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Reshaping the Future of Clinical Trial

Dynamic Data Monitoring for Clinical Trials

Tai Xie, Ph.D., Peng Zhang, Ph.D.

Telephone
908-557-9366

Address
285 Davidson Ave.
Suite 305
Somerset, NJ 08873
USA

Website
www.cims-global.com

Speakers

Tai's Bio

Dr. Tai Xie, the CEO and founder of CIMS Global with over three decades of expertise in clinical trial design, data management, statistical analysis, and reporting.

Peng's Bio

Dr. Peng Zhang, Manager of Innovative Data Sciences at CIMS Global with expertise in clinical trial design, statistical analysis, and R/R-Shiny.

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Success Rates in Clinical Trials

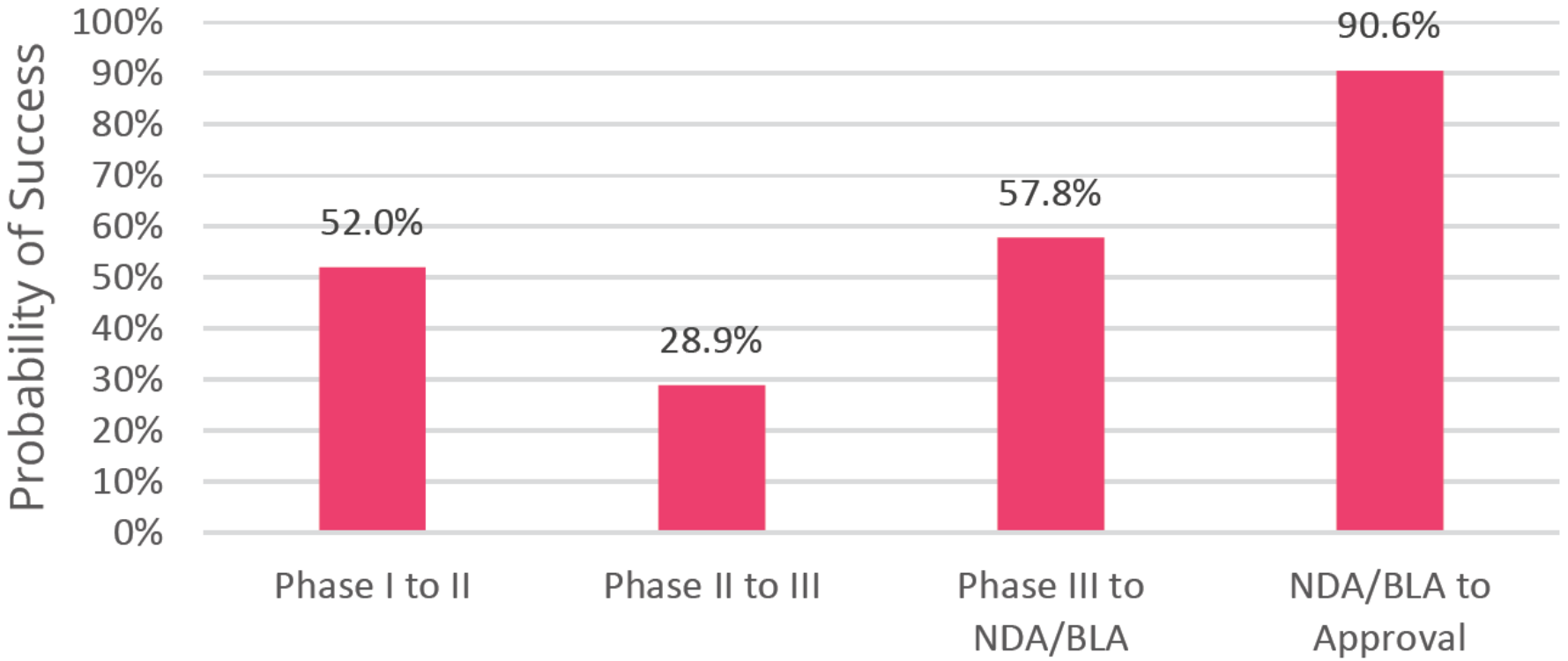
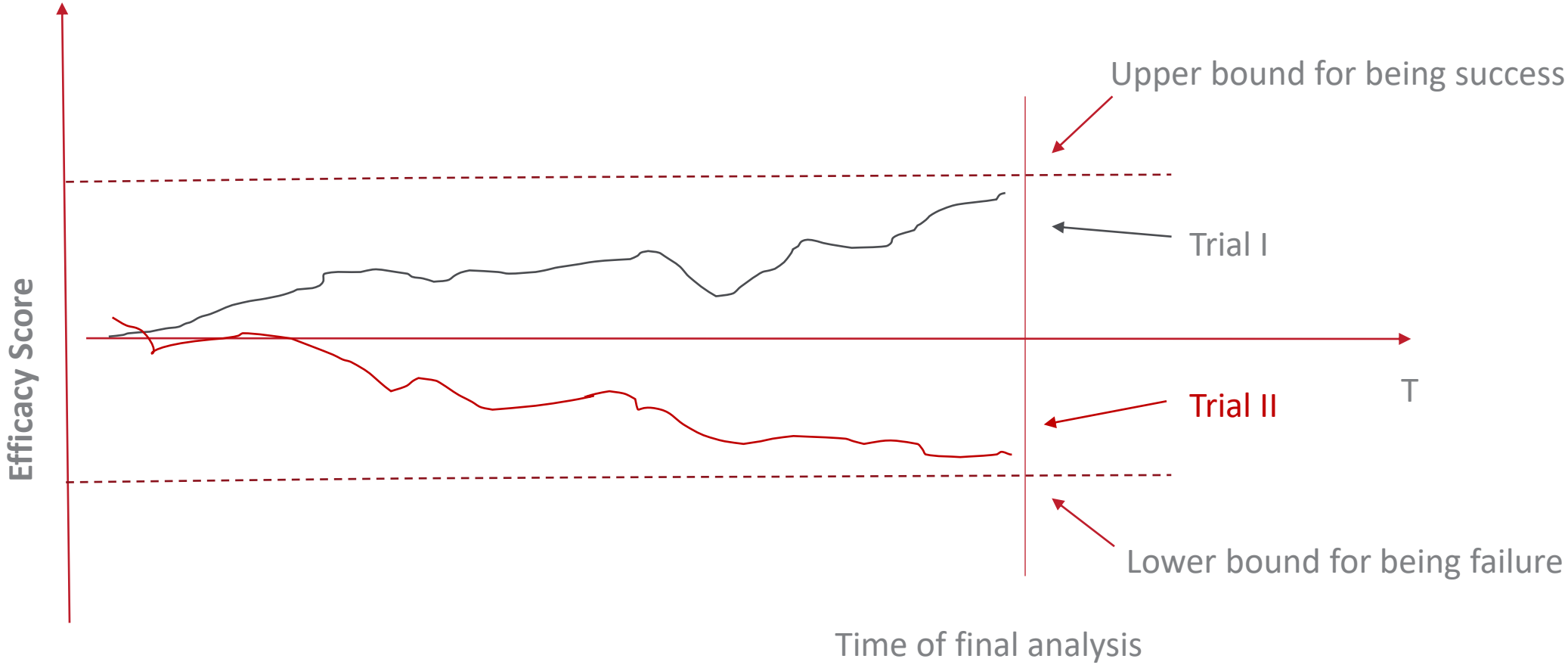


Figure 1: Phase transition success rates from Phase I for all diseases, all modalities. Source: Biomedtracker® and Pharmapremia®, 2020.

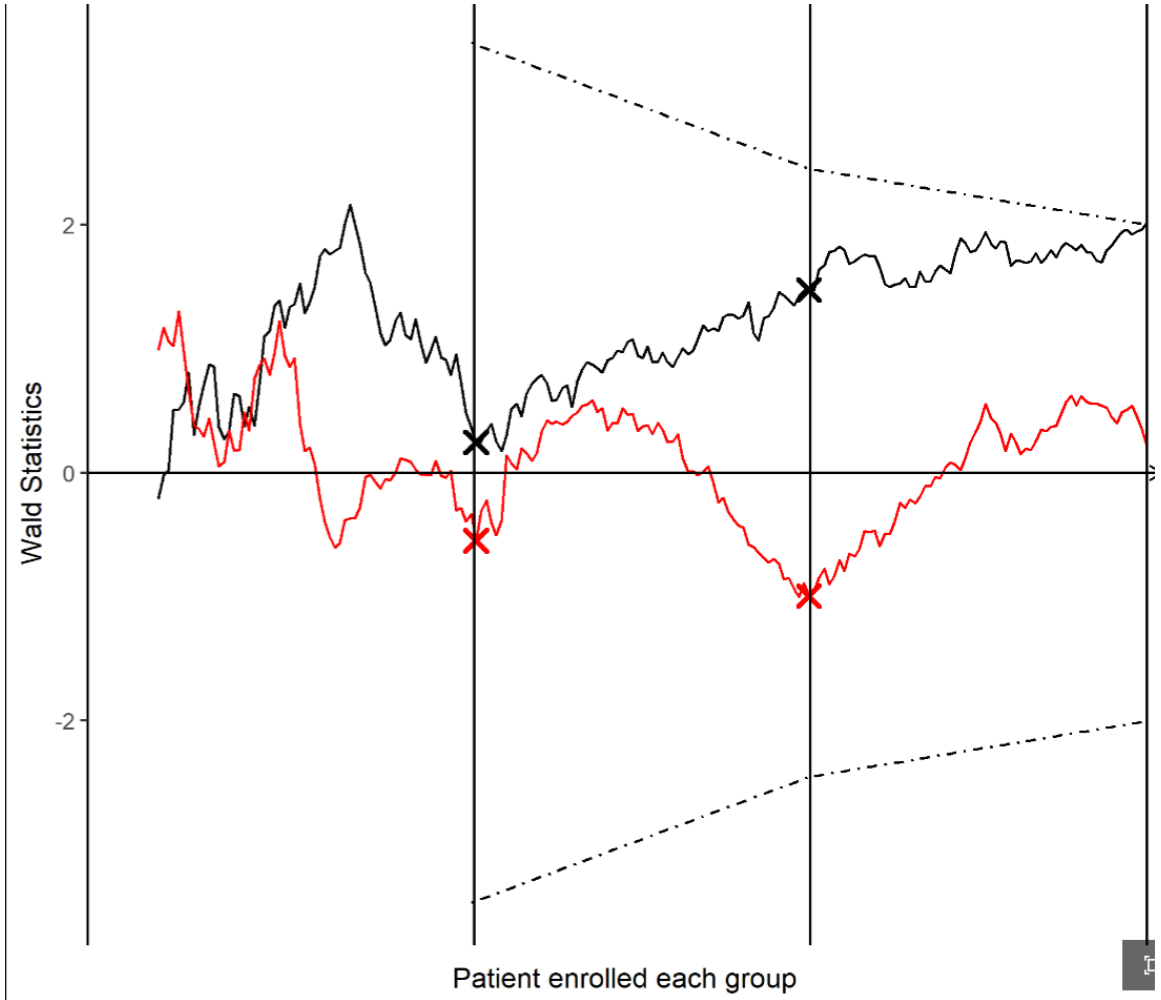
Over 70% Phase II trials failed to enter into Phase III

Traditional Trial Design with Single Analysis



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

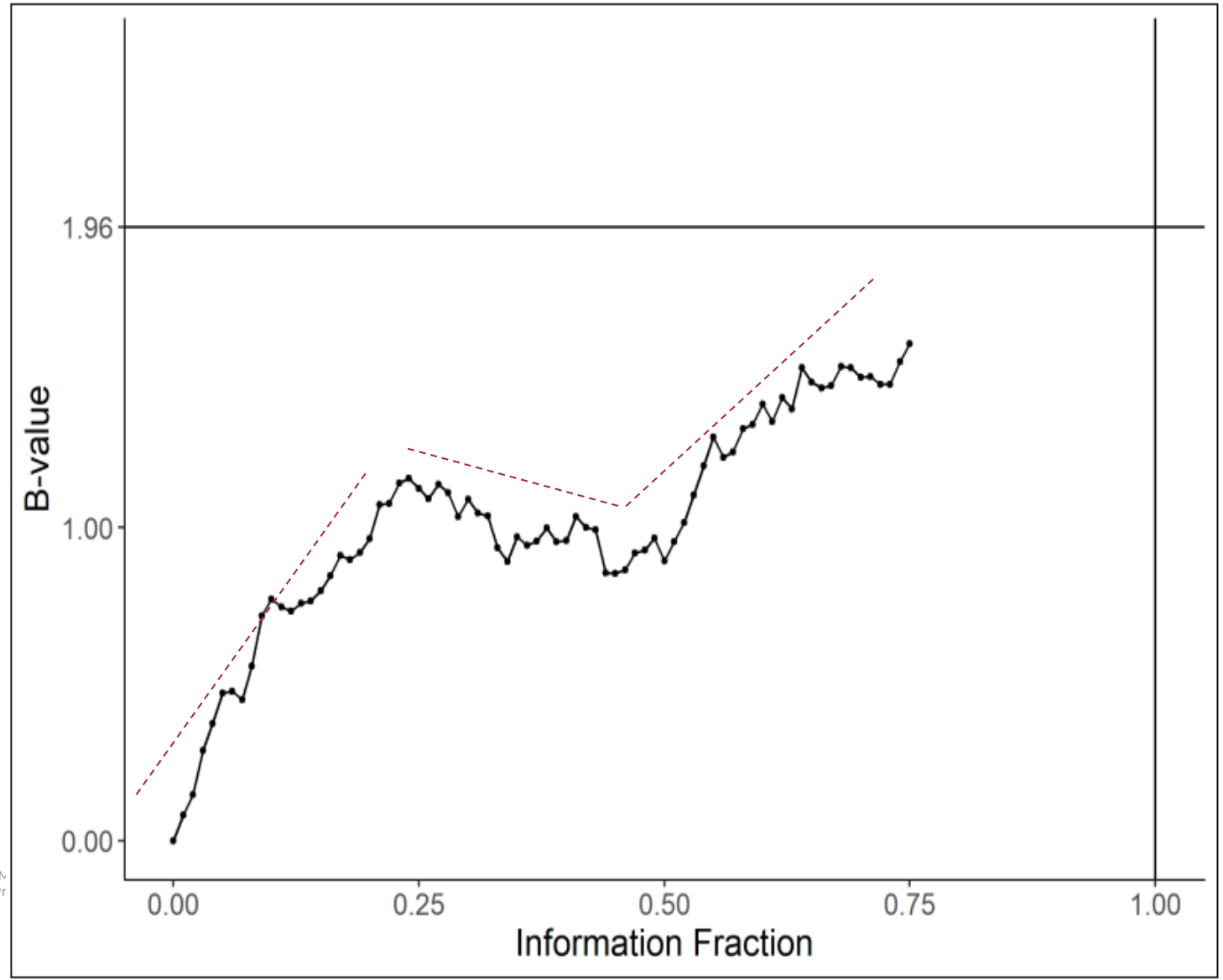
Advanced Design with Interim Analyses



- The data are fluctuated, especially at early stage
- They show notable trend at later stage
- Pre-planned interim analyses may be at a wrong spot
- Wrong decision could be made based on a snapshot at interim without seeing the trend of the cumulative treatment effect
- A dynamic approach is needed for monitoring ongoing clinical trials

Data with non-linear trend

- Conventionally, we assume a linear trend on the treatment effect to be observed
- The linear trend is valid when observations are i.i.d.
- In reality, the i.i.d. condition may not be valid, for example
  - Changing in entry criteria
  - Procedure for assessing primary endpoint were changed
  - The clinical centers/laboratories had imposed a “learning period”, etc.
- Non-linear trend was not timely detected in conventional interim analysis
- What are the solutions?
  - Continuous accessibility
  - Automatic trend-assessment
  - New statistical methods



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Limitation in current interim analysis with GSD and ASD

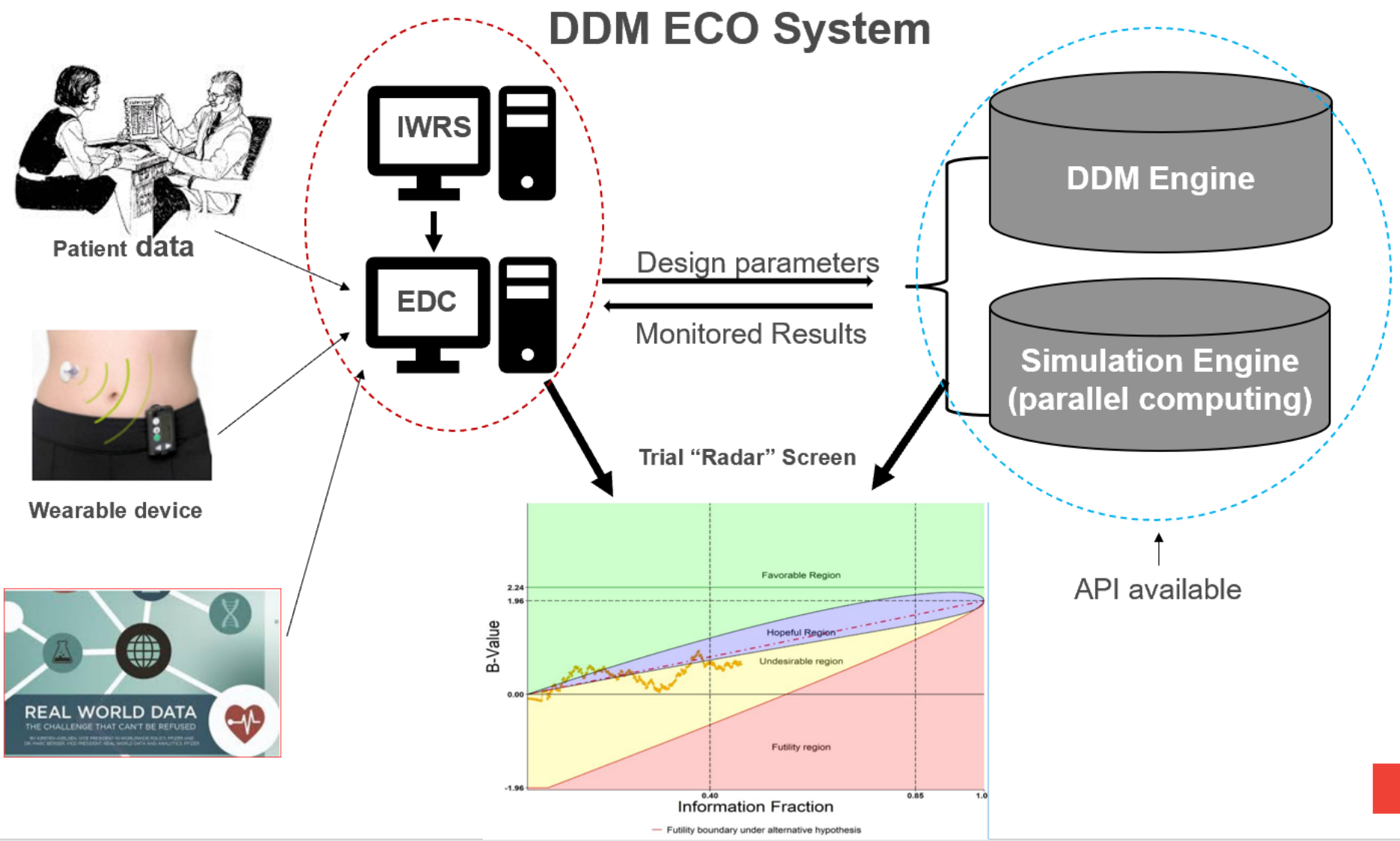
- The planned sample size is based on assumed treatment effect θ
- Pre-define timepoints for interim looks
- If the θ_{assume} is off too much from the true θ, the timing for sample size re-estimation may be too early or too late, for example:

90% design power and assume σ =1.

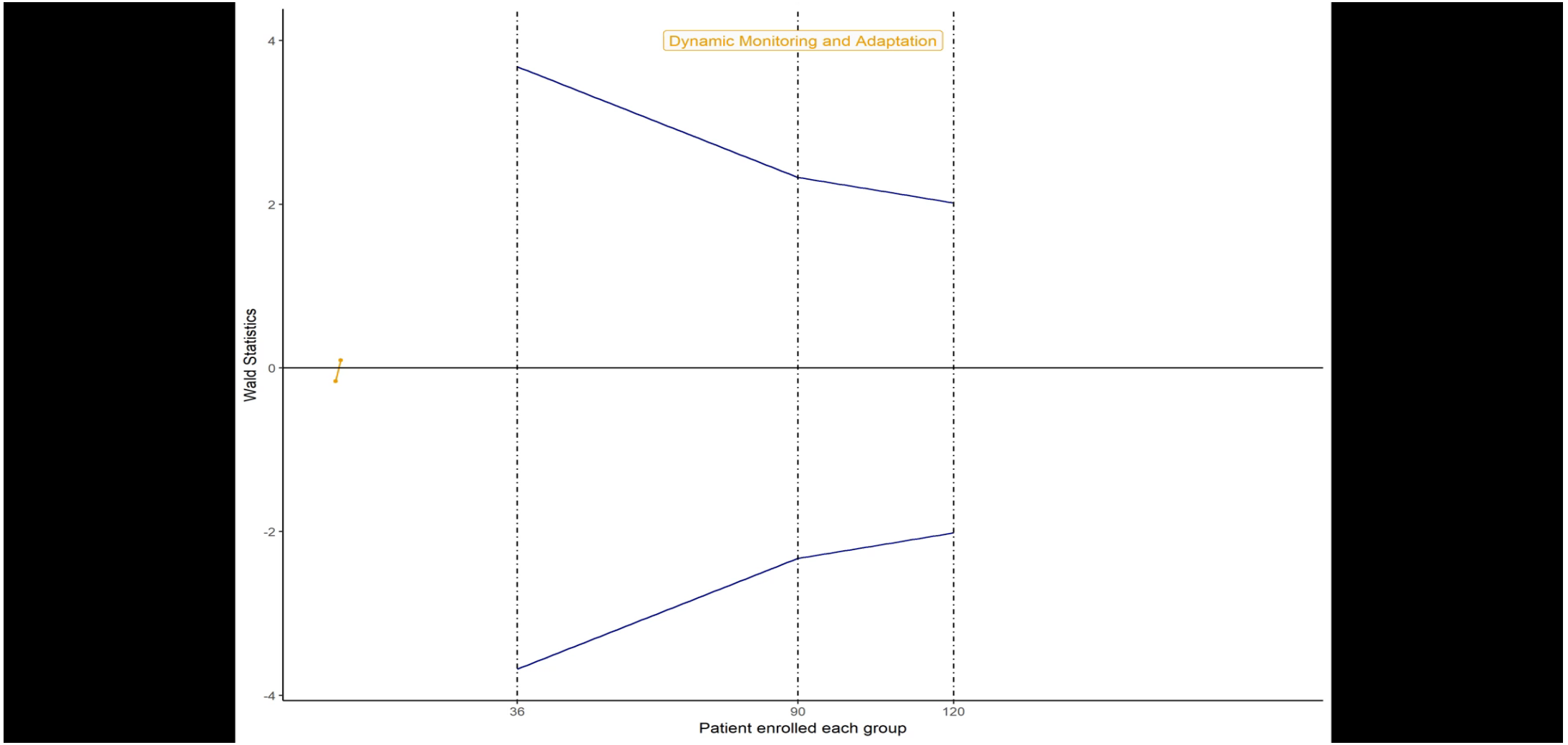
True θ	SS based on true	Assumed θ	SS based assumed	50% of planned	Comment
0.2	526	0.4	133	67	Too early
0.4	133	0.2	526	263	Too late

- Only a “snapshot”, not the whole picture is presented to IDMC
- Without examination of trend and linearity of the accumulated data
- Binary “go/no-go” recommendation is generally made by IDMC

Dynamic Data Monitoring Illustration



Video: make a promising trial to be successful



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DDM could save huge for future clinical trials

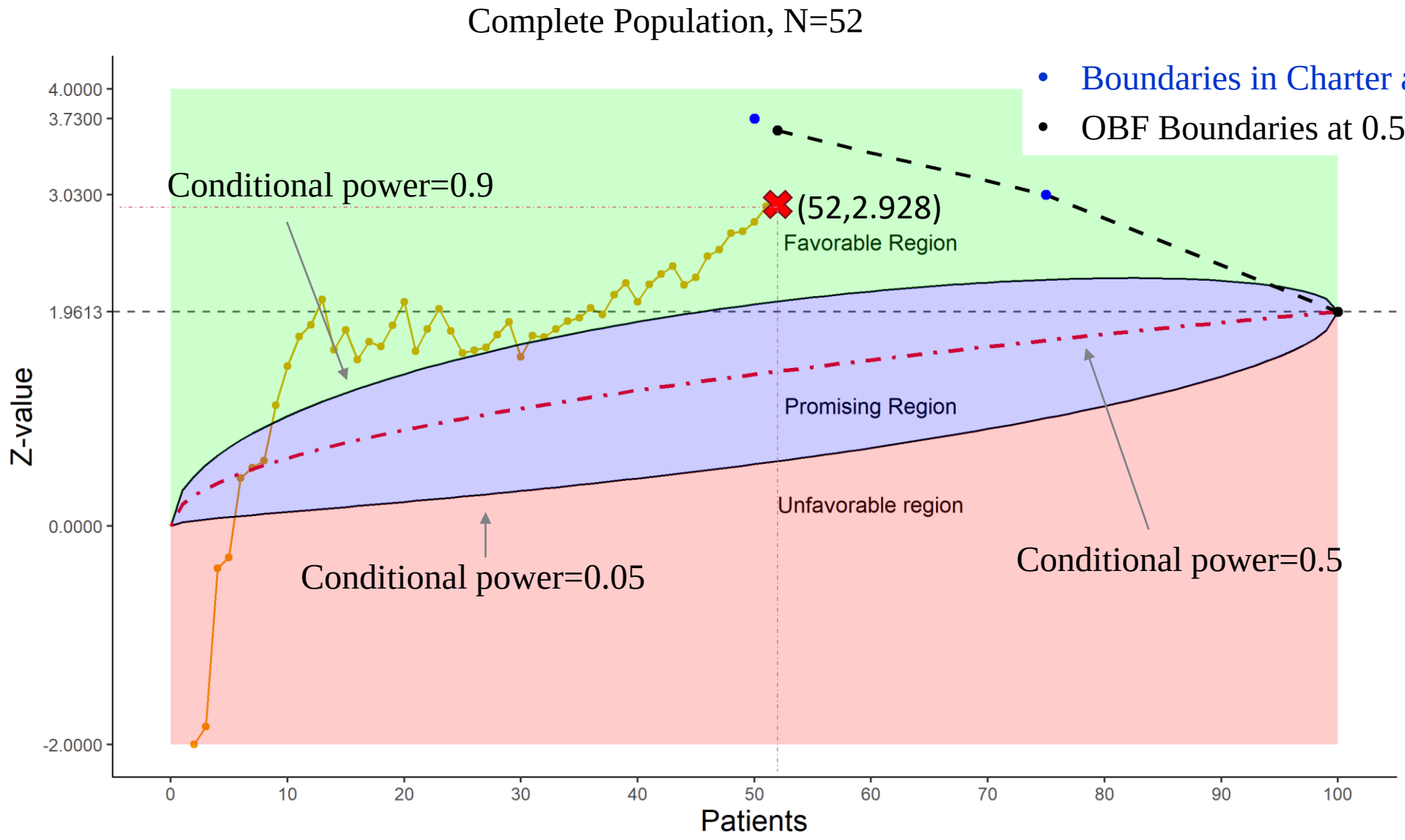
- Assume that we design an oncology trial. Sponsor claim (expect) 30% better than standard of cares in treatment benefit.
- Based on the assumption, this trial needs at least 350 subjects to achieve 90% statistical power.
- Cost in cancer clinical trial is at least $100,000/subject.
- This trial needs a budget at least $35MM
- We simulated 10,000 trials and applied DDM to the simulated trials.
  - ➢If no treatment effect (θ=0), in 92% of times DDM will stop the trial. Thus, DDM could save about $18MM unnecessary financial loss;
  - ➢If the treatment effect is better than expected, DDM will reduce about 35% sample size. Thus DDM could save about $12.6MM cost;
  - ➢Regardless the accuracy of the guessed treatment effect, DDM will guide the trial to right sample size and correct treatment effect estimate

Based on 10,000 simulated trials

True treatment effect	Stopping rate	Power (design)	Power (actual)	Average sample size per arm	Actual cost	Saving
0	92%	0.025	0.0236	86	$17,140,680	$18,059,320
0.30	13%	0.7616	0.809	159	$31,714,360	$3,485,640
0.46	1%	0.9324	0.9558	113	$22,550,740	$12,649,260

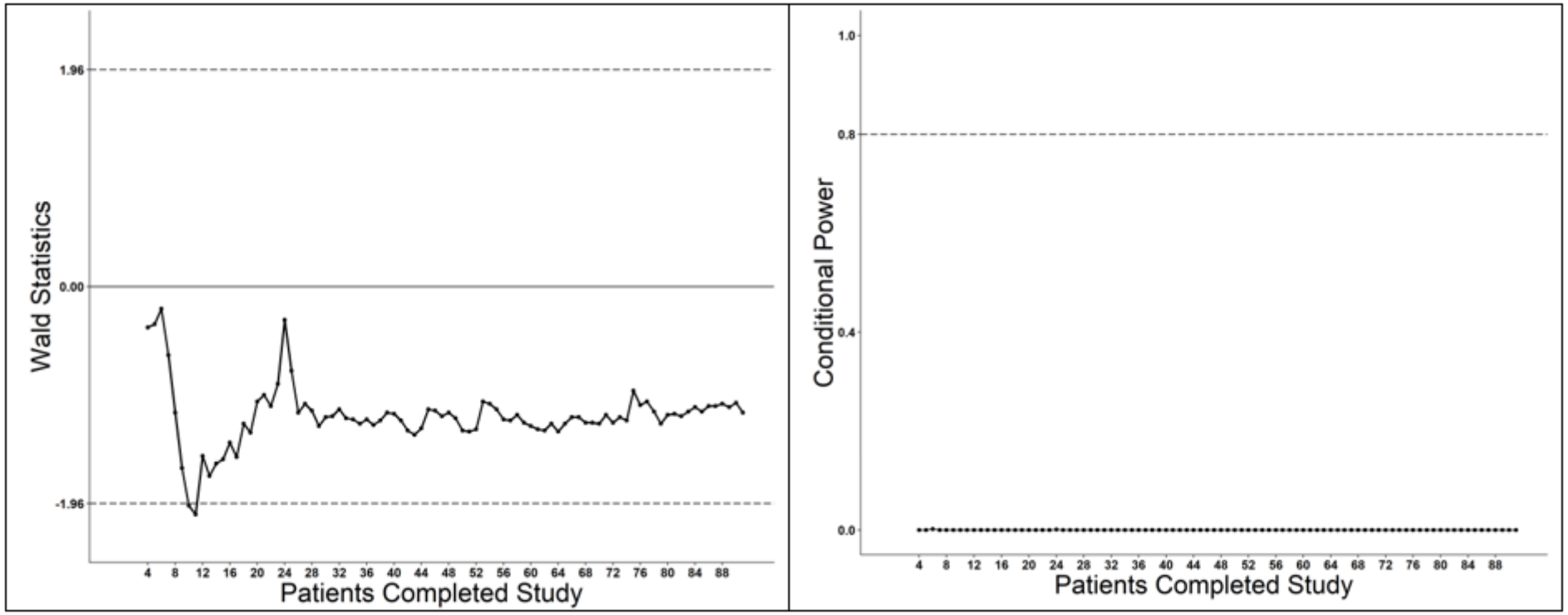
Starting with N=100/group. But based on sample size formula, 176 per arm are needed.

DDM Applied to A Promising Study



- Boundaries in Charter at 0.5 and 0.75.
- OBF Boundaries at 0.52 and 1.

Apply DDM to a real (failed) study



A Randomized, Double-Blind, Placebo-Controlled, Exploratory Phase IIa Study to Assess the Safety and Efficacy of oral drug in NAFLD Patients. N=96, the study took 2 years to finish.

The First Remdesivir Trial on COVID-19

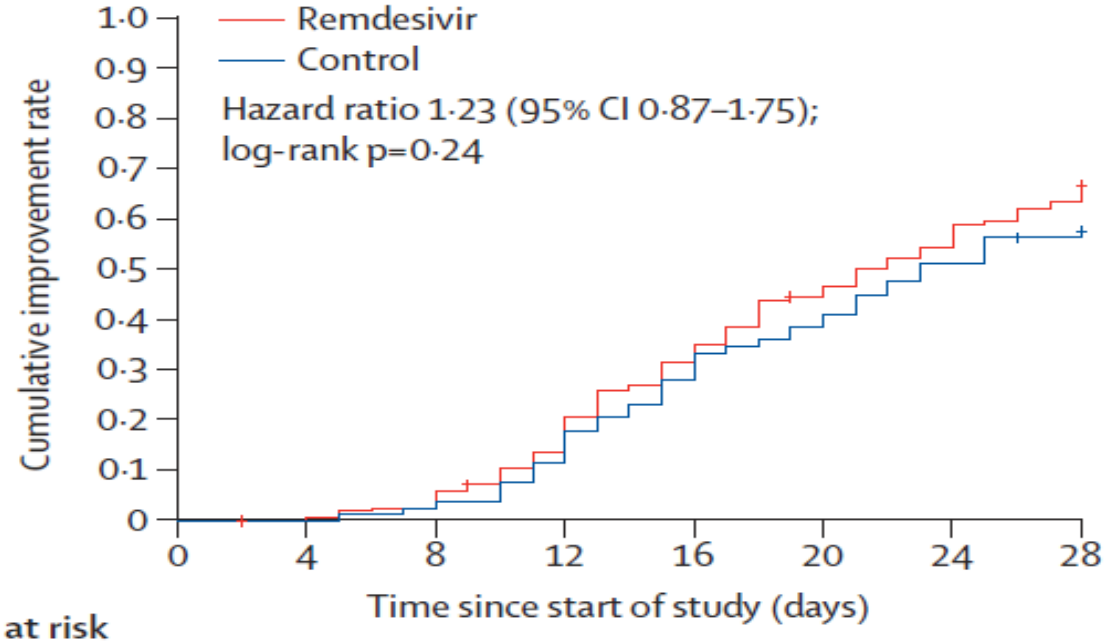
- Sponsor: Institute of Respiratory Medicine, Chinese Academy of Medical Science
- Investigation team:
  - PI: Wang Chen, MD
  - Co-PI: Cao Bin, MD
  - Sites: 10 hospitals in Wuhan City
  - CRO: Tigermed Consulting, Hangzhou
  - eDMC and DDM system provider: CIMS Global, Somerset, NJ

Results published on Lancet on 4/29/20 morning

- Trial results were hopeful, but inconclusive
- Median TTCI (Time-to-clinical improvement) = 21days vs. 23days for remdesivir vs. control
- But the trial was terminated earlier due to lack of patients when pandemic was under control in China

Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial

Yeming Wang*, Dingyu Zhang*, Guanhua Du*, Ronghui Du*, Jianping Zhao*, Yang Jin*, Shouzhi Fu*, Ling Gao*, Zhenshun Cheng*, Qiaofa Lu*, Yi Hu*, Guangwei Luo*, Ke Wang, Yang Lu, Huadong Li, Shuzhen Wang, Shunan Ruan, Chengqing Yang, Chunlin Mei, Yi Wang, Dan Ding, Feng Wu, Xin Tang, Xianzhi Ye, Yingchun Ye, Bing Liu, Jie Yang, Wen Yin, Aili Wang, Guohui Fan, Fei Zhou, Zhibo Liu, Xiaoying Gu, Jiuyang Xu, Lianhan Shang, Yi Zhang, Lianjun Cao, Tingting Guo, Yan Wan, Hong Qin, Yushen Jiang, Thomas Jaki, Frederick G Hayden, Peter W Horby, Bin Cao, Chen Wang



Number at risk (number censored)								
Remdesivir	158 (0)	155 (2)	147 (0)	123 (1)	101 (0)	82 (1)	63 (0)	25 (26*)
Control	78 (0)	78 (0)	75 (0)	64 (0)	52 (0)	46 (0)	38 (0)	17 (16*)


Fauci: Remdesivir trial is 'opening the door' to possible coronavirus treatments
MOMENTS AGO
APRIL 29, 2020 / 04:38
BREAKING NEWS
FAUCI: INITIAL RESULTS FROM DRUG TRIAL "GOOD NEWS"
MSNBC

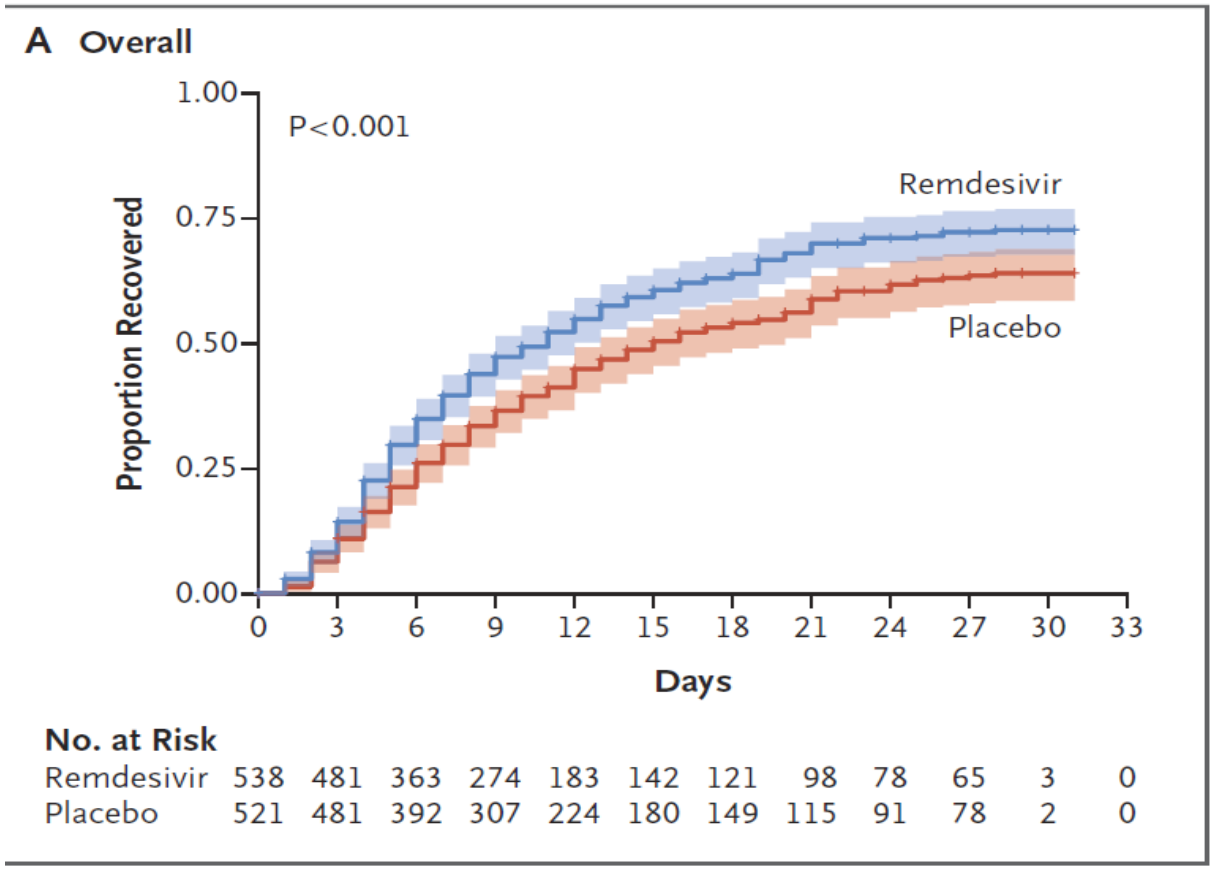
US remdesivir trial (n=1063)

- Randomized, double-blinded,1:1, same treatment plan as for China study.
- The primary outcome was the time to recovery, defined by either discharge from the hospital or hospitalization for infection control purposes only

Table 1 COVID-19 Disease Ordinal Scale Categories in Chinese Remdesivir Trial and in NIAID's ACTT Versions 1 and 2

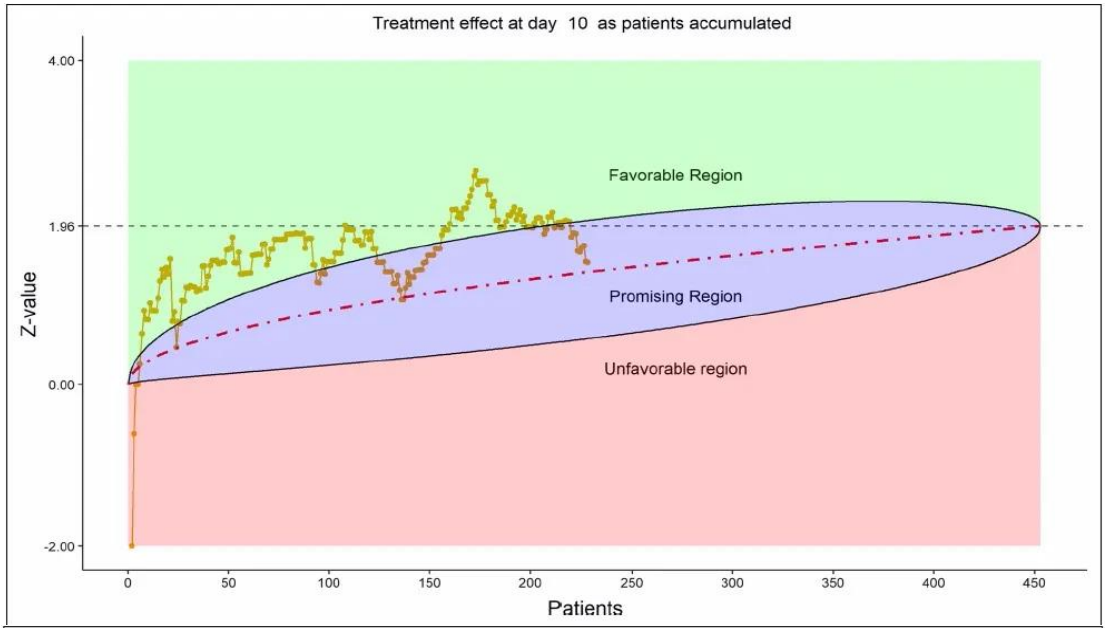
Scale	6	5	4	3	2		1	
Chinese Trial	Death	Hospitalization, requiring ECMO and/or IMV	Hospitalization, requiring NIV and/or high-flow oxygen therapy (HFNC)	Hospitalization, requiring supplemental oxygen (but not NIV/HFNC)	Hospitalization, but not requiring supplemental oxygen		Hospital discharge or meets discharge criteria (discharge criteria are defined as clinical recovery, ie fever, respiratory rate, oxygen saturation return to normal, and cough relief, all maintained for at least 72 hours).	
Scale	1	2	3	4	5		6	7
ACTT – version 1	Death	Hospitalized, on invasive mechanical ventilation or ECMO	Hospitalized, on non-invasive ventilation or high flow oxygen devices	Hospitalized, requiring supplemental oxygen	Hospitalized, not requiring supplemental oxygen		Not hospitalized, limitation on activities	Not hospitalized, no limitations on activities
Scale	1	2	3	4	5	6	7	8
ACTT – version 2	Death	Hospitalized, on invasive mechanical ventilation or ECMO	Hospitalized, on non-invasive ventilation or high flow oxygen devices	Hospitalized, requiring supplemental oxygen	Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care (COVID-19 related or otherwise)	Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care	Not hospitalized, limitation on activities and/or requiring home oxygen	Not hospitalized, no limitations on activities

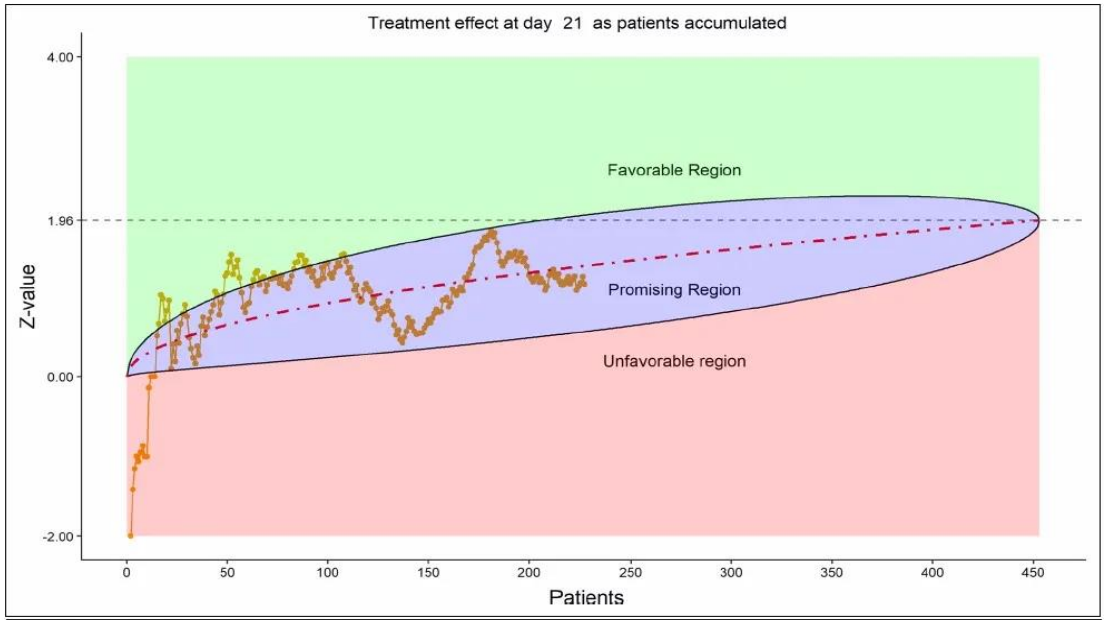
Abbreviations: ECMO, extracorporeal membrane oxygenation; NIV, non-invasive ventilation; IMV, invasive mechanical ventilation; HFNC, high flow nasal cannula.

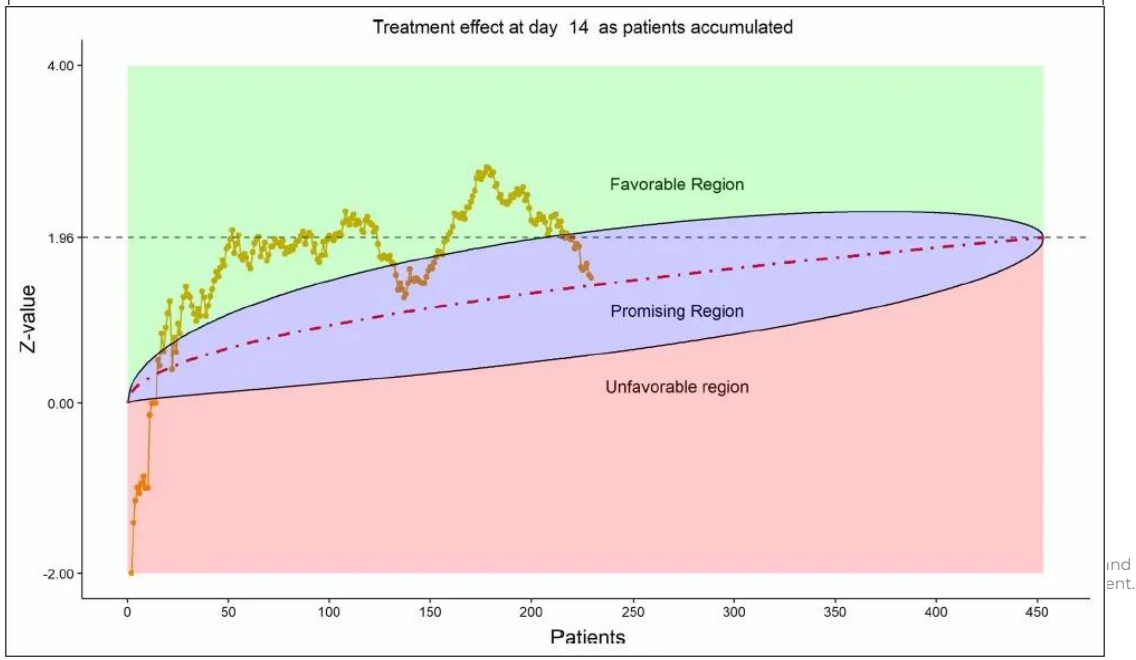


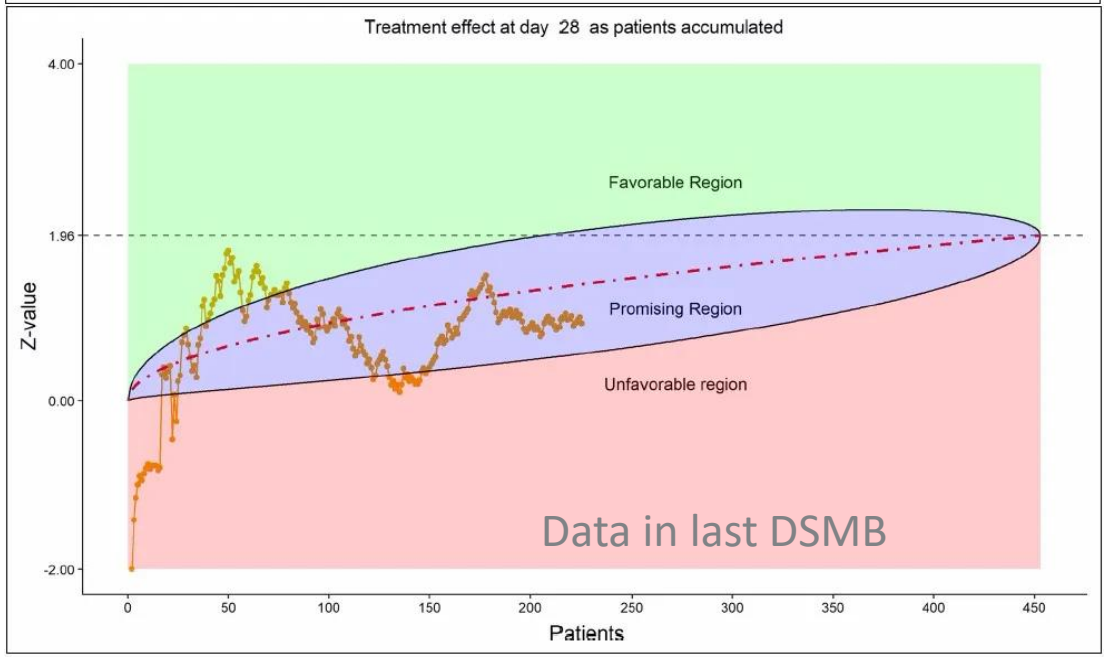
Overall result: 11 vs. 15 days, p<0.001

Retrospective review of DSMB data









Data in last DSMB

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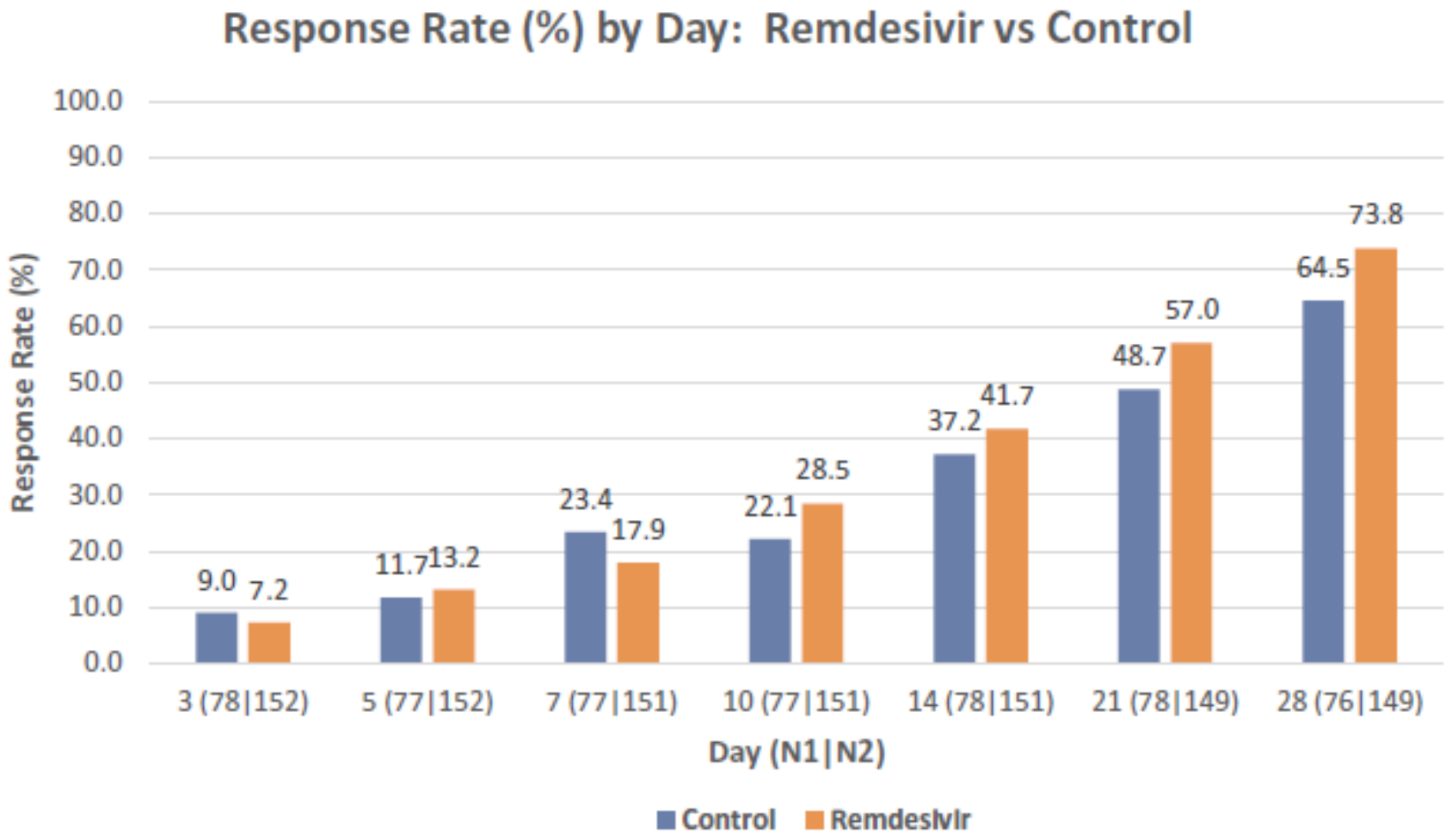
Re-analysis of China study



Publications that applied the DDM

Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial

Yeming Wang, Dingyu Zhang*, Guanhua Du*, Ronghui Du*, Jianping Zhao*, Yang Jin*, Shouzhi Fu*, Ling Gao*, Zhenshun Cheng*, Qiaofa Lu*, Yi Hu*, Guangwei Luo*, Ke Wang, Yang Lu, Huadong Li, Shuzhen Wang, Shunan Ruan, Chengqing Yang, Chunlin Mei, Yi Wang, Dan Ding, Feng Wu, Xin Tang, Xianzhi Ye, Yingchun Ye, Bing Liu, Jie Yang, Wen Yin, Aili Wang, Guohui Fan, Fei Zhou, Zhibo Liu, Xiaoying Gu, Jiuyang Xu, Lianhan Shang, Yi Zhang, Lianjun Cao, Tingting Guo, Yan Wan, Hong Qin, Yushen Jiang, Thomas Jaki, Frederick G Hayden, Peter W Horby, Bin Cao, Chen Wang*

Therapeutic Innovation & Regulatory Science
https://doi.org/10.1007/s43441-020-00159-7

DIA

ORIGINAL RESEARCH

Check for updates

Data Monitoring for the Chinese Clinical Trials of Remdesivir in Treating Patients with COVID-19 During the Pandemic Crisis

Weichung J. Shih[1] · Chen Yao[2] · Tai Xie[3]

STATISTICS IN BIOPHARMACEUTICAL RESEARCH
2021, VOL. 00, NO. 0, 1–12
https://doi.org/10.1080/19466315.2020.1880965

Taylor & Francis
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Check for updates

Dynamic Monitoring of Ongoing Clinical Trials

Tai Xie[a], Peng Zhang[a], Weichung Joe Shih[b], Yue Tu[a], and K. K. Gordon Lan[b]

[a]Department of Biostatistics and Programming, Brightech International, Somerset, NJ; [b]Department of Biostatistics and Epidemiology, School of Public Health, Rutgers University, The State University of New Jersey, Piscataway, NJ

Open Access Journal of Clinical Trials

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ORIGINAL RESEARCH

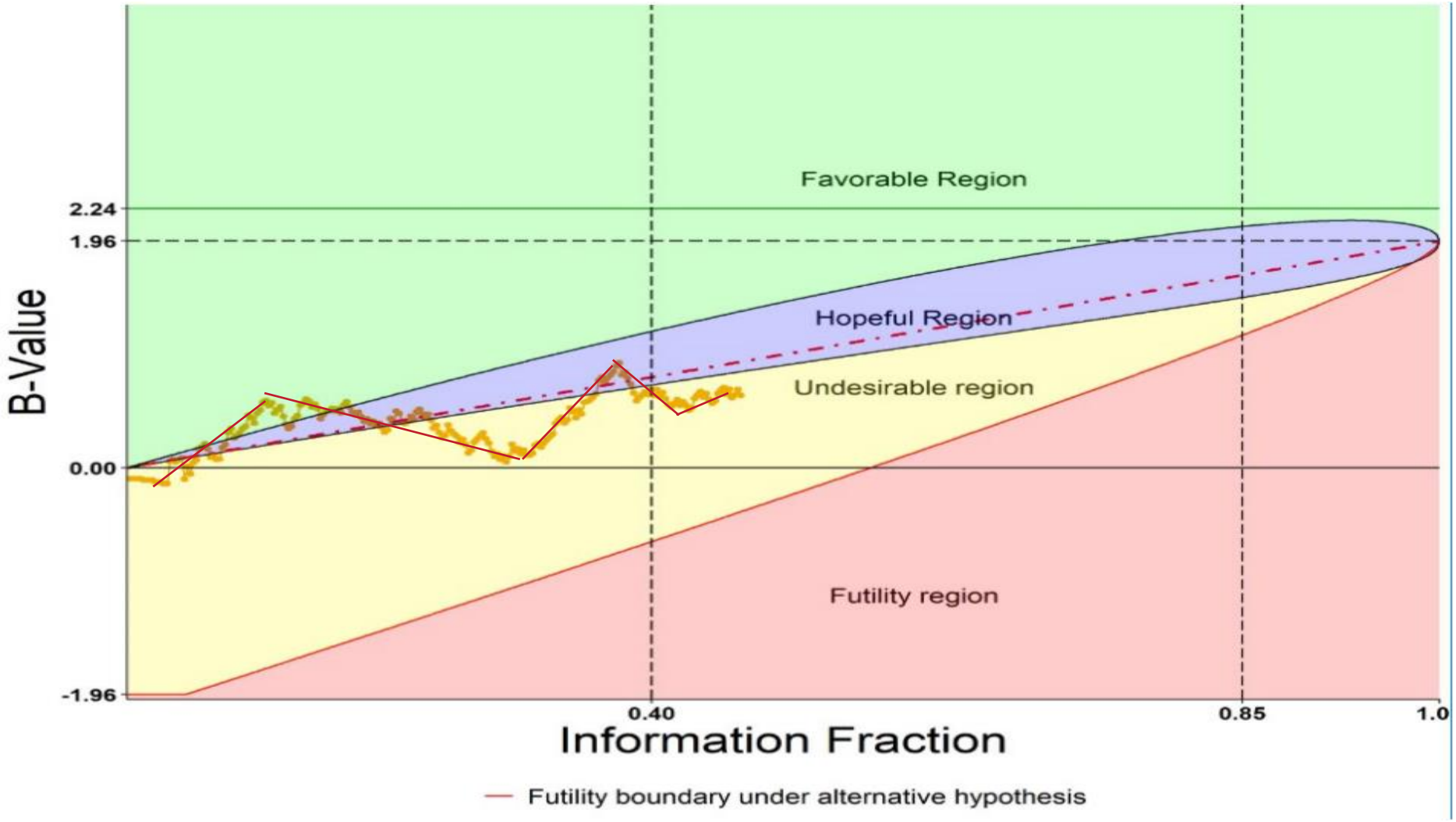
Remdesivir is Effective for Moderately Severe Patients: A Re-Analysis of the First Double-Blind, Placebo-Controlled, Randomized Trial on Remdesivir for Treatment of Severe COVID-19 Patients Conducted in Wuhan City

This article was published in the following Dove Press journal:
Open Access Journal of Clinical Trials

Weichung J Shih[1]
Xin Shen[2]
Peng Zhang[2]
Tai Xie[2]

Introduction: The first clinical trial on remdesivir for treatment of severe COVID-19 conducted in China was terminated prematurely due to limited patient enrollment, which rendered the findings inconclusive. We re-analyzed the efficacy with a statistically more powerful and clinically meaningful method based on published data using the 6-point ordinal scale of patient's disease severity.

Trial Diagnosis



eDMC

- Centralized document management (Charter, protocol, analysis plan, etc.)
- Meeting scheduling and management.
- Direct link or upload clinical database for dynamic data monitoring (DDM) in real-time.
- Enable ad hoc data visualization and analysis during the DMC meeting.
- The platform greatly improves:
  - Efficiency of IDMC's working process.
  - Regulatory compliance.

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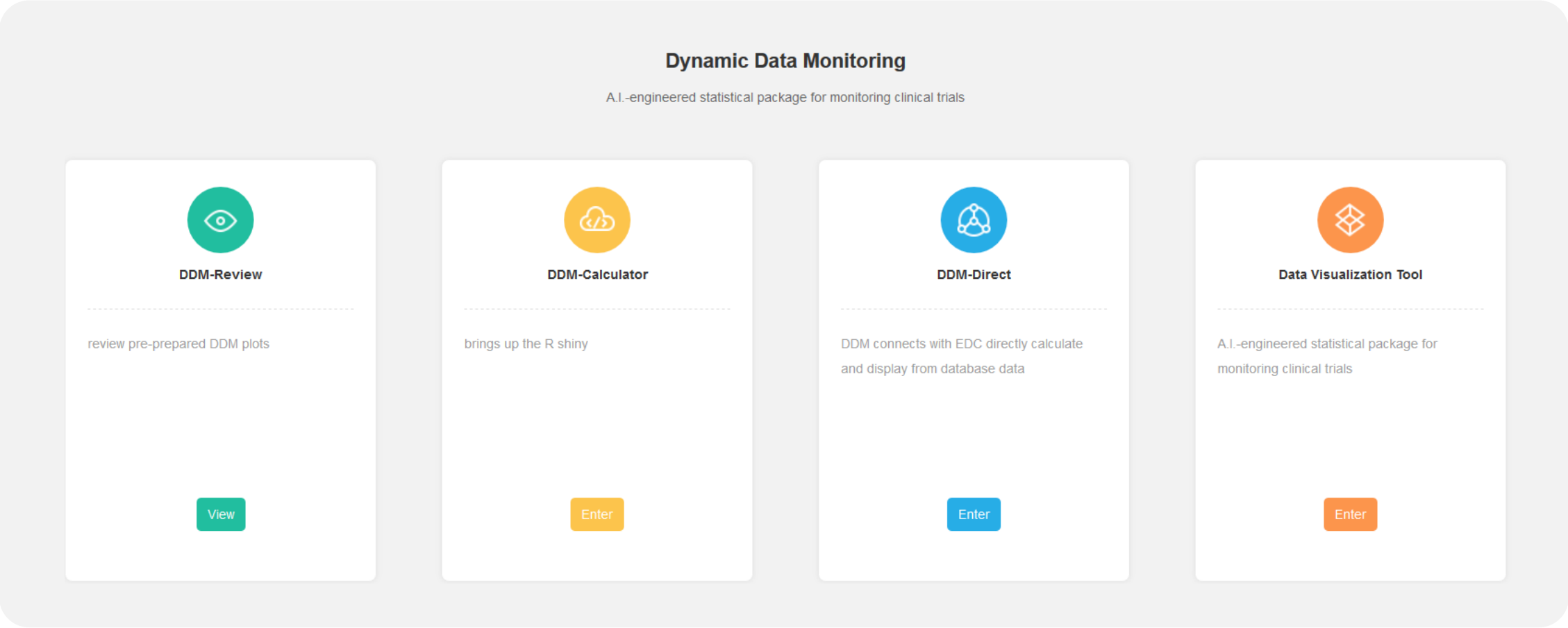
DDM and Data Visualization Tools Embedded



Potential Applications of DDM

- **Trial optimization**
  - Through DDM, we could optimize on-going trial to maximize its success
- **Early stop potentially successful trials**
  - Perform an unscheduled formal interim analysis when DDM shows strong evidence of early stopping
- **Early termination of “hopeless” trials**
  - Given the high rate of failure of phase 2/3 trials, DDM can alert the sponsor to conduct a formal futility analysis
  - Timely terminating “hopeless” trials is both an ethical and financial issue
- **Drug safety detection**
  - Continuous monitoring of drug safet**y (signal detection)**
- **Dose selection**
  - DDM enables a seamless, optimal phase 2/3 combination trial by identifying most potential doses for phase 3.
- **Population selection**
  - DDM can intelligently identify the subpopulation in which the drug is most effective.
  - DDM can be directly applied to RCT or RWE setting for personalized medicine
- **Sample size re-estimation**
  - DDM can intelligently estimate an optimal sample size for a trial and thus maximizes the probability of success of the trial
- **Model checking and correction**
  - Check and verify the assumptions set prior to initiation of the trial
  - Checking linearity

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Thank you

Feel free to contact us with any questions or thoughts you may have.

tomx@cims-global.com / 908.723.1472