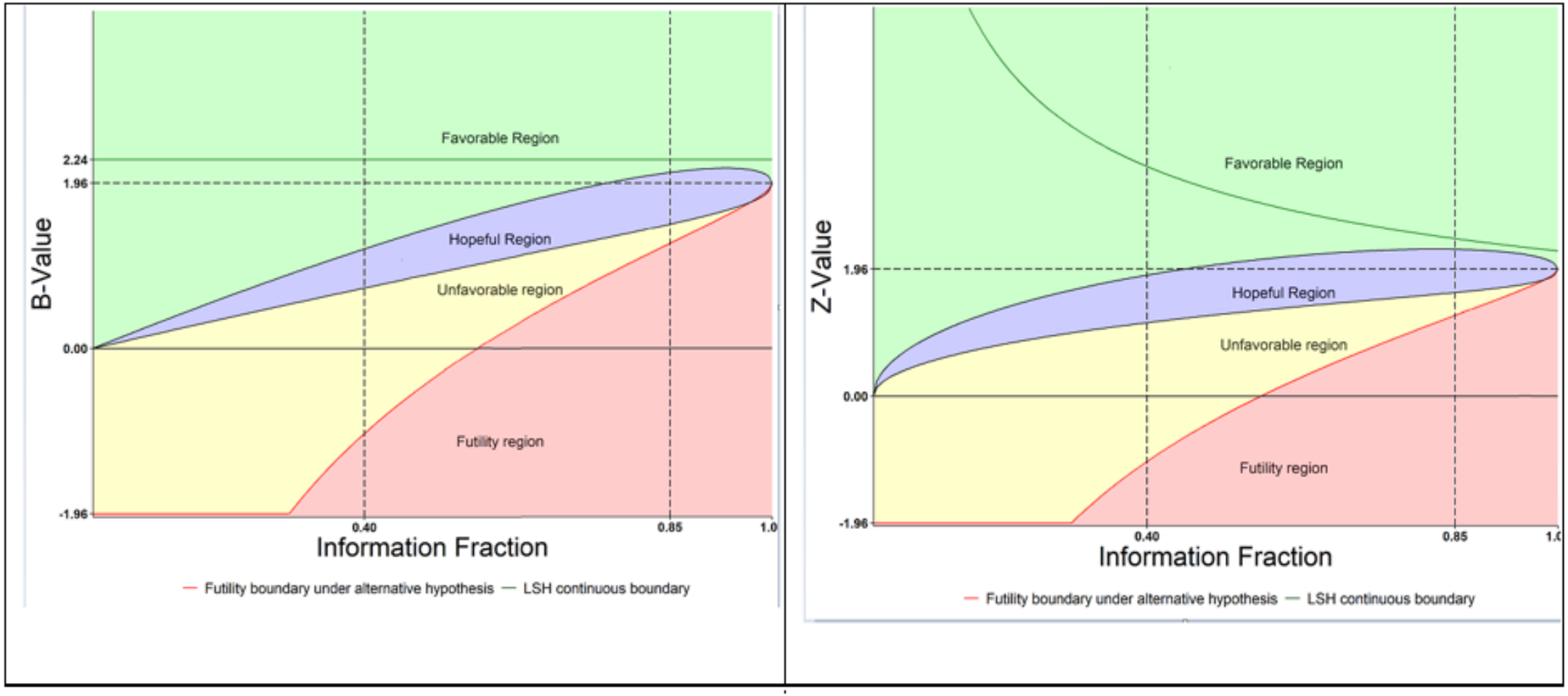
Illustration of Trial “Radar” System



LSH=Lan, Simon and Halperin (1982)

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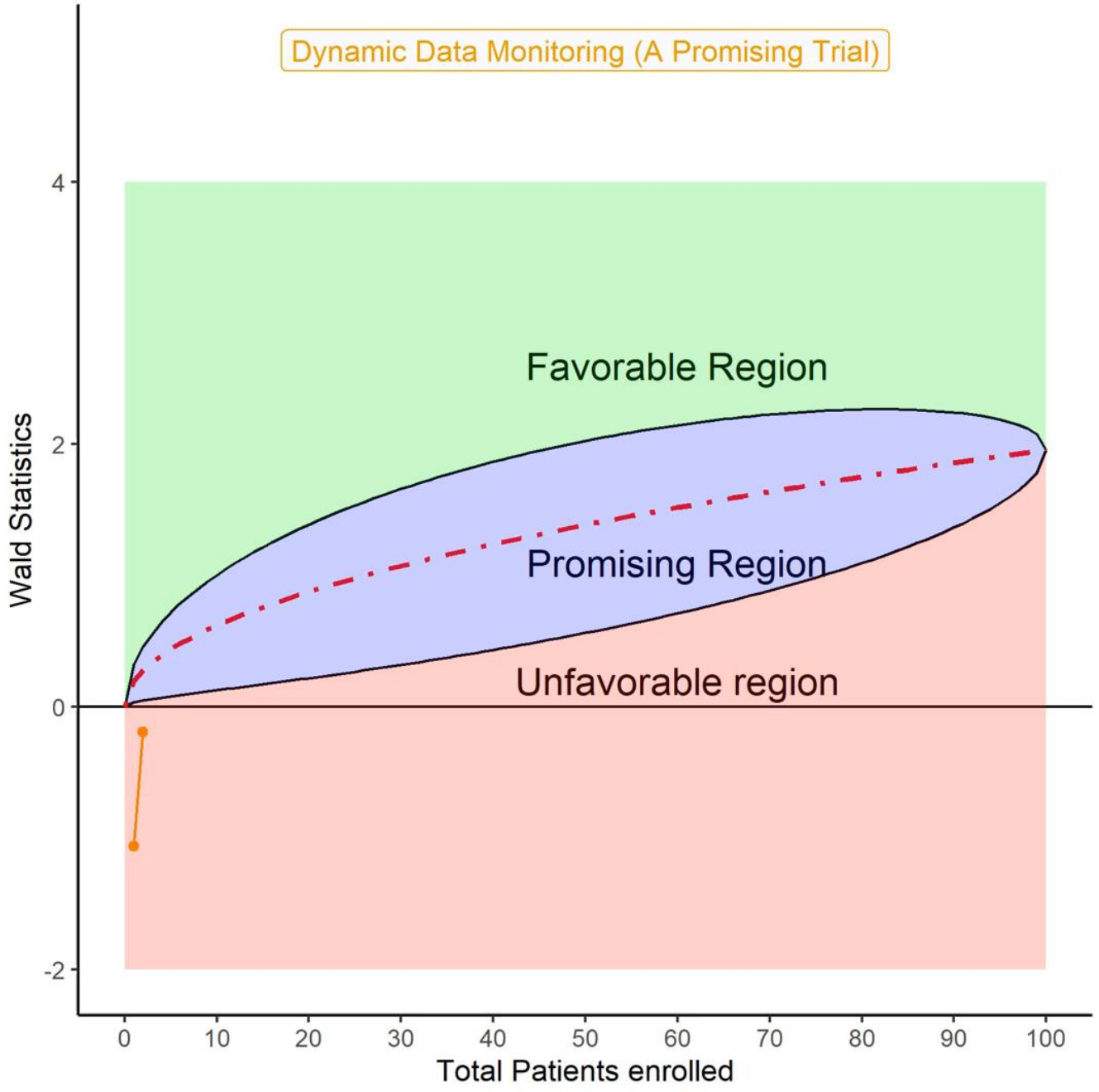
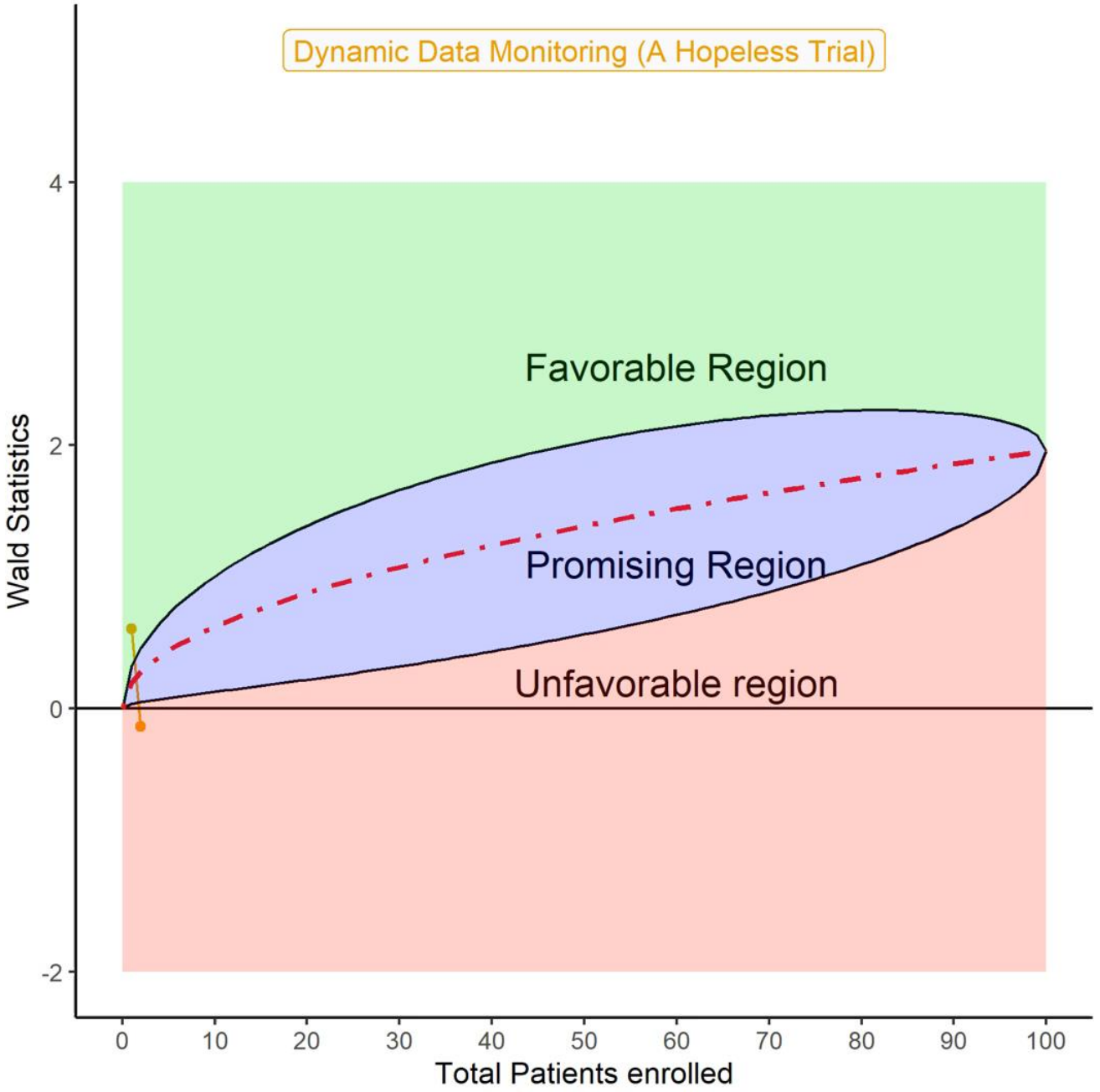

Dynamic Data Monitoring (A Promising Trial)
Favorable Region
Promising Region
Unfavorable region
Wald Statistics
4
2
0
-2
0
10
20
30
40
50
60
70
80
90
100
Total Patients enrolled


Dynamic Data Monitoring (A Hopeless Trial)
Favorable Region
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4
2
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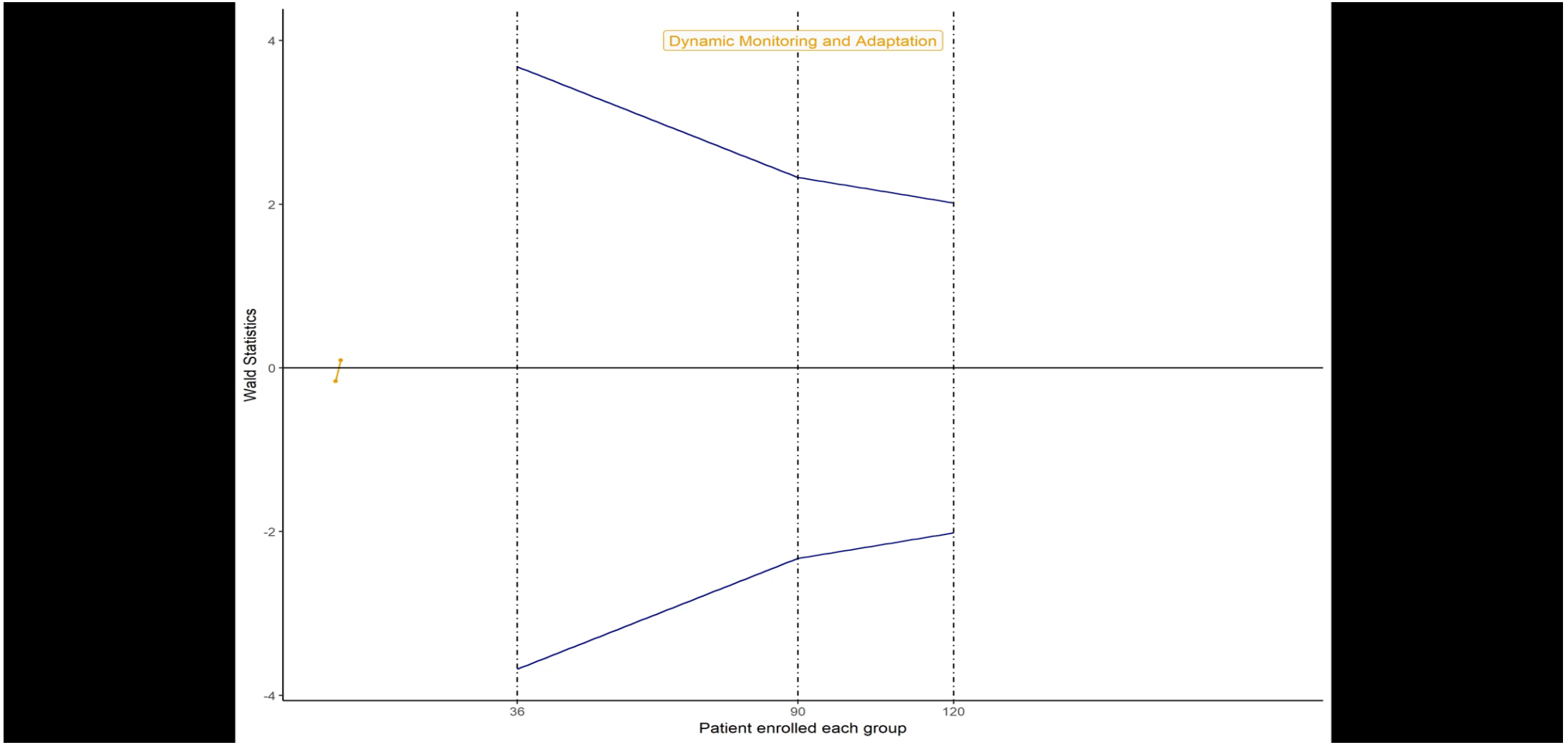
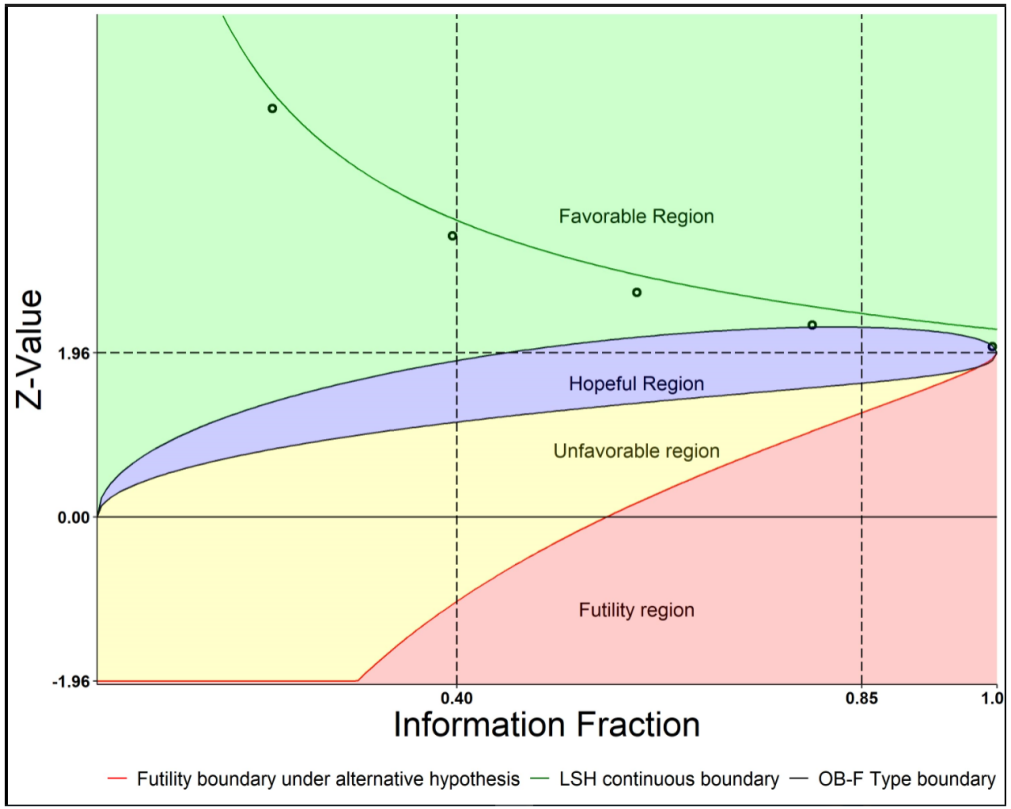
40
50
60
70
80
90
100
Total Patients enrolled

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.



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Simulation Study

δ_{true}	γ_f (CP under H_a)	Futility rate	Rejection rate	Average Sample Size	SSR timepoint	Futility timepoint	Efficacy timepoint
0	0.05	0.887	0.022	213	0.955	0.681	0.998
	0.10	0.888	0.022	202	0.955	0.639	0.998
	0.15	0.889	0.022	194	0.956	0.610	0.998
	0.20	0.891	0.021	187	0.956	0.585	0.998
0.25	0.05	0.304	0.651	365	0.813	0.935	0.931
	0.10	0.311	0.649	362	0.812	0.919	0.931
	0.15	0.318	0.643	357	0.812	0.904	0.931
	0.20	0.326	0.636	351	0.814	0.890	0.930
0.4	0.05	0.052	0.943	309	0.844	0.992	0.788
	0.10	0.056	0.940	307	0.843	0.988	0.787
	0.15	0.061	0.937	305	0.843	0.984	0.787
	0.20	0.065	0.933	302	0.847	0.981	0.786

- $\delta_{assmue} = 0.4\,, N = 132$ 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.

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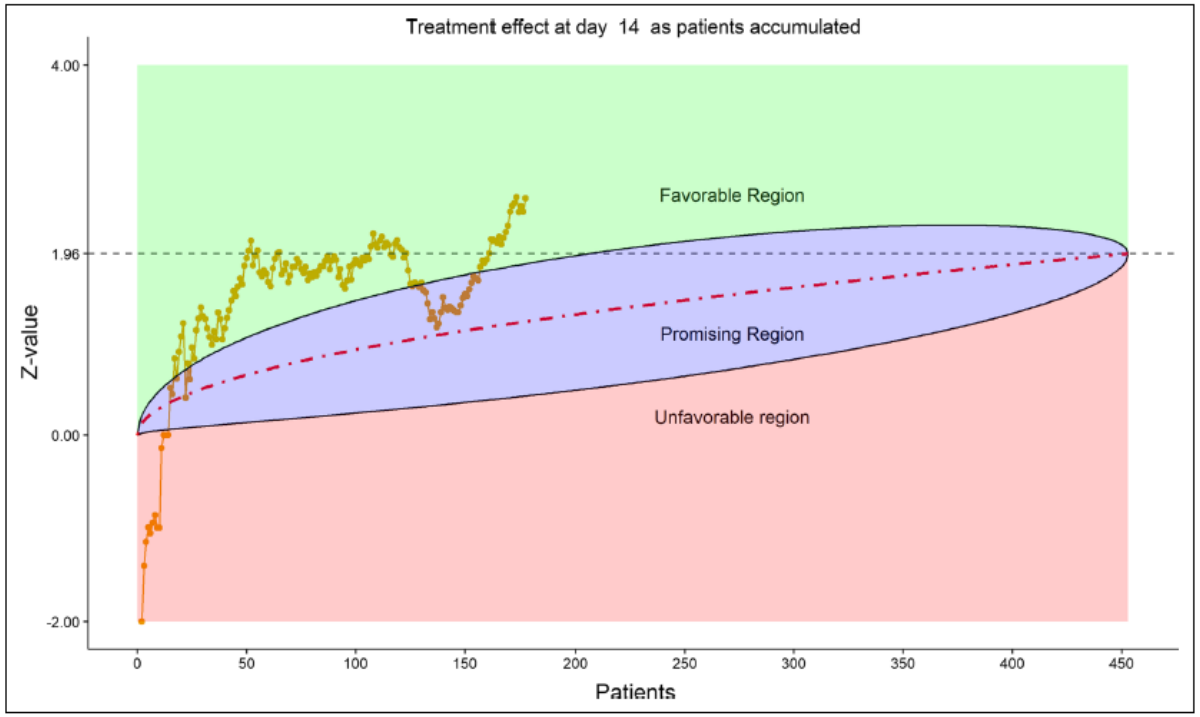
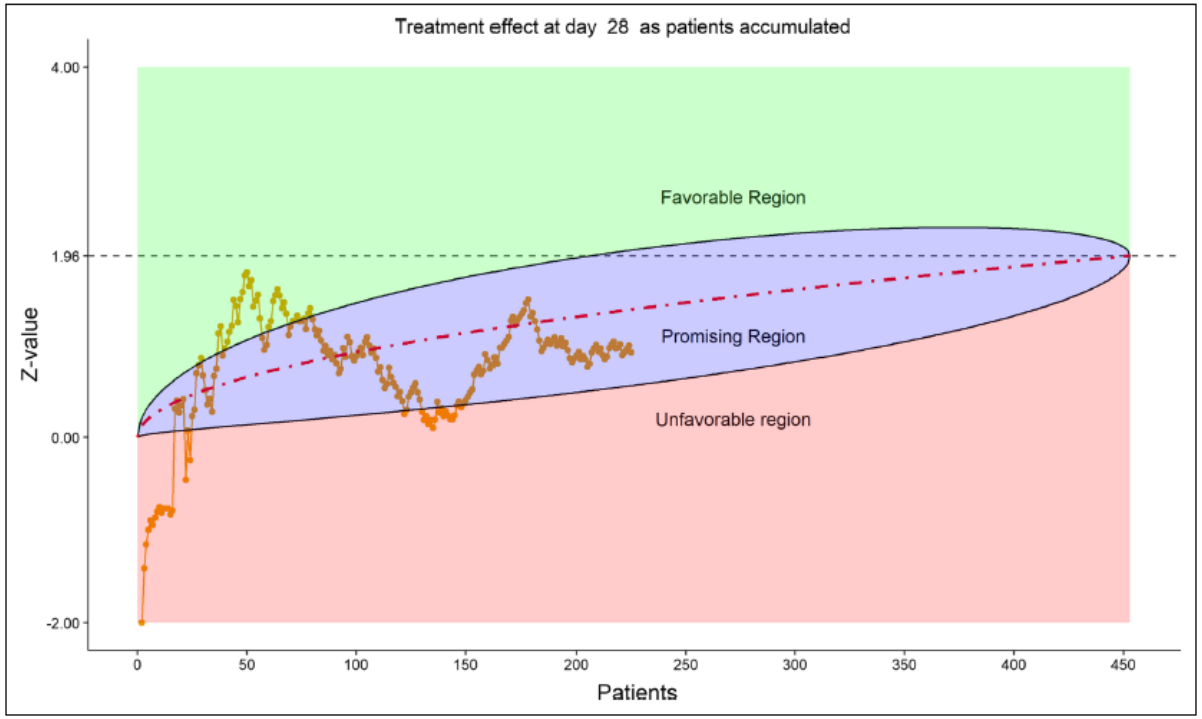
Apply to IDMC of a COVID-19 Trial





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.

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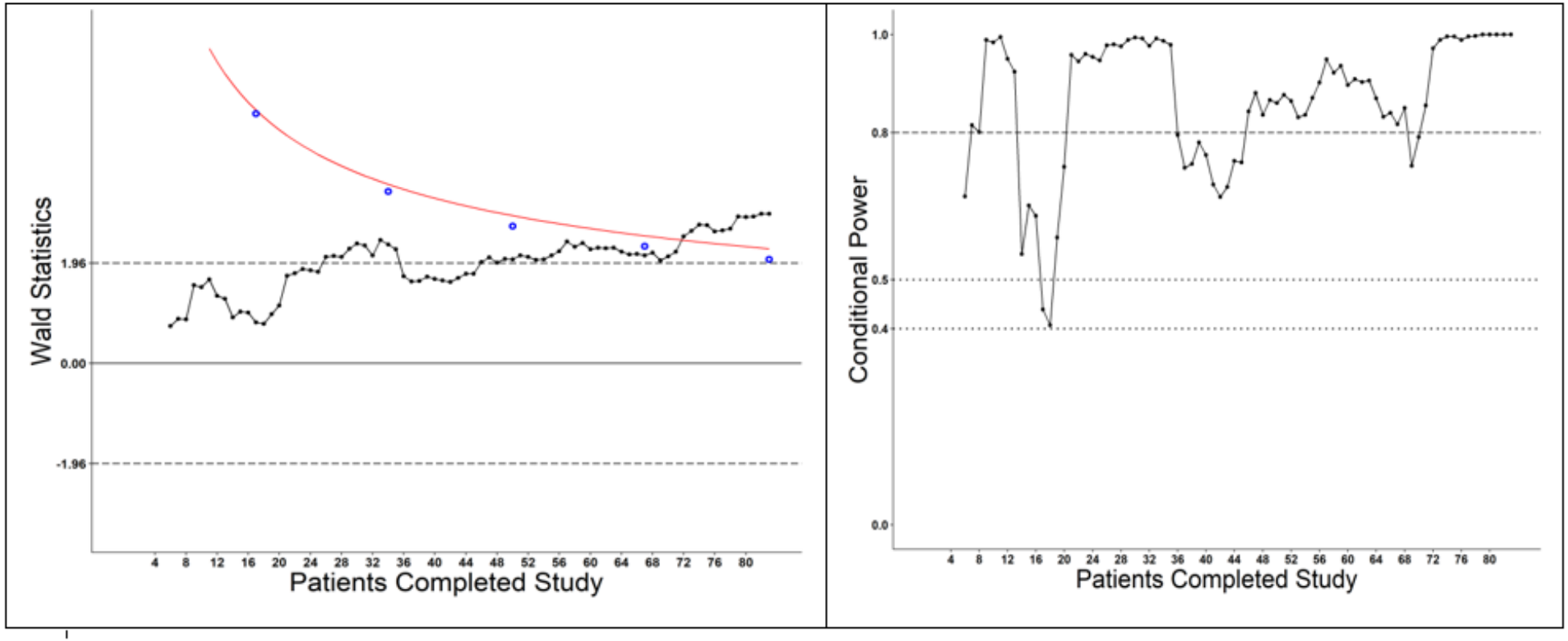
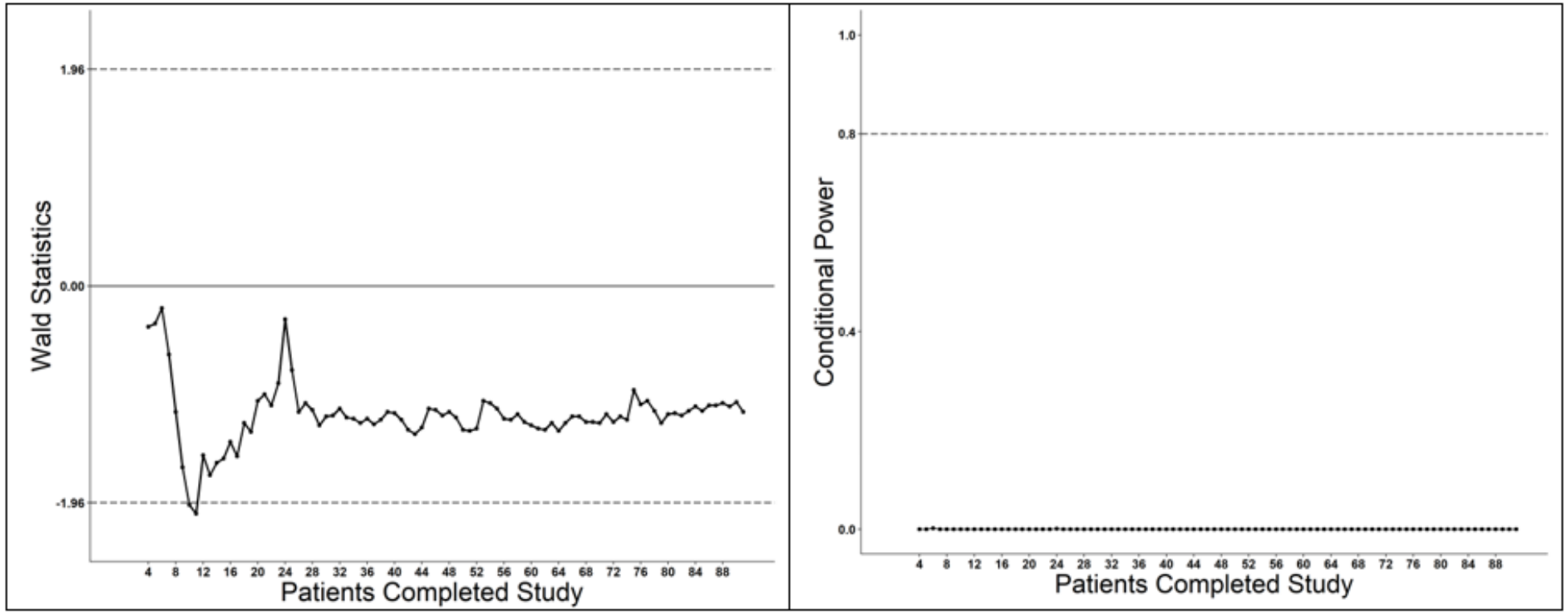
Apply to trial diagnosis for completed study
(Study I: positive one)



A Multi-Center, Randomized, Double-Blind, Placebo-Control Phase II Study with Oral drug treating elderly patients with Nocturia.

Apply to trial diagnosis for completed study
(Study II: a failed one)



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 safet**y; 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

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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!

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Thank you!

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