Cytel

STATISTICAL SOFTWARE & SERVICES

Use of Simulations to Support Decision Making in Future Drug Development

Zoran Antonijevic

PhUSE

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Overview

- Need for simulations of development program scenarios in modern drug development
- Case Study 1; Ulcerative Colitis Development Program
- Case Study 2; Diabetes Development

Pharma Status

- Diminishing returns
  - End of Blockbuster era, same class drugs (statins, Cox-2 inhibitors, SSRIs).
  - Affordable Care Act. Reimbursement, differentiation
- Increased costs
  - Safety issues with some Blockbusters (Vioxx, Avandia…). Demand for larger safety databases (Diabetes, Obesity…)
  - Failures contribute to estimated costs (Andy Witty, GSK)

Pharma Decision Making

- Historically decision making easier
  - Same class drugs - straightforward development
  - Blockbusters - large revenues
  - Most common decision criteria: “gut feeling”
- Current, future
  - More emphasis on PoS, differentiation, then on speed of development
  - Differentiation: dose selection, biomarkers
  - **Optimization**; program, portfolio level
  - **Quantification** and **scenario comparisons** necessary

Changes Necessary

- Lack of Quantitative Decision Making in the Pharmaceutical Industry
  - Decision Analysis not Utilized
  - Inadequate use of Statistical Resource
  - Lack of Utilization of Modeling and Simulations (M&S)

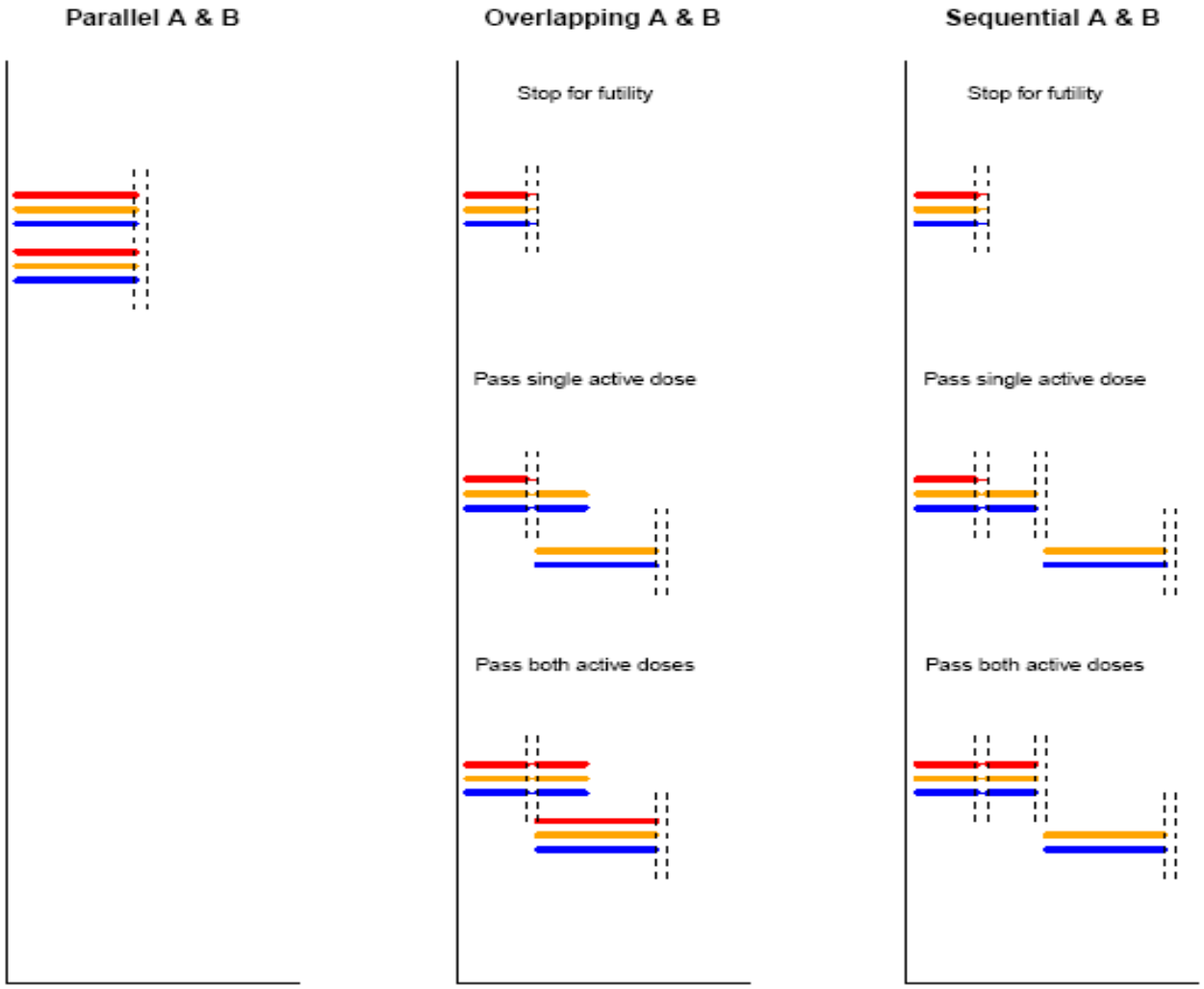
- FDA's March 2006 "Critical Path Opportunities List" calls for Advancing Innovative Trial Designs, including
  - #36 greater use of Adaptive Trial Designs; more use of Bayesian methods in drug development
  - #51 clinical trials simulation

Simulations

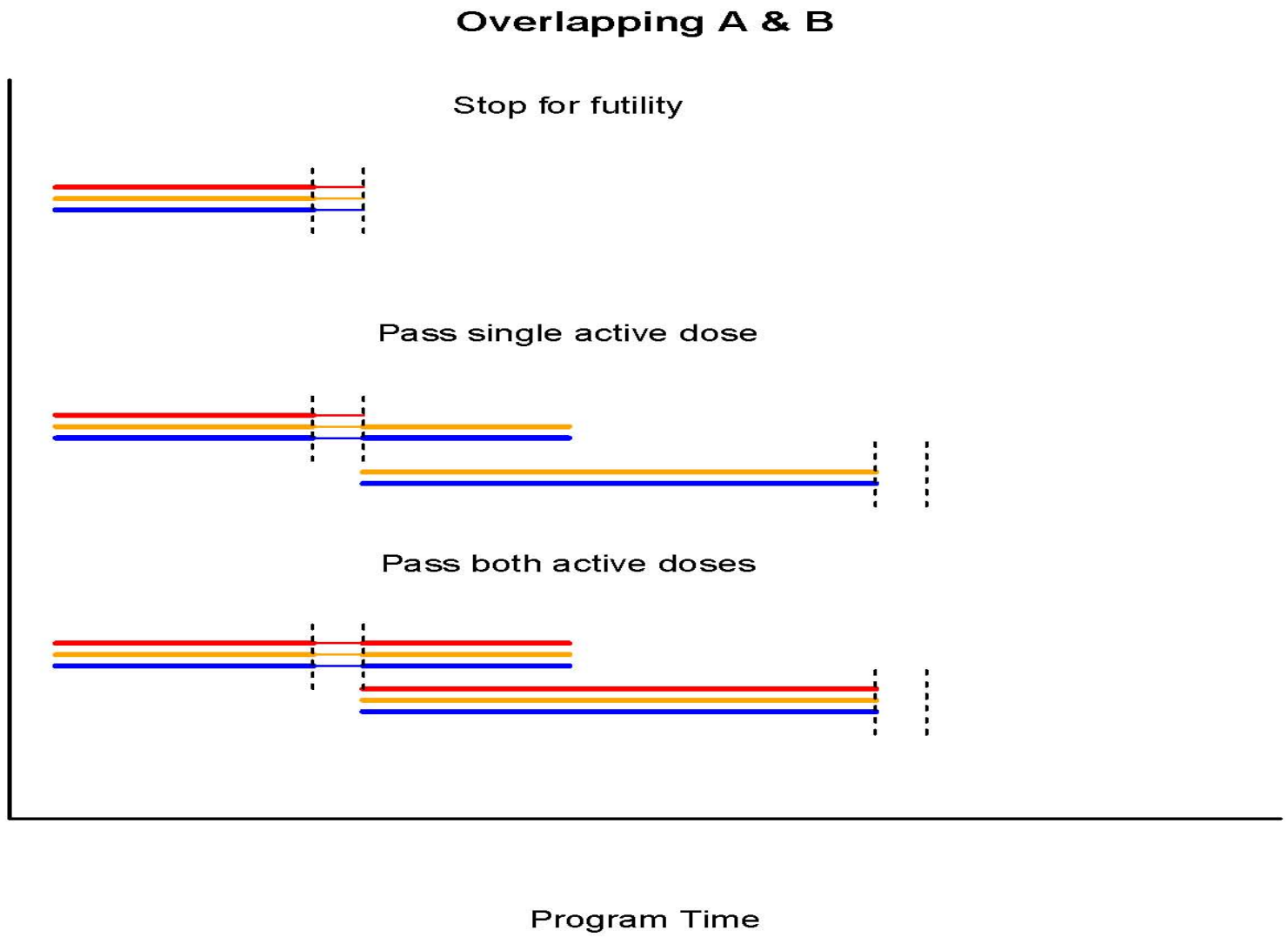
- Integration of information from multiple areas, from pre-clinical development, through the submission stage, to commercial.
  - Outputs from earlier stages can be used to define assumptions for simulation parameters.
- Assessing multiple scenarios such as differing study designs and endpoints
  - Even more diverse inputs such as cost of study start-up, accrual rates, and per-subject costs
- Offer an approach to deal with the computational complexity
- Accounting for uncertainty
  - Distributional output

Case Study 1
Ulcerative Colitis Development Program

Candidate Phase 2b/3 Development Plans



Selected Development Plan



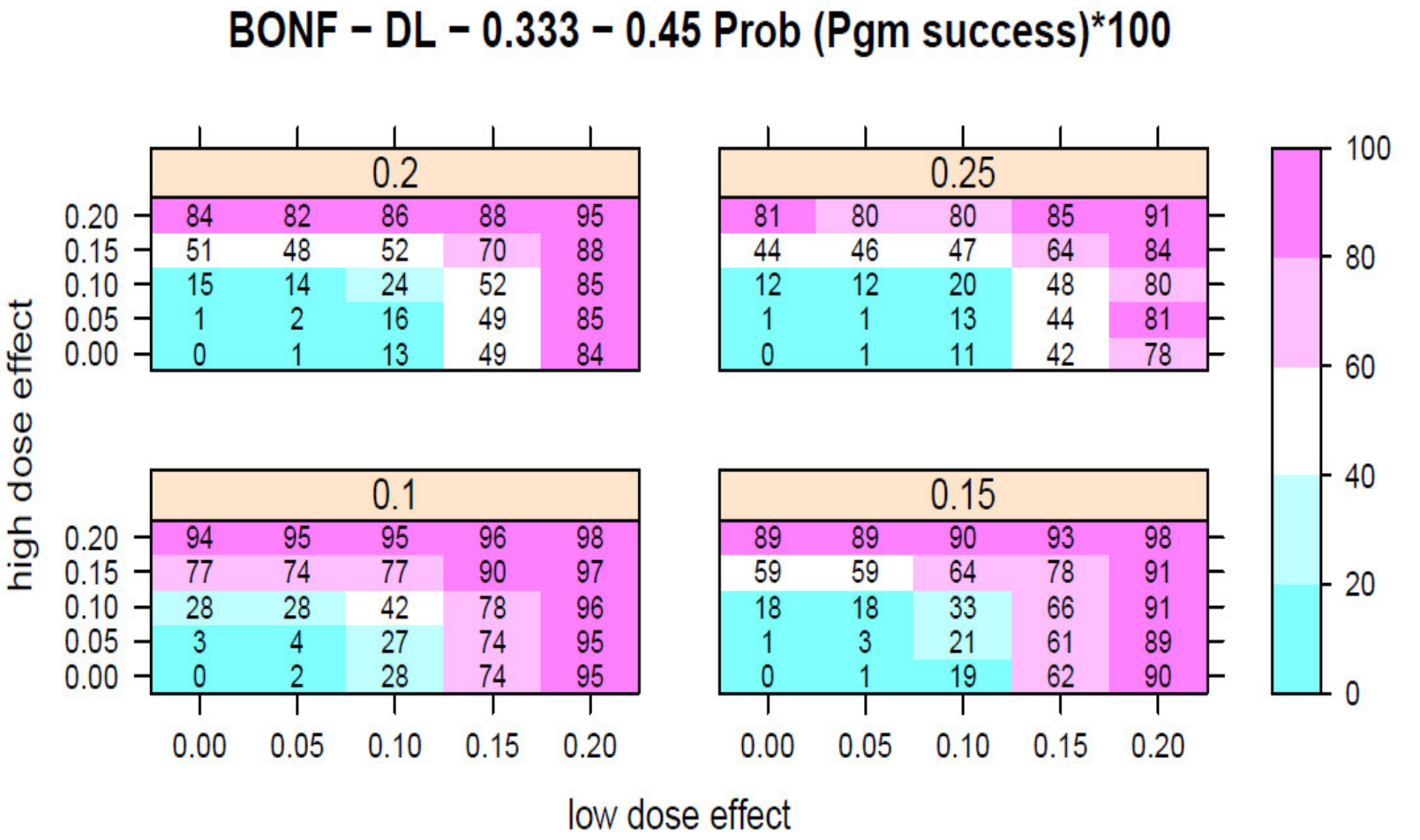
Operating characteristics

N	Characteristics
1	Probability of program success in trial A
2	Expected sample size of the trial A
3	Expected duration of the trial A
4	Probability of success in the trial A
5	Expected sample size of the program
6	Expected duration of the program
7	Probability of going beyond IA

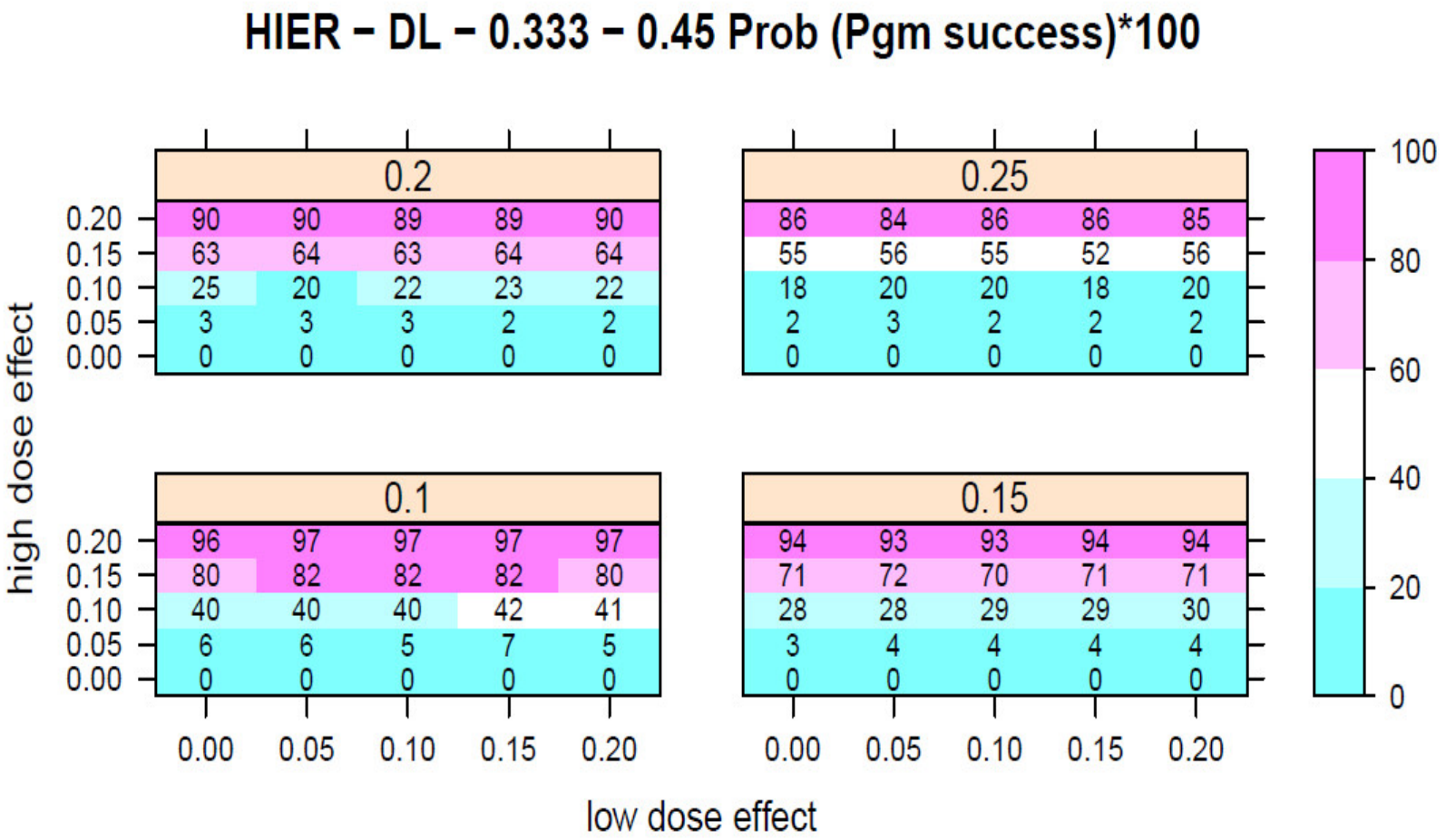
Testing methods

- Applied at the end of each trial
- Bonferroni: tests each dose at = 0.0125 (one-sided)
- Hierarchical: tests each dose at = 0.025(one sided) but only allows to test low dose if the test for the high dose is successful

Bonferroni


BONF – DL – 0.333 – 0.45 Prob (Pgm success)*100
0.2
0.25
0.1
0.15
high dose effect
low dose effect
0.00 0.05 0.10 0.15 0.20
0 20 40 60 80 100

Hierarchical

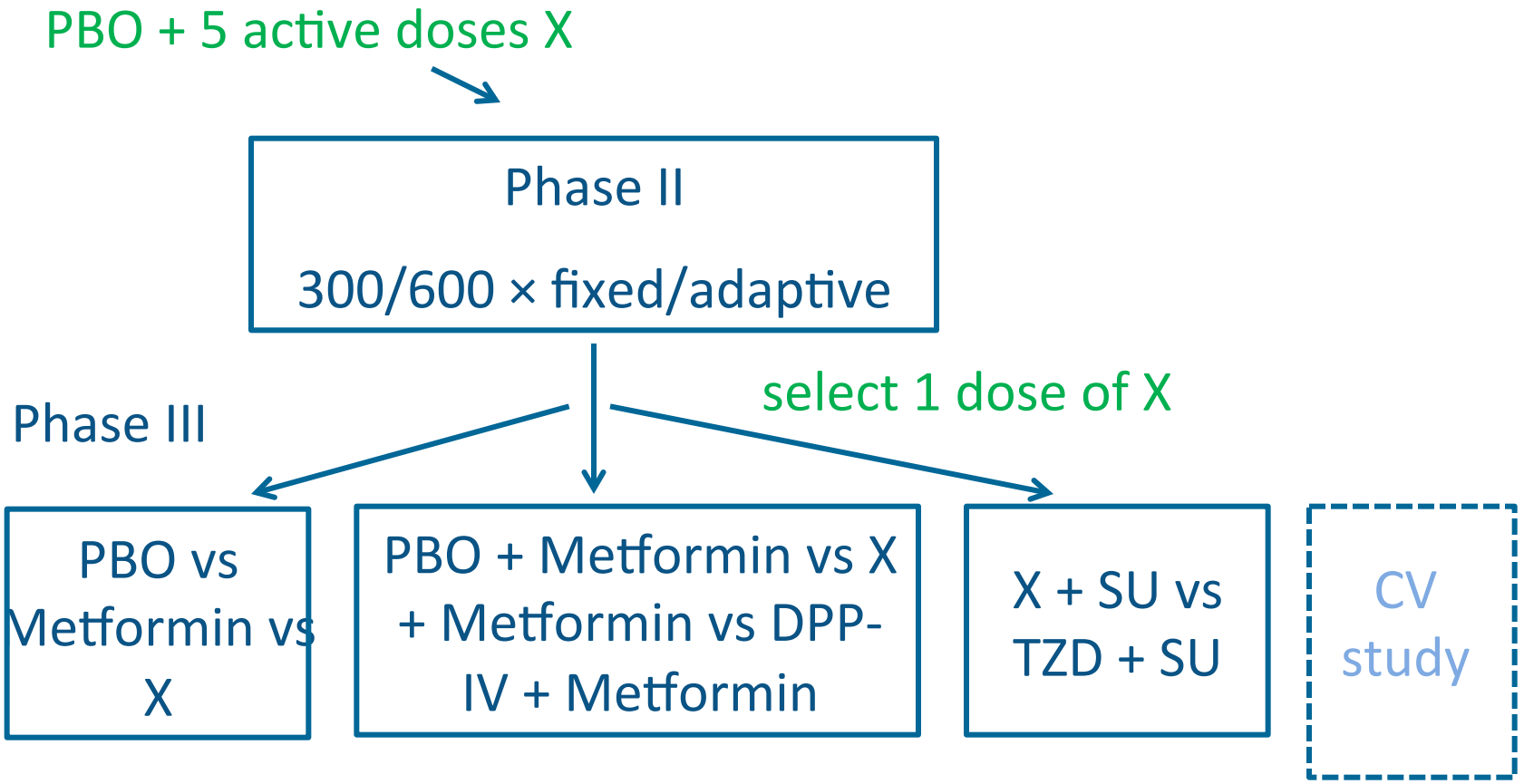


Conclusions

- We used simulations to help sponsor select among many possible development scenarios and statistical procedures
- A number of things need to be considered when making decisions:
  - Which parameters are of most importance?
  - What are most likely scenarios?

Case Study 2
Diabetes Development

Adaptive Program – Phase 2b and 3

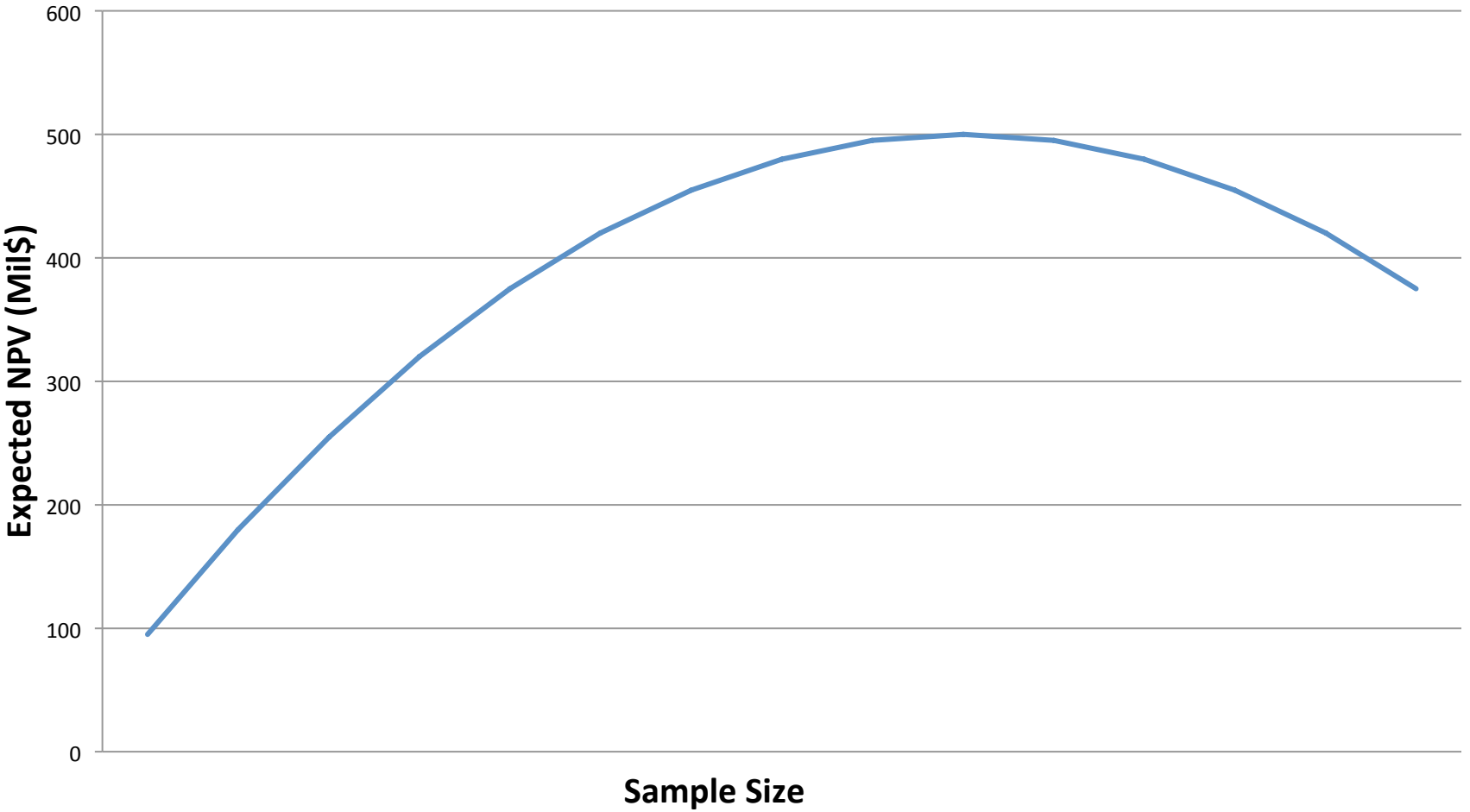


n_3 = 200, 300, 400, 600 per arm

Design Parameters to be Investigated

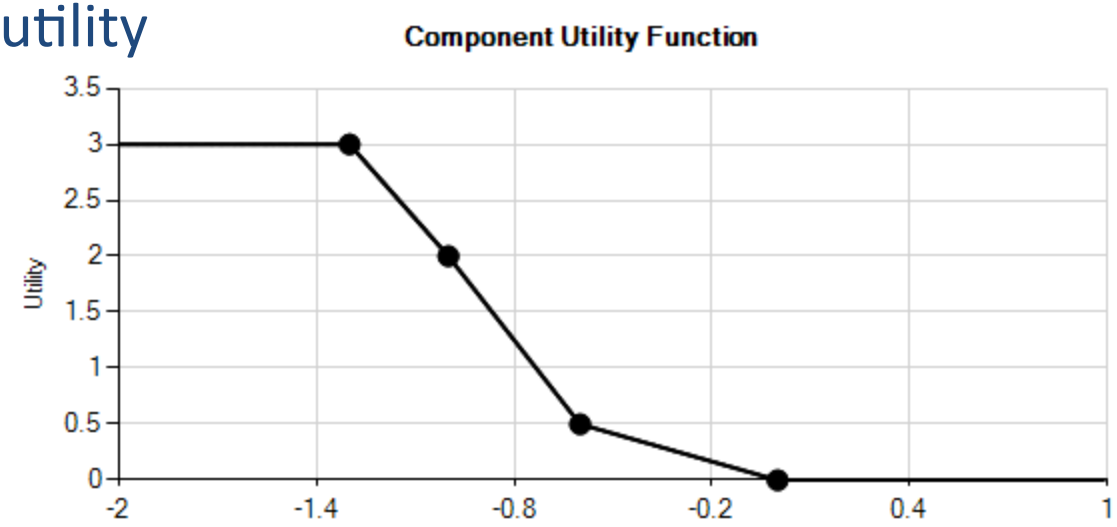
- Phase II Design (adaptive vs. non-adaptive)
- Phase II Sample size (300 vs. 600)
- Phase II follow-up time (12 vs. 24 weeks)
- Phase III Sample size (200, 300, 400, 600 per arm)

Outcome - eNPV



Dose Selection Clinical Utility Function

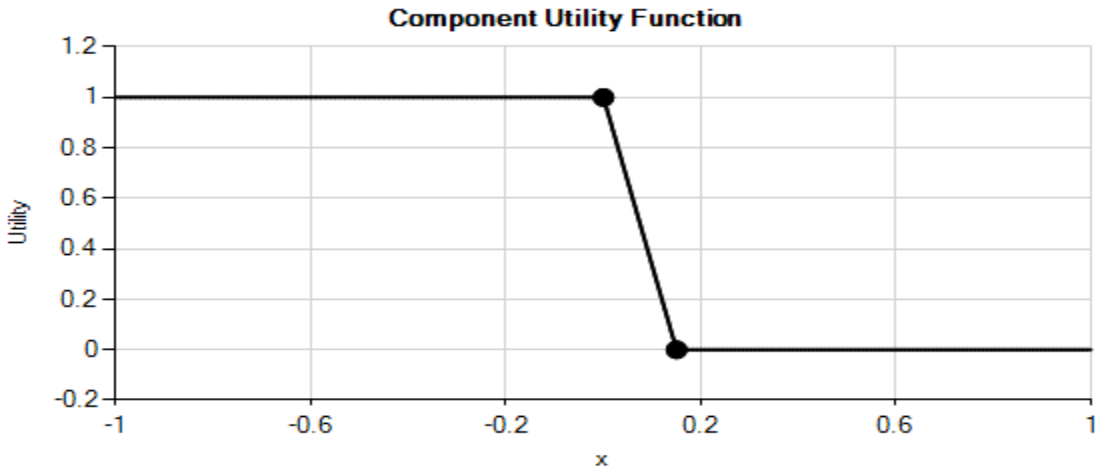
Select dose, and adaptively allocate towards dose with max utility



← HbA1c

×

Probability of hypoglycemic event(s) →



Regulatory Success Criteria

- $\geq$ 2 trials with statistical significance for efficacy (one of these studies has to be Study #1 showing superiority vs. Placebo)
- The safety requirement is that the upper bound of two-sided 95% confidence interval of the risk ratio of treatment over control is less than 1.8.
- For a program to be successful, both safety and efficacy criteria have to be met.
- Each indication (monotherapy, add-on to metformin, add-on to sulphonylurea) is approved if general approval is received + statistical significance in the trial for that indication
- For Study #2 (previous slide), DPP-IV's currently not accepted as an active comparator, but this will likely change in future, so keep DPP-IV as active comparator.
- For HbA1c use Non-inferiority margins of 0.3

Revenue Function

- Drug has to beat pbo as the entry ticket to the market. Then:

Percent of max NPV for different probabilities of AE									
Drug	**Test**	**Max NPV B $US**	**% Adverse event (hypoglycemic events)**						
			1	2	4	8	16	32	64
TZD	N.I.	1	100	66.7	33.3	0	0	0	0
	Sup	10	100	90	80	70	35	0	0
DPP-IV	N.I.	1	100	50	0	0	0	0	0
	Sup	3	100	80	60	40	20	0	0

Conclusions

- Larger sample sizes in Phase 2b and Phase 3 studies provide more precise dose selection, and reduce the positive treatment effect bias and uncertainty in estimated ENPV, within the range of sample sizes studied.
- Similar improvements are seen with implementation of an adaptive design over a fixed design in Phase 2b.
- Larger adaptive trials have identified the dose with the maximum utility dose most often, while smaller fixed designs identified this dose least often.
- Larger number of the patients were assigned to the highest utility doses using an adaptive design compared to a fixed design for three different scenarios.
- Dose selection criteria have to be consistent with developers' objectives. It is a very common situation that dose selection criteria are defined by R&D teams, while one of the key objectives is to maximize the expected revenues.
  - We recommend closer collaboration of R&D clinical and commercial groups earlier in development

References

- Antonijevic Z., Kimber M., Manner D., Burman C-F., Pinheiro J., and Bergenheim K. "Optimizing Drug Development Programs: Type 2 Diabetes Case Study". *Therapeutic Innovation & Regulatory Science*, first published on March 25, 2013 as doi:10.1177/2168479013480501